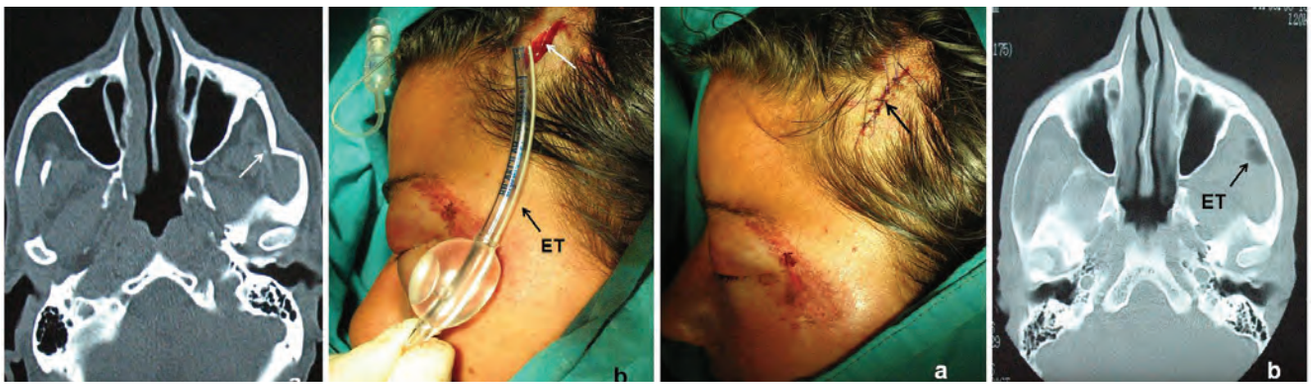
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Internal splinting method for isolated zygomatic arch fracture using endotracheal tube: A new method

Turan A



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Effects of sildenafil citrate on survival in the posterior leg replantation model

Rat arka bacak replantasyon modelinde sildenafil Sitrat'ın sağkalım üzerine etkileri

Sildenafil citrate and leg replantation

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Öz

Amaç: Sildenafil sitrat bir fosfodiesteraz (PDE) enzim inhibitörü ve bir vazodilatör ajandır. Anjiyoprotektif ve anjiyogenetik etkileri önceden bildirilmiştir. Bu çalışmanın amacı, sildenafil sitratın iskemik sıçan arka bacak replantasyonundan sonra sağkalıma olan etkisini araştırmaktır. Gereç ve Yöntem: Bu çalışmada Sprague-Dawley dişi sıçanlar kullanılmıştır. Çalışmanın ilk evresinde sildenafil sitratın sağkalım etkileri araştırıldı. Bu amaçla, kontrol ve çalışma gruplarında iskemik sıçanlara arka bacak replantasyonu yapıldı ve postoperatif dönemde 7 gün boyunca çalışma gruplarına 10 mg/kg/gün sildenafil sitrat uygulandı. İkinci aşamada, sildenafil sitratın doku etkisi analiz edildi. Çalışma grubuna iskemik sıçan arka bacak modeli için sildenafil sitrat uygulandı ve gastrocnemius kası ve femoral ven alınan doku örnekleri histolojik olarak analiz edildi. Damar dokusuna Ang-1, VEGF immünohistokimyasal boyaları uygulanırken, kas dokusunda PCNA immünohistokimyasal boyaları uygulandı. Kan numunelerinin katalaz düzeyleri biyokimyasal olarak analiz edildi. Bulgular ve Tartışma: Sildenafil sitratın anlamlı şekilde sağkalımı artırdığı gözlemlendi. Kas dokusunda nekrozu azalttığı, ayrıca endotel hasarını azaltırken antioksidan aktiviteyi arttırdığı da gözlendi.

Anahtar Kelimeler

Sildenafil Sitrat; Replantasyon; Revaskülarizasyon; Angiopoetin; İskemi-Reperfüzyon Hasarı

Abstract

Aim: Sildenafil citrate is a phosphodiesterase (PDE) enzyme inhibitor and a vasodilator agent. Its angioprotective and angiogenetic effects are widely known. The aim of this study was to investigate the effects of sildenafil citrate on survival of ischemic rat hind leg amputation after replantation. Material and Method: Sprague-Dawley female rats were used in the study. The survival effects of sildenafil citrate were investigated in the first phase of the study. For this purpose, ischemic rat hind leg replantation was performed on control and study groups and 10 mg/kg/day sildenafil citrate was administered to study groups for 7 days in the postoperative period. In the second phase, the tissue-level effects of sildenafil citrate were investigated. Tissue samples were taken from gastrocnemius muscle and femoral vein and they histologically analyzed. Ang-1 and VEGF immunohistochemical stains were applied to vein tissue, whereas PCNA immunohistochemical stains were applied to muscle tissue. Blood samples were analyzed for catalase. Results and Discussion: It was observed that sildenafil citrate macroscopically and significantly increased survival after hind leg replantation. It reduced necrosis. It also reduced endothelium damage and increased antioxidant activity.

Keywords

Sildenafil Citrate; Replantation; Revascularization; Angiopoietin; Ischemia-Reperfusion Damage

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Introduction

Peripheral organ amputations are problematic injuries in Plastic and Reconstructive Surgery practice. Proper timing of the surgery, meticulous surgical technique, and appropriate surgical and anesthetical environments and techniques are indispensable for a successful outcome. However, in order to increase the chance for survival or to cope with the consequences of less than ideal conditions, researchers try to find remedies for reducing the expected ischemic-reperfusion damage, by increasing the regenerative capacity of vascular endothelium, protecting the anastomosis from thrombotic events, and promoting vasodilator activity.

A specific phosphodiesterase (PDE-5) enzyme inhibitor, sildenafil citrate, is currently used for erectile dysfunction treatment due to its peripheral vasodilator effect. Its known effect is to ensure the progression of vasodilatation by preventing the degradation of c-GMP (guanidine monophosphate), which is the secondary messenger of nitric oxide (NO), primarily in vascular smooth muscle cells (1). The vasodilator effect of PDE-5 inhibitors was presumed to release endogenous mediators that would result in cardioprotective effects against ischemia/reperfusion injury of cardiac muscle. Treatment with sildenafil was also established to mediate increased levels of VEGF in the ischemic brain and induce capillary-like tube formation in a culture of both brain-derived endothelial cells and coronary arteriolar endothelial cells, suggesting neoangiogenetic properties (2). On the other hand, inhibition of PDEs was shown to exert a platelet-inhibitory effect by increasing the intracellular cyclic nucleotide content of the platelet, thus blocking cytoskeletal rearrangement, fibrinogen receptor activation, degranulation, and expression of proinflammatory mediators (3).

The aim of the study was to investigate the versatile effects of sildenafil citrate on survival in the ischemic rat hind leg replantation model.

Material and Method

The study was approved by the Eskisehir Osmangazi University (ESOGU) Ethical Committee on Animal Experiments (decision number of 101 dated 18.02.2009). 35 female Sprague-Dawley rats between 250-300 g in weight were used for the study. The rats were kept in the experimental animal laboratory of Eskisehir Osmangazi University Faculty of Medicine at constant room temperature and were supplied with limitless water and dry pellets. A separate cage was provided for each subject. The surgical procedure was performed by the same researcher during the study and the subjects were randomly distributed into groups. Subjects were anesthetized intraperitoneally with 80 mg/kg ketamine (Ketalar 500 mg, solution for injection in vials, Pfizer) for all surgical procedures.

The sildenafil citrate sample to be administered to the subjects was obtained in compliance with Hart et al. using the commercially available product (Viagra tablet 100 mg, Pfizer Inc., NY) (4). The study was planned to be two steps.

In the first part of the study, the effects of sildenafil citrate on survival were determined in the ischemic rat hind leg replantation model. The right hind legs of the subjects were amputated at the inguinal level. Femoral and sciatic nerves were protected during amputation in order to prevent autocannibalization that could arise during the follow-up period. The control group (n=7) received 1 cc of saline and the study group (n=7) received 10mg/kg sildenafil citrate intraperitoneally immediately after amputation (Figure 1).

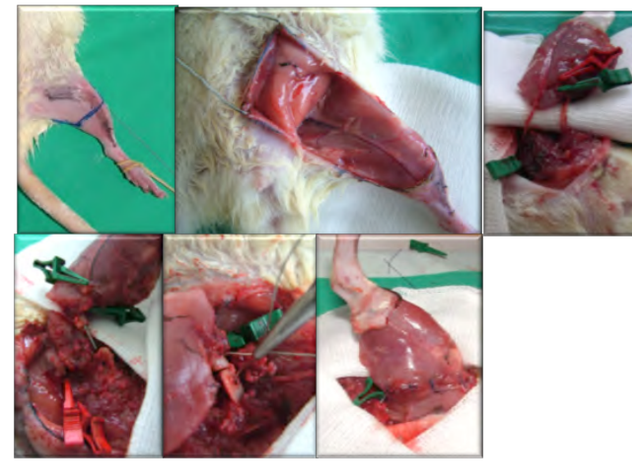


Figure 1. Surgical steps of the first part of the study. Femoral and sciatic nerves remained intact.

Bone fixation, muscle repair, and subsequent anastomosis of femoral arteries and veins were performed; the ischemic period from the amputation to the opening of the arterial clamps after revascularization was 180 minutes. Anastomoses were performed by the same surgeon under operating microscope with a 25x magnification. A total of 8 separate sutures were used in end-to-end fashion with 10/0 Prolene for each vascular anastomosis.

The subjects in the control and study groups were followed for a total of 7 days. 10 mg/kg/day sildenafil citrate was administered to subjects of the study group and 1 cc of saline solution was administered to the subjects of the control group as placebo; both were applied intraperitoneally for a 7 day period (5,6). Pictures of all subjects were taken on the 1st, 3rd, 5th, and 7th days postoperatively and potential necrosis and their levels on replanted legs were detected. Subjects having no ischemia or necrosis on the replanted leg were scored as 0, subjects having partial necrosis were scored as 1, and subjects having total necrosis were scored as 2. The results were statistically evaluated.

For the second part of the study, the aim was to investigate the effects of sildenafil citrate on ischemia-reperfusion damage on the tissue level of the control (n=7) and study (n=7) groups. The right hind legs of subjects from the control and study groups were incompletely amputated at the inguinal level and their femoral arteries, veins, and nerves remained intact. Ischemia was initiated by putting two vascular clamps to each femoral artery and vein during amputation. Subsequently, 10 mg/kg/day sildenafil citrate was administered to the study group and 1 cc saline solution was administered to the control group, intraperitoneally as a single dose. It was performed just after the clamping. At the end of a 180-minute (3-hour) ischemic period, reperfusion was obtained by opening the clamps. Tissue samples were taken from femoral vein and gastrocnemius muscle at the 4th hour of reperfusion for histological and biochemical analyses. The subjects were sacrificed after taking intracardiac blood samples.

The femoral vein and gastrocnemius muscle samples for histological assays were kept in 10% formalin. Direct microscopic and immunohistochemical assays were performed on samples of femoral veins and muscles. For direct microscopic assay, the tissue samples were dyed with Hemotoxylin-Eosin (H&E) and Masson's trichrome stains and muscle samples were scored for necrosis, loss of striation, edema, leukocyte infiltration, and nucleus centralization, indicating the severity of inflammation caused by ischemia-reperfusion (7,8); whereas the femoral vein samples were scored for endothelial damage, tunica media damage, and presence of thrombus in lumens (9-11).

For immunohistochemical analysis the presence of satellite cells indicating muscle regeneration was evaluated by immunohistochemical marking of PCNA (proliferating cell nuclear antigen) protein in muscle tissue samples. Furthermore, angiopoietin (Ang-1) and vascular endothelial growth factor (VEGF) immune dyes were applied to femoral vein tissue samples (12,13) to interpret endothelial cell survival and angiogenesis. Catalase levels were analyzed with ELISA in blood samples.

All data obtained from measurements and scorings were evaluated with MINITAB 14. For all variables, the Shapiro Wilk Normality Test was performed. Since the variables of the study were not normally distributed, the Kruskal-Wallis Test was used for evaluation. For the variables differing between the groups, the Hollander Wolfe Multiple Comparisons Test was applied.

Results

Macroscopic Evaluation:

In the first part of the study, four subjects were diagnosed with total hind leg necrosis and two subjects were diagnosed with partial necrosis in the 7th day results of the control group. The leg of one control subject was completely healthy. No necrosis or ischemia finding was detected in the study group at the end of the follow up (Figure 2, Figure 3).

The results of the study group was statistically and significantly different compared to the control group (p<0.05).



Figure 2. Macroscopic view of the control group.

Histological Evaluation:

When the histological scoring of muscle tissue samples were statistically evaluated; the variables of necrosis, loss of striation, and leukocyte infiltration were significantly lower in the study group (p<0.001, p<0.05, and p<0.05 respectively). Nucleus centralization was not extensive in either group and there was no difference between groups in terms of edema and nucleus centralization variables (Figure 4,5).

When the histological scoring of vein tissue samples were statistically evaluated, tunica media damage was significantly higher in the control group compared to the study group (p<0.05). Although endothelial damage and the presence of intraluminal thrombus was higher in the control group than the study group, the difference was statistically insignificant.

Immunohistochemical Evaluation:

For PCNA immune-staining of gastrocnemius muscle tissues a low number of PCNA (+) cells was detected in the control group. On the other hand, a high number of PCNA (+) cells was detected in the study group, statistically different from the control group (p<0.05).

For Ang-1 immune-staining of femoral vein samples, a slight staining was detected in the control group, while there was moderate level of staining in the study group, a statistically significant difference (p<0.05) (Figure 6 A-F).

For VEGF immune-staining of femoral vein samples, moderate



Figure 3. Macroscopic view of the sildenafil citrate group.

Parameters	Control	Study	
Necrosis	++++++	+	p< 0.001
Striation loss	+++++	+	p<0.05
Nukleus centralization	+	++	p˃ 0.05
Leukocyte infiltration	+++++	+	p<0.05
Edema	+	++	p˃0.05

Figure 4. Histologic parameters of the muscle tissue after replantation.

level of staining was detected in all groups and there was no difference between the groups (Figure 7 A-C).

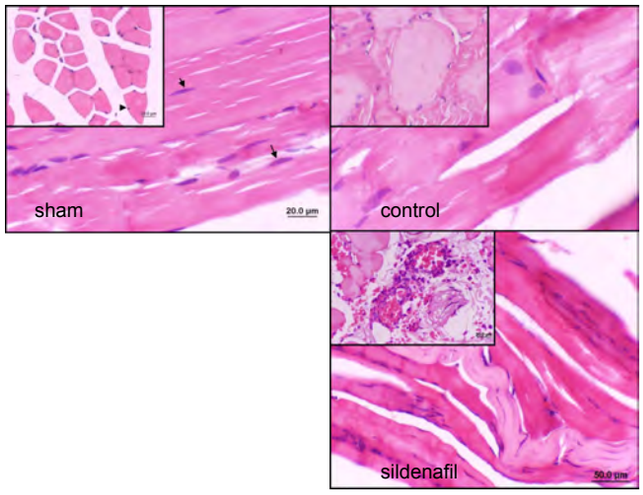


Figure 5. Microscopic image of the striation loss of the groups

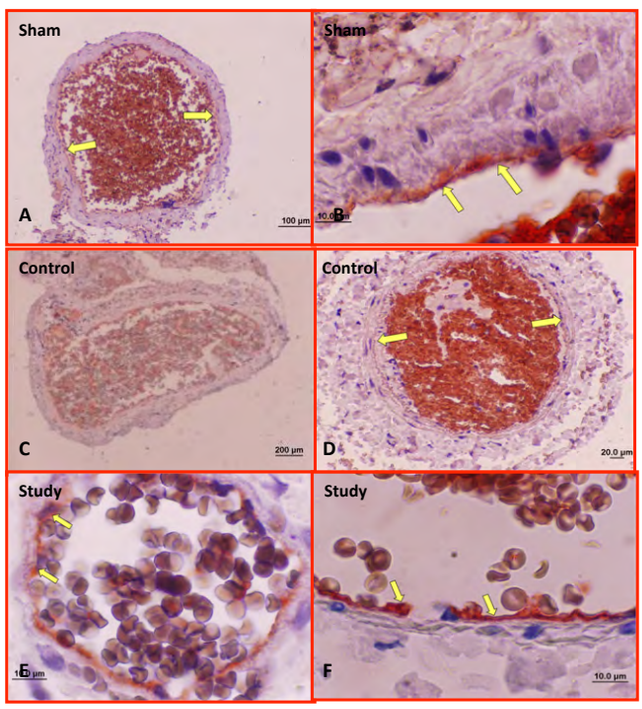


Figure 6. Ang-1 for the sham group applied light microscopic image of the femoral vein. Faint staining of endothelial cells (arrow) (bar: A:100 µm, B: 10,0 µm) (Ang-1). C,D: Ang-1 for the control group, light microscopy image of the femoral vein. Faint staining of endothelial cells (arrow) (bar: C: 200µm, D: 20.0µm) (Ang-1). E,F: Ang-1 for the study group applied light microscopic image of the femoral vein. Intense staining of endothelial cells (arrow) (bar: 10.0µm) (Ang-1) (A,B).

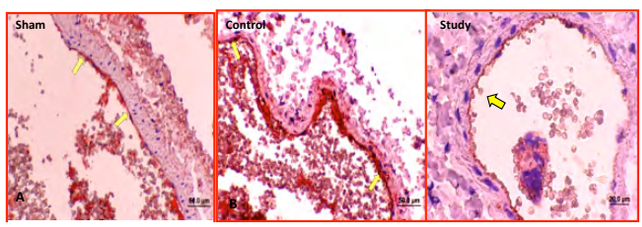


Figure 7. Light microscopic image of the femoral vein of the VEGF in the sham group. Faint staining of endothelial cells (arrow) (bar: 50.0µm) (VEGF)(A), Light microscopic image of the femoral vein of the control group, faint staining of endothelial cells (arrow) (VEGF). (bar: 20.0µm)(B), Light microscopic image of the femoral vein of the study group of VEGF. Faint staining of endothelial cells (arrow) (bar: 20.0µm) (VEGF)(C).

Biochemical Evaluation:

Catalase level was significantly higher in blood samples of the study group compared to other groups ($p<0.05$).

Discussion

The rat hind leg replantation model was used in this study since numerous research studies have been performed with this model and its anatomy is well-known. The ischemia time changes are reported as between 2-6 hours for hind leg ischemia-reperfusion models in the literature (14,15). After two hours of ischemia, minimal ultrastructural damages occur. In order to see histological changes, 4 hours of ischemia is necessary. Irreversible muscle damage occurs after 6 hours of ischemia. In our study, the critical ischemia time was determined to be 3 hours, both to observe some histologic changes and to see if they are effected in some way from sildenafil. When the macroscopic results of the study were evaluated, it was thought that sildenafil citrate significantly enhanced survival. Because all of the surgical procedure was performed by the same surgeon, the difference between groups cannot be attributed to the surgeon's skills; the survival success in the study group may be attributed to effects of sildenafil citrate at both the vascular and tissue levels. Vascular smooth muscle is under the control of endothelial nitric oxide (NO) which is synthesized by NO synthase. NO's main action is to activate the soluble guanylyl cyclase to produce cGMP. A very potent inhibitor of PDE-5, sildenafil citrate, blocks the degradation of cGMP to 5'GMP. The amplification of cGMP signaling enables relaxation of vascular smooth muscle activity by causing relaxation of smooth muscle cells through potassium (K+) channels. However, PDE-5 selectively hydrolyses cGMP and causes vascular resistance. PDE-5 is mostly present in vascular smooth muscle, intestine, heart, platelets, placenta, and chondrocytes, making them putative targets for sildenafil (1). The number one factor in the success of microsurgery is the prevention of vasoconstriction which is induced by several factors such as hypothermia, blood loss, and desiccation of the operative field. Sildenafil is thought to relieve the vasoconstriction by potentiating the cGMP concentration.

According to the histological evaluation results, sildenafil citrate significantly reduced the leukocyte infiltration, loss of striation, and the necrosis ratio in the ischemic hind legs of the subjects, whereas it did not show any difference regarding oedema and nucleus centralization. Cellular or intercellular oedema, inflammatory infiltration, and alterations in striation bands are some of the histopathological changes of muscle in response to ischemia. According to Akar et al., while striation loss is a minor and initial change after ischemia, necrosis and nucleus centralization represent a more serious and advanced injury (7). In contrast, Zhang et al. consider loss of striation in muscle to be irreversible muscle damage by (16). In any case, sildenafil restrained the ischemic damage in the muscle. In many ischemia reperfusion studies, sildenafil was demonstrated to attenuate the injury by decreasing leukocyte infiltration (8,17).

The major cause of replant loss after replantation is thrombus formation at the anastomosis. Veins are more susceptible to thrombus formation after microsurgery because the flow is slower. Endothelial damage is an initiator factor in thrombus formation. Regardless of the initial stimulus, suppressing the

platelet activation may inhibit thrombus formation. Platelets contain three types of PDE isoenzymes: PDE2, PDE3, and PDE5. Platelet PDE5 is inhibited by sildenafil but the Gresele at al. study was unable to prove that sildenafil can inhibit collagen-induced thrombosis alone (3). But, Berkels et al. showed that sildenafil significantly prolonged bleeding time in healthy men (18). Based on the results of the first phase of the study, we were expecting to see statistical difference on the femoral vein samples between the control and study groups with regard to luminal thrombus presence and endothelial damage. Thrombus, endothelium damage, and tunica media damage were detected in the control group in the histological evaluation of the femoral vein samples. In contrast, a minimum level of endothelium and tunica media damage was present in the study group, while no thrombus was detected. Sildenafil's effects on platelet aggregation is not yet clearly defined in the literature, but we believe that its ability to augment nitric oxide synthase levels may account for inhibition of thrombus formation by increasing the amount of a strong antiaggregant, nitric oxide (19).

The satellite cells are located under the basal lamina and are in charge of creating new muscle fibers in response to any damage. They proliferate after acute injury and repair the muscular tissue considerably. PCNA is used to indicate the activation of satellite cells. PCNA (+) staining was shown to be higher in the study group in immunohistochemical analysis supporting the histological data indicating recovery after injury. Armstrong et al. assessed the apoptosis by evaluating caspase-3 expression in soleus muscle after ischemia reperfusion in the rat hind leg ischemia model. The apoptotic rate in the sildenafil-treated group was significantly lower than the control group after 6 hours ischemia-24 hours reperfusion cycle. From a different perspective, but parallel to our results, they concluded that sildenafil citrate administration after the onset of ischemic injury reduced the cellular damage (17)

Angiogenesis is a process requiring growth factors such as VEGF and angiopoietin that affect the proliferation and differentiation of endothelial cells (20). VEGF is the main factor that initiates the accumulation and proliferation of endothelial cells; it induces endothelial cell mitosis and promotion of capillary sprouting (2,21). The angiopoietins are responsible for the formation of new blood vessels from proliferating endothelial cells as Ang-1 and Ang-2. They function by binding their physiologic cell surface receptors, Tie-1 and Tie-2. Vidalavur et al. demonstrated that sildenafil strongly induced VEGF, Tie-1, and Tie-2 in human coronary arteriolar endothelial cells in vitro and concluded that it is a very potent pro-angiogenic factor (2). Many other studies state that sildenafil citrate significantly induces VEGF and Ang-1 in ischemic myocardium tissue. The neoangiogenetic and angioprotective effects of Ang-1 and VEGF on cardiac tissues are also emphasized (19,22). In a study on Ang-1's effect on neurovascular regeneration after stroke, it is stated that Ang-1 represses perivascular inflammation and decreases ischemia-reperfusion damage by protecting the stability of vascular endothelium and preventing the disruption of permeability (25). In the present study, it was investigated whether sildenafil citrate might induce Ang-1 and VEGF levels in peripheral endothelium, which is similar to myocardial and neural tissues. In the Vidalavur et al. study, sildenafil mediated the tube formation of endothelial cells in low doses, but in higher doses endothelial cells showed more ring-like structures, indicating that sildenafil triggered Ang-1 expression (2).

In our study, through immunohistochemical evaluation Ang-1 protein staining of the study group was found to be significant when compared to the control group. The femoral vein was stained moderately, at the same level, for VEGF immunohistochemically in both groups. But Ang-1 staining was statistically different in the study group than in the control group.. VEGF is known to be up-regulated by tissue hypoxia and it is significantly elevated in ischemic muscles after arterial occlusion. We were unable to show a difference in VEGF levels between ischemic and sildenafil-treated ischemic in femoral vein samples; muscle sample evaluation might deliver different VEGF levels.

Catalase activity is used as a marker of enzymatic defense against reactive oxygen species. Catalase is frequently used by cells to rapidly catalyze the decomposition of harmful hydrogen peroxide into less-reactive gaseous oxygen and water molecules. After ischemia reperfusion injury, the catalase levels are expected to be decreased (24). In the present study, biochemically high level of catalase in the sildenafil-treated ischemic hind leg group demonstrates that sildenafil citrate may have an antioxidant effect. On the other hand, an interesting finding revealed by Urao et al. suggested that endogenous endothelial cell-derived H2O2 plays a critical role in reparative neovascularization in response to ischemia by upregulating adhesion molecules and activating eNOS in endothelial cells and that high levels of catalase are shown to be antiangiogenic by degrading H2O2 (25). Although it is known that an excess amount of H2O2 in pathological conditions has a negative impact on endothelial function, neovascularization and tissue repair, Yun et al. have shown that optimal levels of H2O2 are required for signaling and for normal biological function (26).

In addition, Urao et al. found that VEGF level is markedly reduced in the ischemic tissue in catalase transgenic mice (25). The overexpression of catalase resulted in disorganized microvasculature formation and caused a substantial decrease in the number of microvessels. They explained that endothelial H2O2 can regulate endothelial functions independent of VEGF. It is clear that sildenafil treatment did not affect VEGF levels. Either the increased levels of catalase caused by sildenafil suppress VEGF or another mechanism is responsible for static VEGF levels despite an increase in Ang-1.

In conclusion, our study demonstrated that sildenafil citrate has significantly increased the survival of the replant in the ischemic rat hind leg replantation model. The mechanism of increased hind leg survival by sildenafil may mainly rely on its vasodilatory effect provided by smooth muscle relaxation or partly on the protective effect against ischemic reperfusion injury and antioxidant activity. The present study was unable to show any antithrombotic activity of sildenafil. Further investigation of this important topic with a larger number of subjects is necessary because the c-GMP-NO pathway is a critical intracellular inhibitory messenger that interferes with platelet activation signaling.

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Competing interests

The authors declare that they have no competing interests.

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Is there any somatosensory amplification in patients with irritable bowel syndrome?

İrritabl barsak sendromlu hastalarda Somatik abartılı algılama var mı?

Ibs and somatosensory amplification

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Öz

Amaç: Uzunca bir süre bir çeşit somatizasyon bozukluğu olduğu düşünülen irritabl barsak sendromu (IBS), günümüzde işlevsel gastrointestinal hastalıklar içinde yer alan bir hastalıktır. İrritable barsak sendromunun altında yatan etiyolojik düzenek tam anlaşılmamasına rağmen beyin-barsak ekseninin bir bozukluğu olduğu düşünülmektedir. Bu çalışmada amaç psikiyatri polikliniğine konsültasyon ile çeşitli polikliniklerden gelen hastalarda ve bir grup IBS hastasında depresyon, anksiyete ve bedensel duyumlarını abartılı algılama belirtilerini değerlendirmek ve karşılaştırmaktır. Gereç ve Yöntem: Çalışmaya psikiyatri polikliniğine gastroenteroloji konsültasyonu ile gelen IBS'li 158 hasta, diğer polikliniklerden (Noroloji, genel cerrahi ve acil) konsültasyonla gelen 79 hasta ve kontrol grubu olarak 55 sağlıklı gönüllü olmak üzere toplam 292 kişi katılmıştır. Bedensel duyumları abartılı algılamayı ölçmek için Bedensel Duyumları Abartma Ölçeği (BDAÖ) kullanılmıştır. Ayrıca anksiyete ve depresyon belirtilerini incelemek için Hastane Anksiyete ve Depresyon ölçeği (HAD) hasta grubuna verilmiştir. Bulgular: IBS grubunda BDAÖ ölçümleri, diğer polikliniklerden gelen hastalar ve kontrol grubu ile One-way ANOVA testi ile karşılaştırıldığında fark istatistiksel olarak anlamlı yüksek bulunmuştur. IBS hastaları ile diğer polikliniklerden gelen hastaların HAD-A ve HAD-D alt ölçek verileri arasında istatistiksel olarak anlamlı fark bulunmamıştır ($p>0.05$). Tartışma: Psikiyatri kliniğine konsultasyonla gelen hastalarda beden duyumlarını abartılı algılama eğilimi olduğu gösterilmiştir. Özellikle IBS hastaları gibi konsültasyon gruplarında beden duyumlarını daha fazla abartılı algılama saptanmıştır.

Anahtar Kelimeler

İrritabl Barsak Sendromu; Beden Duyumlarını Abartma; Depresyon; Anksiyete

Abstract

Aim: Irritable bowel syndrome, once thought to be a type of somatization, is now regarded as a disorder taking its place among functional gastrointestinal diseases. Even though the etiologic mechanism underlying irritable bowel syndrome is not precisely understood, it is thought to be a disorder of the brain-bowel axis. The aim of this study is to compare and evaluate the depression, anxiety symptoms, and the amplification of physical symptoms in a group of Irritable Bowel Syndrome patients and patients referred from other clinics who consulted to the Department of Psychiatry. Material and Method: The study group consists of 292 cases in total: 158 patients with Irritable Bowel Syndrome (IBS) and referred to the department of psychiatry, 79 patients coming from Other Clinics (Neurology, General Surgery, and Emergency) for Consultation (OCC), and a control group of 55 healthy volunteers. The Somatosensory Amplification Scale (SSAS) was used to measure the exaggerated physical perception of somatosenses. For establishing the symptoms of anxiety and depression, the Hospital Anxiety and Depression Scale (HAD) was applied only to the patient groups. Results: When compared to the OCC patient group and the control group, the SSAS scores of the IBS patient group were found to be statistically higher and significant by one-way ANOVA test ($F:43.141$, $p=0.000$). The difference of HAD-A and HAD-D subscale results between the IBS and OCC groups was not found to be statistically significant ($p>0.05$). Discussion: It was shown that the patients referred to the department of psychiatry for consultation would probably have exaggerated perception of somatosenses; in particular, some consultation groups such as those with IBS perceived more amplification of somatosenses.

Keywords

Irritable Bowel Syndrome; Somatosensory Amplification; Depression; Anxiety

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Introduction

Somatization is identified as a physical response, and correspondingly a behavior searching for medical aid under psychosocial stress. The idea of somatosensory amplification has been suggested as a central predisposing factor to explain somatization. Accordingly, somatic individuals tend to perceive normal physical sensation intensely, detrimentally, and irritatingly [1]. Excessive perception of physical sensation is a way of perceiving normal or light physical indications as a catastrophe. Barsky et al. [2, 3] suggested somatosensory amplification hypothesis to explain this situation. In a general population, while the ratio of no organic pathology detection in outpatients visiting the internal medicine department with physical complaints was 2.6%, this ratio rose to 22% [4, 5] in primary health care studies. It is known that these patients generally have been sent to the department of psychiatry for consultation [5]. It is known that there is a close relationship between the existence of chronic pain and somatization findings [6,7]. There are psychodynamic interpretations to explain the etiology of psychosomatic diseases that remain valid today. Firstly the body communicates with the environment. Body language is the first means of communication that evolved from ontogenetic development, much earlier than verbal narrative. When there is a problem that the person cannot cope with in the cognitive field, he returns to the path known from the ontogenetic development process [8]. Another psychodynamic theory is that there is a correlation between increased bodily symptoms and high neuroticism personality traits (dependency, low self-esteem, diffidence, introversion, vulnerability, etc.). It is known that these people focus more on physical senses. People with high levels of neuroticism may have difficulty coping with life events. This can create a feeling of weakness. Bodily symptoms may be an expression of desperation [9].

In published studies, somatization findings have been determined in 12% of chronic pain patients and in 17% of patients having Irritable Bowel Syndrome (IBS) [7,10,11]. In a survey carried out with undergraduate students, a positive relationship between the existence of chronic pain and illness and somatization findings has been found [12].

IBS is a functional bowel disease, not attributable to an organic etiology, appearing in periods when emotional tension is high, especially with accompanying stomachache and changes in defecation habits such as diarrhea and constipation. The prevalence of the disorder among adults is between 3-22%, and it is known to be seen at least twice as much in women [7].

In DSM classification, as well as in DSM-V, the disorders accompanied by pain and other somatic complaints have been associated with somatoform disorders. Somatic symptomatic disorders are mentioned in the DSM-V, such as fibromyalgia syndrome, chronic fatigue syndrome, and IBS. These are the illness groups that are admitted to other internal clinics, and are frequently seen and difficult to treat. In all these illnesses, pain, exhaustion, fatigue, intestine problems, distress, and concentration difficulty are the common findings. There is a tendency to collect these illnesses under the title of Functional Somatic Syndrome (FSS) and this has been emphasized in prominent journals [13, 14, 15]. In the studies carried out, it is thought that patients with FSS have shown similarities in behavior, cognitive, and emotional patterns. In one study, it was pointed out that the patients in this group had somatosensory amplification composed of similarities in cognitive, emotional findings, and personal characteristics [16].

The aim of this study was to compare and evaluate the depression, anxiety symptoms, and the amplification of physical symptoms in a group of IBS patients and patients referred from other clinics who were consulted to the Department of Psychiatry. Also, the groups were compared to the healthy control group with regard to the somatosensorial amplification data.

Material and Method

The study group consists of 292 cases in total: 158 patients with Irritable Bowel Syndrome (IBS) who were consulted to the department of psychiatry, 79 patients coming from Other Clinics (Neurology, General Surgery, and Emergency) for Consultation (OCC), and a control group of 55 healthy volunteers. The most common complaints of the IBS group were abdominal pain, abdominal discomfort, and disruption in the habit of defecation. The definition of IBS has been determined by two gastroenterologists according to the Roman III definition system. The OCC patient group, 51 from neurology, 16 from the department of chest diseases, and others from the emergency room, was consulted to the department of psychiatry. The patients referred to the study were determined to have (a) nonspecific symptoms of shortness of breath, cough, feeling of globus hystericus for the department of chest diseases and (b) syncope of a non-convulsive nature, headache, and neck and muscle pain for the emergency room group. Because no findings were found suggesting the organicity of symptoms in the examinations and tests of the patients, a psychiatric consultation was requested. The study is a cross-sectional study designed for collecting qualitative and quantitative data. Information about the study was given to the all patients and control group participants and their written consents were obtained. The study was carried out in the Departments of Psychiatry at Adana Numune Training and Research Hospital and Kozan State Hospital. The Socio-demographic Data Form and Somatosensory Amplification Scale (SSAS) were applied to the patient and the control groups. A diagnostic interview was applied to all participants in the patient groups by a psychiatrist. Additionally, the Hospital Anxiety and Depression Scale was administered only to the patient groups.

Instruments

Socio-demographic Data Form: This form assesses age, sex, marital status, educational status, occupation, socio-economic level, medical and psychiatric illnesses, alcohol and drug addiction, and regular medicine use.

SSAS: The Somatosensory Amplification Scale evaluates sensitivity to mild bodily sensations that are unpleasant and disturbing but are non-pathological. This self-evaluating scale developed by Barsky et al. consists of 10 items that are estimated on a five-point scale ranging from 1 ('not at all') to 5 ('extremely') [3]. The statements describe physical discomforts that do not indicate a disease. Somatosensory amplification is a useful construct in assessing perceptual styles of patients with psychosomatic illness. By summing up the scores, a total amplification score is obtained. The validity and reliability study of the

Turkish version was conducted by Güleç et al. [17].

Hospital Anxiety and Depression Scale (HADS): HADS is not used for diagnosing the patients with physical illness and those who apply to the primary health care services, but it is used for identifying the anxiety and the depression levels in a short span of time and for determining the risk group. Of the 14 questions, odd numbers measure anxiety and even numbers measure depression. Answers are graded between 0-3, quadruplet Likert-type responses. The lowest possible grade for either subscale is 0 and the highest grade is 21. The cutoff score in the Turkish HAD form for the anxiety subscale (HAD-A) was determined to be 10, and the cutoff score for the depression subscale (HAD-D) was determined to be 7. The scale was developed by Zigmond and Snaith in 1983 [18], and its reliability and validity study was carried out by Aydemir et al. [19].

Statistical Analysis

The compatibility of the data obtained from the study to the normal distribution was analyzed by Smirnov/Shapiro-Wilk tests. The identificatory statistics were summarized in terms of mean +/- standard or percentage depending on the distribution formation of the numeric data. On the other hand, categorical data was summarized in terms of number and percentage. Pearson chi-square statistics, one of the cross table statistics, was used for the relation between categorical variabilities. In comparing the two groups in terms of numerical variabilities depending upon the distribution formation of the data, and in comparing the mean of the parametrical independent two groups, Independent sample t-test was used. One-way ANOVA and Scheffe post hoc tests were used in the analysis of the comparison of the IBS patient group, OCC patient group, and control group. The conditions in which P value was <0.05 were accepted as statistically significant. In the analysis of data, SPSS 17.0 statistical packaged software was used.

Results

The age range of the IBS patients participating in the study was 18-64, and the mean± standard deviation (mean±SD) was 34.60±8.13; the age range of the OCC group was 18-52, and mean±SD was 32.13±8.43; and the age range of the healthy control group was 19-63, and mean±SD was 32.98±10.00. The difference by one-way ANOVA was not statistically significant [F:2.415, p=0.091]. As the other socio-demographic data were categorical data, statistical analysis was done with the chi-square (x2) test. The difference among the groups participating in the study in terms of gender, education, socio-economic level, marital status, and occupational status was not statistically significant: (x2=3.606, p=0.536; x2=13.498, p=0.096; x2=1.513, p=0.822; x2=8.351, p=0.213, x2= 6.711, p=0.392). No alcohol and drug addiction were found in any participants of the patient and control groups. Also, no participant had regular medicine intake in the patient groups. All the socio-demographic data and statistical analysis are given in Table 1.

According to the SSAS data of the IBS patient group, the OCC patient group, and the control group, the difference was found statistically significant by the one-way ANOVA test (F: 43.141, p=0.000). The difference between the groups was determined by applying the Scheffe post hoc test (IBS patient group vs. OCC patient group, IBS patient group vs. control group). The SSAS mean score of the IBS patient group was higher compared to the SSAS mean score of the OCC patient group. The difference was statistically significant between these two groups, determined by applying the Scheffe post hoc test.

The results of the HAD-A scale and HAD-D scale of the IBS patient and OCC groups were analyzed with the student t-test and the difference was not statistically significant (Table 2).

At the end of the psychiatric interviews, while no psychiatric diagnosis was made in 73 participants in the IBS patient group, minor depression in 39 participants, anxiety disorder in 27 participants, and somatoform disorder in 19 participants were diagnosed. While no psychiatric diagnosis was made in 34 participants in the OCC patient group, minor depression in 21 participants, anxiety disorder in 21 participants, and somatoform disorder in 8 participants were diagnosed. No intergroup difference was statistically significant regarding sickness diagnosis (x2= 0.213, p=0.679).

Discussion

It is known that patients with medical conditions who are consulted to the departments of psychiatry might have somatosensory amplification [2, 3, 4]. In comparison to the healthy group, somatosensory amplification was found high in both patient groups coming to our polyclinic and undergoing psy-

Table 1. Demographic characteristics of three groups.

	IBS Group		OCC Group		Healthy control		Statistical Test	
	n:158		n:79		n:55			
	n	%	n	%	n	%	x^2	p
Age (Years) (mean±SD)	34.60±7.92		32.13±8.43		32.98±10.00		F=2.415	0.091
Gender								
Men	40	25.3	19	24.0	10	18,2	x^2= 3.606	0.536
Women	118	74.7	60	76.0	45	81.8		
Education								
Elementary	26	16.6	5	6.3	6	10.9		
Middle	92	58.2	40	50.6	28	50.9	x^2=13.498	0.096
High	20	12.6	21	26.6	9	16.4		
Graduate	20	12.6	13	16.5	12	21.8		
Income								
Low-middle	128	81.0	64	81.0	48	87.2	x^2=1.513	0.822
High	30	19.0	15	19.0	7	12.8		
Marital Status								
Single	23	14.6	21	26.6	15	27.2		
Married	121	76.6	54	68.4	37	67.3	x^2=8.351	0.213
Divorse-other	14	8.9	4	5.1	3	5.5		
Occupational Status								
Non-working, Housewife	118	74.7	64	81.0	45	81.8	X^2=6.711	0.392
Working	40	25.3	15	19.0	10	18.2		

IBS: Irritable bowel syndrome

OCC: Patients coming from other polyclinics with consultation

Table 2. Psychological characteristics of three groups

	IBS Group		OCC Group		Healthy control	Statistical Test	
	n:158		n:79		n:55	F	p
SSAS	36.15±8.13*α		29.77±7.37*		25.52±7.87α	43.141	0.000
HAD-A	11.48±4.29		11.56±4.41				0.882
HAD-D	9.41±4.12		9.87±4.55				0.455
	n	%	n	%			
Disorder							
+	85	53.8	45	57.0		x^2= 0.213	0.644
--	73	46.2	34	43.0			

IBS: Irritable bowel syndrome
OCC: Patients coming from other polyclinics with consultation
One-Way Anova
Post Hoc Scheffe test: *IBS patient group vs OCC patient group, αIBS patient group vs Control group).

chiatric consultation. Another important point of this study is that IBS patients were found to have statistically significant higher somatosensory amplification than the OCC patients. In patients having functional gastrointestinal complaints, it is not adequately understood how motility response differs from healthy individuals, and whether this situation stems from an inadequacy in the autonomic nervous system or somatosensory amplification. On the other hand, it is suggested that both central and peripheric mechanisms take part in the etiopathogenesis. Current hypotheses include motility variations, visceral hypersensitivity, inflammation/infection, changes in the brain and intestine systems, and genetic and psychosocial factors [20, 21, 22]. Limbic and prelimbic zones are referred to as emotional zones. The emotional variations originated in these zones reach the intestines by means of the autonomic nervous system [23]. In addition, gastrointestinal motility variation occurs due to psychological stress, having characteristics of emphasizing the psychopathological importance of the variations in the brain and the intestine axis modulation [24, 25]. It is thought that the intensive somatosensory amplification that takes place in IBS patients is a result of the cognitive and emotional factors in which the limbic system takes part.

Another finding of our study is that the depression and anxiety results of IBS patients and OCC patients were found to be alike. However, in both patient groups results were determined to be higher than the average anxiety breakpoint of 10/11. Similar results for depression were obtained. The population of the patients sent to the department of psychiatry by other polyclinics showed the characteristics of the existence of a psychiatric illness (anxiety disorders and depression) anticipated by a clinician. However, in some studies, despite the high anxiety and depression scores in IBS patients, when these patients were given a diary to take notes, much lower anxiety and depression scores were seen in their diaries [26, 27]. These researchers commented that it is not sufficient to limit the IBS patients only to psychosomatic explanations.

The important result of this study is that IBS patients have higher somatosensory amplification results than the OCC patients coming from other polyclinics for consultation and that there is also a difference between these two groups in terms of other psychiatric symptomatology, which make us think that this finding is compatible with the literature mentioned above. Duruk et al. observed in their study that the patients having fibromyalgia were different in means of somatosensory amplification when compared to the healthy controls and to the patients having chronic medical disorders referred to the psychiatry policlinic for consultation. These researchers stated that this result might indicate that Fibromyalgia Syndrome be evaluated under the Functional Somatic Syndrome (FSS) classification. They emphasized the necessity of different implementations in the modalities for patients in this classification (Irritable Bowel Syndrome, Fibromyalgia Syndrome, and Chronic Fatigue Syndrome) [28]. Our study verifies the necessity of evaluating IBS under the FSS title.

One of the advantages of our study is that the IBS group was selected with regard to age, gender, education, and socio-economic level, with similar characteristics to the OCC and control groups. Furthermore, in addition to making an assessment and applying scales in the study, having a psychiatric interview was another advantage. However, a disadvantage was that our findings were not supported by neurocognitive tests, neuroimaging, or biological markers.

In summary, somatosensory amplification has been found high in the patients consulted to the department of psychiatry when compared with healthy controls. High somatosensory amplification findings were determined in IBS patients. It was revealed that psychiatric symptomatology in IBS patients is not only restricted to anxiety and depression. When all these findings are evaluated under the title of the Functional Somatic Syndrome for IBS patients, it is clear that a multi-disciplinary approach that includes a psychiatric treatment is needed.

Competing interests

The authors declare that they have no competing interests.

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Evaluation of hemostasis with thromboelastometry during the diagnosis and at 24th hours in sepsis

Sepsis tanılı hastaların yatış ve 24. saatte tromboelastometri ile hemostazının değerlendirilmesi

Using rotem in the sepsis's first hours and 24th hours

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*Bu makale 17. Ulusal Yoğun Bakım Kongresi'nde Poster Sunumu Olarak Kabul Edilmiştir.

Öz

Amaç: Tromboelastometri yöntemi konvansiyonel tekniklerin yerine, hemostaz aksını tek başına gösterebilen bir tekniktir. Gereç ve Yöntem: Çalışma için yoğun bakım ünitesinde sepsis tanısı almış 50 hasta ve yerel popülasyon içerisinde yaşayan sağlıklı 50 gönüllü çalışmaya dahil edildi. Çalışma grubu Grup S ve Grup C olarak 2 gruba ayrıldı. Yoğun bakım ünitesinde sepsis tanısı almış hastalar Grup S, yerel popülasyonda yaşayıp koagülasyon profilini değiştirebileceği bilinen bir hastalığı olmayan gönüllüler Grup C olarak adlandırıldı. Tüm gruplara tromboelastmetri yöntemi uygulandı. Bulgular: Grup S de Grup C'ye kıyasla PT ve PTT değerlerinde anlamlı bir yükselme görülürken, platelet düzeylerinde anlamlı bir azalma görülmüştür. Tromboelastometri parametreleri değerlendirildiğinde INTEM testinin tüm parametrelerinde, EXTEM testinin ise CT parametresi hariç tüm parametrelerinde gruplar arasında anlamlı bir farklılık görülmüştür. EXTEM testinin CT parametresinde ise gruplar arasında herhangi bir farklılık görülmemiştir. Grup S'de tanı sırasında ve 24. saatte bakılan konvansiyonel testler ve tromboelastometri testleri arasında herhangi bir farklılık görülmemiştir. Tartışma: Sonuçlarımız göstermiştir ki sepsis intrensek yolak üzerinde daha çok etkindir. Tromboelastometri yöntemi sepsis tanısında kullanım için uygun bir teknik iken sepsis takibinde anlamlı bir sonuç göstermemiştir. Sepsis tanısı için tromboelastometri kullanılmasını önermekteyiz.

Anahtar Kelimeler

Tromboelastometri; Koagülasyon; Kan Koagülasyon Testleri; Sepsis; Yoğun Bakım Ünitesi

Abstract

Aim: Thromboelastometry shows the monitorization of the hemostasis axis with the use of a single method instead of conventional techniques. Material and Method: This study was conducted on 50 patients who were admitted to the intensive care unit and diagnosed with sepsis together with 50 healthy volunteers from the local population. The patients were divided into two groups. Group S consisted of patients who were diagnosed with sepsis in the intensive care unit. Group C consisted of healthy volunteers who were selected from the local population and had no impairments of their coagulation profile. Thromboelastometry measurements were performed for both groups. Results: While elongation was observed in PT and aPTT between Group C and Group S, a decrease was observed in platelet counts ($p<0.05$). When analyzing thromboelastometry parameters, significant differences were seen between groups ($p<0.05$) in all parameters in INTEM and all parameters except CT in EXTEM. There was no significant differences in the CT parameter of the EXTEM measurement between groups ($p>0.05$). Within Group S, when the results from the time of diagnosis and the 24th hour were compared, no significant difference was observed in PT, aPTT, platelet count, or in all INTEM and EXTEM parameters examined. Discussion: Our results revealed that sepsis was clinically more disruptive of the intrinsic pathway. Thromboelastometry was a suitable technique for use in the diagnosis of sepsis, but did not show a significant effect in the follow-up of sepsis. We recommend using thromboelastometry for the diagnosis of sepsis.

Keywords

Thromboelastometry; Coagulation; Blood Coagulation Tests; Sepsis; Intensive Care Unit

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Introduction

Sepsis, defined as the systemic inflammatory response to infection, is created by a hereditary response of the individual against infection. [1-3]. An extremely severe response of the host against infection leads to sepsis. This may be followed by severe clinical sepsis, which is accompanied by hypotension that is unresponsive to fluid resuscitation [4]. In sepsis, the coagulation system is exposed to injury by systemic activation of multiple intermediate pathways involving a complement system and cytokine network, resulting in a complex relationship between the host and infectious agent [5]. An irregular hemostasis axis is formed in sepsis by the simultaneous activation of the anticoagulant and fibrinolytic systems. While progressive coagulopathy, disseminated intravascular coagulation, multiple organ failure, and death may occur, extensive bleeding diathesis as a result of hypocoagulation may also be seen in clinical sepsis [6].

Rotational thromboelastometry is an evaluation method of the coagulation process that shows all of the steps from the beginning of hemostasis to the fibrin degradation process with whole blood. It displays the dynamic interactions among platelets, coagulation and fibrinolytic factors, activators, and inhibitors within the coagulation process [7]. In terms of coagulation parameters, more significant determinations can be made for rapid results and the selection of the proper blood components to replace by using the thromboelastometry method instead of conventional laboratory data to determine factors such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and platelet (Plt) counts [8].

The rotational thromboelastometry method, which assesses the coagulation profile and monitors hemostasis as a whole, may show the monitorization of the hemostasis mechanism by a single method instead of conventional techniques that investigate the coagulation process part by part. We aimed to evaluate the coagulation profiles of patients with sepsis and compare them with healthy individuals, using the rotational thromboelastometry method.

Material and Method

Study Design and Population Group

Following approval of the Atatürk University Clinical Research Center Ethics Committee, this study was conducted on 50 patients who were diagnosed with sepsis and admitted to the Atatürk University Medical Faculty Hospital, Intensive Care Unit between December 2012 and December 2013. Another group of 50 healthy volunteers, workers at the hospital, who were without any impairments of their coagulation profile, also signed informed consent forms. The total study population of 100 was divided into two groups. Group S (n = 50; Sepsis) consisted of patients in intensive care units who were diagnosed with sepsis. Group C (n = 50; Control) was comprised of individuals chosen from healthy volunteers who were from the general population and had no impairments of their coagulation profile. The diagnosis of sepsis was based on the consensus criteria of the International Working Party Consensus Definitions for Sepsis and Septic Shock [3].

Exclusion Criteria

Patients excluded from this study were those with a medical history of bleeding diathesis, or current usage of a drug or food that can impair the coagulation cascade, and individuals under 18 years or over 65 years of age.

Demographic datas, such as age and gender, of patients with sepsis and the healthy volunteers were obtained and recorded. After patients had given their written informed consent, blood was obtained in 10 cc volumes in both groups to study all parameters in each sample. In Group S, blood samples were obtained through the arterial system on the day sepsis was diagnosed and on the following day, at hour 24, with the first option being the radial artery. In Group C, samples were obtained through the venous system only on day one, with the first option being the antecubital system [9]. Blood samples were placed into test tubes for analysis of platelet count, PT, aPTT, and for study in the rotational thromboelastometry device (ROTEM® delta, Tem International GmbH, Munich, Germany). The tubes were gently turned upside down four to five times to prevent clotting. These blood samples were sent to the related laboratory unit within 30 minutes. The blood samples were placed into citrated blood test tubes (BD Vacutainer, UK, REF 363048). Following the notification that ROTEM measurements could be launched, equipment referred to as "cup" and "pin pro" were placed as described by the manufacturer, the device was brought to the "completely ready to run" position, and the thromboelastometry device was started. In our study, we performed measurements of intrinsic activation of thromboelastometry (INTEM) and extrinsic activation of thromboelastometry (EXTEM), which are the two basic measurements used in thromboelastometry analyses [10]. In circumstances in which heparin was used, heparinase was added to the INTEM reagent to prevent any probable differences in the results [11]. We also used heparinase in our INTEM measurements for patients in our intensive care unit in order to prevent the likely effects of low molecular weight heparin (LMWH). Test samples were prepared in 20 seconds and measurements were initiated.

Rotational Thromboelastometry

With regard to rotational thromboelastometry measurements, there are some parameters specific to the measurements. One of these parameters is the clotting time (CT, s), which continues until the occurrence of thrombin formation, platelet aggregation, and the initiation of polymerization. Another parameter is the clot formation time (CFT, s) in which the initiation of platelet aggregation is observed in a gross view, fibrin polymerization and platelet aggregation are accelerated, stabilization is enhanced by factor XIII, and this parameter continues until platelet aggregation occurs to a size of 20 mm in diameter. The angle created by the curve of the line, drawn from the starting point of the CFT parameter and tangential to the ascending slope of the curve, is called α (°). If the platelet functions are powerful, the degree of the angle increases; alternatively, if the functions are weak, it is reduced. The value of the clot width at the end of the first 10 minutes of the platelet plug formation process was named A10 (mm x 100), and the value of the clot width at the end of the first 20 minutes was named A20 (mm x 100). The maximum value of the clot width was named maximum clot formation, (MCF, mm x 100) [12].

Statistical Analysis

In the power analysis for this study, which was performed to determine the sampling adequacy, the power of the study was 0.99 and the effect size was 1.75 for the Mann-Whitney U test with 50 people in both groups at the 0.05 significance level and 95% confidence interval. This figure showed that sampling of the study was sufficient [13, 14]. All statistical calculations were performed by SPSS 17.0 (Statistical Program for the Social Science) statistical software. The Shapiro-Wilk test was used to determine the distribution of data, and to compare data the Wilcoxon sign-rank test and the Mann-Whitney U test were used. In all statistical analyses, results were considered significant when P values were < 0.05 and highly significant when < 0.001.

Results

There were no significant differences (P > 0.05) in the demographic data for gender and age between the two groups in our study. The patients' demographic data are shown in Table 1.

The conventional coagulation tests, such as platelet count, PT, and aPTT values for both groups, showed highly significant differences between Groups C and S (P < 0.001) (Table 2).

By using thromboplastin-phospholipid in the INTEM measurement, the intrinsic pathway was initiated with the aim of controlling the process through the intrinsic pathway. When analyzing the INTEM parameters, highly significant differences were seen between groups in the CT, CFT, and MCF parameters. In addition, significant differences were seen in the α, A10, and A20 parameters of the INTEM measurement between groups. By using the tissue factor in the EXTEM measurement, the extrinsic pathway was initiated with the aim of controlling the process through the extrinsic pathway. When analyzed, the EXTEM parameters showed highly significant differences between groups in the CFT, α, A20, and MCF parameters. In addition, significant differences were seen in the A10 parameters of EXTEM measurement between groups. There were no significant differences in the CT parameter of the EXTEM measurement between groups. Laboratory data of the groups are shown in Table 3.

Table 1. Demographics Data of Patients

Characteristics of 50 Patients with Sepsis and 50 Healty Volunteers		
Variables	Group S	Group C
Age*	50.61 ± 5.54	50.94 ± 6.03
Gender *(Male/Female)	20 / 30	22 / 28
Procalcitonin	16.06±27.78	-
C-reactive Protein	121.60±67.21	-
Day of Diagnosed Sepsis	3.14±3.76	-
Apache II Score	22.66±6.70	-
Pulmonary disease	15 (%30)	-
Postoperative patient	12 (%24)	-
Neurologic disease	10 (%20)	-
Trauma (Without operation)	6 (%12)	-
Post-CPR patient	7 (%14)	-

* P > 0.05

Table2. The comparison of Laboratory Data for the 1st Days Between Group S and Group C*

	Plt(x10^9)	PT	aPTT
Group S	207.0(111.0)**	16.6(6.8)**	37.7(16.0)**
Group C	327.3(33.6)	12.7(0.65)	29.4(0.98)

(Plt : platelet; PT : Prothrombin time ; aPTT : activated partial thromboplastin time ; * denote data presented as mean (SD), ** denotes p<0.001.

The comparisons of the first and second day Plt, PT, and aPTT values for Group S are shown in Table 4. According to these figures, in conventional coagulation measurements in the patients with sepsis, there were no significant differences between the INTEM and EXTEM parameters (Table 4).

The comparison of the first and second day (hour 24) INTEM and EXTEM parameters of Group S are shown in Table 3. According to these findings, in the INTEM and EXTEM measurements of Group S by the thromboelastometry method, there were no significant differences between any of the INTEM and EXTEM parameters (Table 5).

Discussion

Excessive activation of coagulation in sepsis results with increased coagulation system consumption. As a consequence of this consumption, during the acute period augmentation of coagulation and during the following hours, deficiency in coagulation is seen. Consumption of the coagulation system is increased following severe activation of coagulation in sepsis. At the end of the consumption, while there is an increase in the acute period of coagulation, when the coagulation system is evaluated by thromboelastometry in sepsis, the exaggerated increase of the ML parameter shows that hyperfibrinolysis and hypocoagulation can occur with an increase of CT, CFT, α, A10, A20, and MCF parameters.

The early detection of disorders in the coagulation profile, which is developed through the mediators of the coagulation system not only alerts physicians to the need for a resuscitation procedure for the coagulation system, but also an important step in the treatment of sepsis. In our study, by using thromboelastometry with control and sepsis groups, and by evaluating CT, CFT, α, A10, A20, and MCF parameters of INTEM and EXTEM measurements, highly significant differences were determined between the sepsis and healthy control groups. These differences suggest that, by using thromboelastometry, significant improvements can be made in the diagnosis.

Durilla et al. showed that measurements performed by a thromboelastography (TEG) device were faster and more effective in planning treatments directed at the cause of the basic problem when compared to using laboratory test results, such as PT, aPTT, INR, etc. [15]. In our study, we also determined that a more rapid evaluation of the coagulation profile on the first and second days could be made by thromboelastometry in the sepsis group. We obtained the results for the CT, CFT, and α parameters with the thromboelastometry device in short periods of 10 minutes, unlike the longer durations required to determine PT, aPTT, and INR using conventional techniques.

In the study by Nates et al., endotoxemic sepsis was created in pigs by lipopolysaccharide induction [16]. In their TEG test, they determined an increase in the k parameter, which corresponds to the CT parameter in thromboelastometry. They also determined reductions in the α and MA parameters in the TEG test, which are the same parameters determined in thromboelastometry. Sucker et al. evaluated the thromboelastometry results

Table 3. The comparison of 1st day ROTEM parameters between Group S and Group C*

	Groups	CT(secs)	CFT(secs)	MCF(mm)	α (°)	A10(secs)	A20(secs)
INTEM	Group S	170.3(53.6)***	107.4(57.8) ***	63.1(15.4) ***	70.3(14.7)**	54.6(16.8)**	60.6(16.0)**
	Group C	206.2(12.5)	102.9(33.9)	58.5(3.7)	70.3(5.89)	50.1(5.3)	56.6(4.2)
EXTEM	Group S	123.2(69.9)	142.7(51.2)***	65.1(13.3)***	71.2(14.7)***	56.2(16.3)**	62.6(14.9)***
	Group C	117.3(13.1)	123.6(32.0)	59.1(3.7)	66.0(5.5)	49.5(7.1)	57.2(4.6)

INTEM : intrinsic activation of thromboelastometry ; EXTEM : extrinsic activation of thromboelastometry ; CT : Clotting time; CFT : Clot formation time ; MCF : Maximum clot firmness ; A10 : The value of clot width at the end of the first 10 minutes ; A20: The value of clot width at the end of the first 20 minutes). * denote data presented as mean (SD), ** denotes p<0.05; *** denotes p<0.001.

Table 4. The comparison of Laboratory Data for the 1st and 2nd Days in the Group S*

	Plt(x10^9)	PT	aPTT
1st day	207.0(111.0)	16.6(6.8)	37.7(16.0)
2nd day	192.7(101.3)	17.18(7.16)	38.18(16.55)

(Plt : platelet; PT : Prothrombin time ; aPTT : activated partial thromboplastin time ; * denote data presented as mean (SD)

that they performed in sepsis models created by induction with lipoteichoic acid (LTA) under in vitro conditions. As a result, they concluded that endotoxemia induced by LTA affected CT, but had no effect on other parameters including CFT, MCF, and α as determined by thromboelastometry [17]. Daudel et al. performed thromboelastometry on 30 patients with sepsis who were treated in the intensive care unit and reported the results of the CT, CFT, α, and MCF parameters of the INTEM, EXTEM and the heparinase-modified thromboelastometry (HEPTEM) tests. While no significant changes were found in patients with sepsis, increases in the CT and CFT parameters, together with a reduction in MCF, were determined in EXTEM tests in severe sepsis patients when normal target ranges for each parameter were compared [11]. In the study conducted by Velik et al. on pigs administered an Escherichia coli endotoxin, a reduction in platelet levels after the endotoxin infusion was observed; however, no changes were observed in PT and aPTT values. When the thromboelastometry values were examined, a reduction was observed in the CT value in INTEM analysis, but there was no change in the CT value in EXTEM analysis. Furthermore, an increase in CFT values and decreases in α and MCF values were observed in both INTEM and EXTEM analyses. As a result of this study, it was demonstrated that use of the thromboelastometry method can provide for more positive outcomes in the early period in the evaluation of an early-period coagulation profile compared to conventional methods [18]. Intrinsic pathway activity that could not be specified by conventional techniques in the early period could be determined by thromboelastometry. In the present study, we partially determined the elongation by conventional methods in the intrinsic pathway and observed a decrease in the CT parameter of INTEM analyses [18].

Andersen et al. studied severe sepsis and septic shock patients and found that platelet counts decreased over time and PT values decreased during the early period followed by a later increase. Furthermore, an elongation was observed in aPTT values, and, parallel to the conventional tests, the elongation was observed in the CT parameter in INTEM and EXTEM analyses. When the literature was examined, we observed that, parallel to this study, a rapid activation in the intrinsic pathway during the early periods of sepsis increased in the forthcoming days as shown by the CT parameter in the INTEM analysis, which was parallel with aPTT values. Similarly, the CT reductions were dependent on rapid consumption in the intrinsic pathway during the early period via thromboelastometry. However, since the present study examined the early period, during the diagnosis and at 24th hours, it could not reveal this elongation that would be expected in the forthcoming days; this would transfer the patient to the dissemine intravascular coagulation (DIC) picture and would show a rapid consumption and would cause an increase in the INTEM CT value [19]. When our results were taken into consideration, except for the CT parameter of the EXTEM measurement, all thromboelastometry parameters were significantly affected. This was concluded to be related to a thrombocytopenia reduction in factors of intrinsic pathway levels, which were caused by an uncontrolled consumption occurring in clinical sepsis. Furthermore, when CT parameters in EXTEM and INTEM measurements were considered, significant differences were found in INTEM measurements, which showed the intrinsic pathway, while the EXTEM measurements, showing the extrinsic pathway, did not reveal any significant difference. This result revealed that sepsis was clinically more disruptive of the intrinsic pathway. Although the definitive distinction of the intrinsic and extrinsic pathways of the coagulation system has not been achieved yet, our results suggest that sepsis-induced coagulation disorders do not initiate through the tissue factor-induced pathway. This result was explained by the reduction of a special factor (or factors) of the intrinsic pathway, which was analyzed together with conventional tests. In a study by Yaşar et al., increases in the CT parameter and reductions in the MCF parameter of INTEM and EXTEM tests were detected in patients with Behçet's disease and compared to a control group consisting of healthy volunteers [20]. Although their etiologies are different, Behçet's disease and sepsis cause similar clinical

Table 5. The comparison of 1st and 2nd day ROTEM parameters in the Group S*INTEM : intrinsic activation of thromboelastometry ; EXTEM : extrinsic activation of thromboelastometry ; CT : Clotting time; CFT : Clot formation time ; MCF : Maximum clot firmness ; A10 : The value of clot width at the end of the first 10 minutes ; A20: The value of clot width at the end of the first 20 minutes). * denote data presented as mean (SD)

	Day	Groups	CT(secs)	CFT(secs)	MCF(mm)	α (°)	A10(secs)	A20(secs)
INTEM	1.Day	Group S	170.3(53.6)	107.4(57.8)	63.1(15.4)	70.3(14.7)	54.6(16.8)	60.6(16.0)
	2.Day	Group S	159.4(40.3)	102.2(54.3)	65.0(11.6)	73.1(10.7)	56.7(13.8)	62.7(12.7)
EXTEM	1.Day	Group S	123.2(69.9)	142.7(51.2)	65.1(13.3)	71.2(14.7)	56.2(16.3)	62.6(14.9)
	2.Day	Group S	116.2(54.2)	149.4(52.4)	65.0(12.8)	69.2(16.1)	54.8(16.3)	61.8(14.9)

outcomes since both have clinical courses involving features of vasculitis. In our study, we also obtained similar thromboelastometry results.

In conclusion, the rotational thromboelastometry method, with its rapid diagnosis and point-detection properties, seems to be one step ahead in the identification of impairments developing in the coagulation system when compared to other methods. We suggest that the probability of error might be higher in conventional methods, which evaluate coagulation profiles part by part, compared with thromboelastometric/thromboelastographic methods, which enable in vitro evaluations and evaluate the coagulation profile as a whole. Considering the results of previous studies together with our results, we suggest that the rotational thromboelastometry method is useful in evaluating the coagulation profile and predicting a sepsis prognosis.

Competing interests

The authors declare that they have no competing interests.

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The frequency of depressive mood and associated factors in pregnant women in a semi-urban region

Yarı kentsel bir bölgede gebe kadınlarda depresif duygudurum sıklığı ve ilişkili faktörler

Antepartum depressive mood and associated factors

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Öz

Amaç: Ülkemizin başkentinde yarı-kentsel bir bölgede gebelikte depresif duygu durum sıklığı ve ilgili risk faktörlerinin belirlenmesi. Gereç ve Yöntem: Çalışmaya gebeliğin son trimesterinde olan 600 gebe dahil edildi. Depresyon skorları "Edinburgh Depresyon Skalası" ile belirlendi. 13 ve üzerinde alanlar depresif Kabul edildi. Depresif olan ve olmayan gebeler, sosyo-demografik özellikleri, ailesel ve medical özellikleri açısından karşılaştırıldı. Bulgular: Çalışmaya alınan altıyüz gebeden 153'ü depresif bulundu (25.5%). Düşük/ileri yaş, eşin/gebenin düşük eğitim seviyesi ve/veya işsiz olması, istem dışı yapılan evlilik, eşin akrabaları ile birlikte yaşama, planlanmamış gebelik ve kronik hastalık varlığı depresif duygu durum sıklığını arttıran faktörler olarak bulundu (p<0.001). Tartışma: Gebeliğin son trimesterinde depresif duygu durumun sık görüldüğü göz önünde tutulmalı ve depresyon taraması rutin gebelik takibi programlarının bir parçası haline getirilmelidir. Depresif duygu durum tanısı alan gebeler için de ileri tanı ve tedavi hizmetleri mutlaka sağlanmalıdır.

Anahtar Kelimeler

Gebelik; Depresif Duygu Durum; Risk Faktörleri

Abstract

Aim: To determine the antenatal depressive mood frequency and associated risk factors in a semi-urban region in the capital of our country. Material and Method: Six hundred pregnant women within their third trimester were included. Depression levels were evaluated according to the "Edinburgh Postnatal Depression Scale". Those scoring 13 and over were considered as depressed. Depressed and non-depressed pregnant women were compared according to socio-demographic characteristics, family, and medical features. Results: One hundred and fifty-three patients out of 600 were found to be depressive (25.5%). Low/advanced maternal age, low education level and unemployment of the women/husband, involuntary marriage, living with spouse's relatives, unplanned pregnancy, and existence of a diagnosed chronic disease were found to increase the frequency of depression (p<0.001). Discussion: Because of its high frequency among women in the third trimester, depression screening should be included in prenatal care routine programs and accessible diagnosis and treatment services should be provided for pregnant women diagnosed with depressive mood.

Keywords

Pregnancy; Depressive Mood; Risk Factors

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Introduction

Depression is the most frequently observed psychological disorder during pregnancy and is an important public health issue because it is the most important risk factor for postnatal depression, it may also cause complications and negative fetal results during pregnancy, and its prevalence is even higher than in the postnatal phase [1,2]. Antenatal depression causes a reduction in mother's self-care and therefore may cause insufficient nutrition, alcohol-drug use, insufficient prenatal care, and even suicide attempts. Studies show that mothers experiencing depression during pregnancy have higher premature birth rates and give birth to infants with lower birth weights and lower APGAR scores [3,4]. It is also known that such mothers' children have a higher probability ofdeveloping behavioral and emotional problems/disorders in the future [5].

It has been reported that approximately 50% of women undergoing depression during pregnancy also suffered from postnatal depression [6]. There are many factors contributing to development of antenatal depression such as previously experienced depression attacks, marital problems, lack of spouse and social support, negative life experiences, domestic violence, low socio-economic level, unintended pregnancy, and pregnancy at younger ages; these factors vary among different cultures [7,8]. Research studies conducted regionally in Turkey on smaller populations report antenatal depression frequency between 27.9%-33.0%[9-11]. Despite this high frequency of antenatal depression and the importance of prenatal care in Turkey, psychological support during this stressful period does not have any standard care procedure. In this study, we intend to determine the frequency of depressive mood during pregnancy and the associated risk factors in order to contribute to preventative care that can be implemented in this area.

Material and Method

This descriptive study was conducted from February to July 2012 at the antenatal clinic of a major maternity hospital in Ankara, Turkey, a semi-urban region. Of the five Gynecology and Obstetrics polyclinics existing in the study hospital, one was randomly selected. Pregnant women within their third trimester visiting this outpatient polyclinic were included each day in the study. 600 pregnant women were included in the study within a period of six months. Pregnant women were divided into two groups as depressed or non-depressed according to their EPDS results. The study was approved by the Ethics Committee and all pregnant women were informed about the study and an informed written consent was obtained.

After collecting the socio-demographic characteristics and fertility features of patients by face-to-face interview using a questionnaire, depressive symptoms were determined with the Edinburgh Postnatal Depression Scale, the most widely used screening instrument used for antenatal depression in research. Although developed by Cox et al. for determination of postnatal depression, the scale is often used during pregnancy as well [12,13].The scale contains 10 Likert-type questions in total and provides 4subscale measurements. Total score is from 0-30. For each item, women are asked to select one of four responses that most closely describe how they have felt over the past 7 days.

The scale was adapted to Turkish by Engindeniz et al. in 1996, its validity and reliability was demonstrated by the same team, sensitivity and selectivity was determined as 84.0% and 88.0%, respectively, and the cut-off score was shown to be ≥13 [14]. The EPDS was filled out by each patiental one in a private and quiet room.

According to sampling volume formulas, the minimum required sample size was calculated as 545 subjects for this study, assuming a depression frequency of 15.0%, accepting an error margin of ±0.03 and with a reliability of 95.0%.

Women with depressive symptoms were referred to a psychiatrist for further evaluation and treatment.

Statistical analysis was performed using Statistical Package for Social Sciences version 17 (SPSS Inc. Chicago. IL). Differences between two groups were assessed using Chi-square test, Fisher's Exact test, and Mann–Whitney U-test for categorized variables, Student's t-test for continuous variables, and Multiple Logistic Regression Analysis as multidimensional analysis during the statistical evaluations. $p<0.05$ was considered as significant.

Results

Average pregnancy week of the subjects was 31.81±2.16 (range,26-36 weeks). One hundred and fifty-three patients out of 600 were found to be depressive (25.5%) in our study group. Socio-demographic findings related to depressive moodare given in Table 1. Lower and advanced age, low educational level

Table 1. Distribution of socio-demographic characteristics of individuals

Features	Depressed n (%)	Normal n (%)	Total n (%)	p
Age				p=0.009
≤19	25 (34.2)	47 (65.3)	72 (12.0)	
20-24	41 (21.5)	150 (78.5)	191 (31.8)	
25-29	48 (26.8)	131 (73.2)	179 (29.8)	
30-34	17 (17.0)	83 (83.0)	100 (16.7)	
≥35	22 (37.9)	36 (62.1)	58 (9.7)	
Education Level				p=0.002
Elementary school or lower High school	106 (30.3) 41 (21.4)	244 (69.7) 151 (78.6)	350 (58.3) 192 (32.0)	
University	6 (10.3)	52 (89.7)	58 (9.7)	
Employment Status				p=0.000
Employed	140 (29.3)	337 (70.7)	477 (79.5)	
Unemployed	13 (10.6)	110 (89.4)	123 (20.5)	
Health Insurance				p=0.000
Yes	137 (24.0)	435 (76.0)	572 (95.3)	
No	16 (57.1)	12 (42.9)	28 (4.7)	
Education level of spouse				p=0.007
Elementary school or lower	90 (30.5)	205 (69.5)	295 (49.2)	
High school	52 (22.8)	176 (77.2)	228 (38.0)	
University	11 (14.3)	66 (85.7)	77 (12.8)	
Employment of spouse				p=0.000
Employed	105 (20.2)	416 (79.8)	521 (86.8)	
Unemployed	48 (60.8)	31 (39.2)	79 (13.2)	
Monthly Income (Turkish Lira)				p=0.000
≤3000	66 (47.1)	74 (52.9)	140 (23.3)	
3001-6000 ≥6001	73 (23.2) 14 (9.6)	241 (76.8) 132 (90.4)	314 (52.4) 146 (24.3)	

of the women/spouse, unemployment, lack of health insurance, and lower monthly income were found to be effective on depression rate (p<0.01).

Correlation between fertility features, chronic conditions, and depressive mood is shown in Table 2. Increased total number of pregnancies, live births, unplanned pregnancy, previous prenatal/postnatal depression diagnosis, depression history in immediate family members, and having a diagnosed chronic disease were found to be correlated with high depression frequency (p<0.01).

Familial factors such as lack of a civil marriage, involuntary marriage, living with spouses' families and the increased number of cohabitants, failure in sharing problems with and receiving support of the spouse/close relatives or friends, and discord/uneasiness within the family were found to be correlated with high depression frequency (p<0.01) (Table 3).

In logistic regression analysis, involuntary marriage, living with spouse's relatives, unplanned pregnancy, existence of a diagnosed chronic disease, not being able to share problems with the spouse and/or with immediate family members/friends were determined as the factors increasing depressive mood risk (Table 4).

Discussion

Frequency of depressive mood within the study group was found as 25.5%. Studies conducted in various countries reported an antenatal depression prevalence of 5.6% in Japan [15], 14.2% in Brazil [8], 17.0% in Sweden [16], and 20.0% [17] in the USA. Various studies performed in Turkey reported an antenatal depression frequency between 27.9%-33.1%, similar to the results of this study [9-11]. These figures are quite high compared to the rest of the world, which are also affected by factors such as getting pregnant at very young ages and even during adolescence, short intervals between pregnancies, economic challenges, low education levels, family problems, and lack of social support.

Among the study results, the effect of socio-demographic factors on depressive mood is significant which is consistent with previous studies where younger-older age, low education level, unemployment, and lack of health insurance were found to be significant predictors of clinical depression [6,7,16]. It can be said that pregnant women tend to get away from the submissive and desperate approach as their educational level increases and they actively participate in work life and education and employment, all of which help in dealing with stress. Social and economic power, better communication and overall supportiveness of the spouses, and higher educational levels are believed to have a positive impact on depression. Association between psychological disorders and economic income is already known. Many studies report that as the income level decreases, the frequency of antenatal and postnatal depression increases, and income level is a significant risk factor for antenatal depression [6,18]. Lack of partner's support, weak communication and lack of harmony with the partner, and marital problems are found to be correlated with pregnancy and depression and marital problems are indicated to be a potential risk factor for prenatal depression [18].

Table 2. Distribution of the reproductive history and chronic conditions of individuals

	Depressed n (%)	Normal n (%)	Total n (%)	p
Number of pregnancy				p=0.000
1	36 (17.7)	167 (82.3)	203 (33.8)	
2-3	78 (25.4)	229 (74.6)	307 (51.2)	
≥4	39 (43.3)	51 (56.7)	90 (15.0)	
Live Birth				p=0.004
0	50 (20.2)	198 (79.8)	248 (41.3)	
1-2	90 (27.8)	234 (72.2)	324 (54.0)	
≥3	13 (46.4)	15 (53.6)	28 (4.7)	
Planned pregnancy				p=0.000
Yes	46 (10.4)	396 (89.6)	442 (73.7)	
No	107 (67.7)	51 (32.3)	158 (26.3)	
Depression History				p=0.000
Yes	62 (74.7)	21 (25.3)	83 (13.8)	
No	91 (17.6)	426 (82.4)	517 (86.2)	
Previous prenatal/ postnatal depression diagnosis				p=0.000
Yes	28 (87.5)	4 (12.5)	32 (8.8)	
No	125 (37.5)	208 (62.5)	333 (91.2)	
Depression history in first degree relatives				p=0.000
Yes	71 (68.9)	32 (31.1)	103 (17.2)	
No	82 (16.5)	415 (83.5)	497 (82.8)	
Diagnosed Chronic Disease				p=0.000
Yes	56 (44.4)	70 (55.6)	126 (21.0)	
No	97 (20.5)	377 (79.5)	474 (79.0)	

Table 3. Distribution of family features of individuals

Features	Depressed n (%)	Normal n (%)	Total n (%)	P
Legally valid marriage				p=0.000
Yes	140 (23.9)	445 (76.1)	585 (97.5)	
No	13 (86.7)	2 (13.3)	15 (2.5)	
Voluntary Marriage				p=0.000
Yes	101 (18.7)	440 (81.3)	541 (90.2)	
No	52 (88.1)	7 (11.9)	59 (9.8)	
Number of individuals living at home				p=0.000
2	20 (11.4)	155 (88.6)	175 (29.2)	
3-4	74 (24.7)	226 (75.3)	300 (50.0)	
≥5	59 (47.2)	66 (52.8)	125 (20.8)	
Association of individuals at home				p=0.000
Elementary family	62 (14.6)	362 (85.4)	424 (70.7)	
With spouse's relatives*	84 (59.6)	57 (40.4)	141 (23.5)	
With own relatives*	7 (20.0)	28 (80.0)	35 (5.8)	
Sharing problems with spouse				p=0.000
Always	30 (7.6)	363 (92.4)	393 (65.5)	
Sometimes	47 (41.2)	67 (58.8)	114 (19.0)	
Rarely	76 (81.7)	17 (18.3)	93 (15.5)	
Discord/uneasiness within the family				p=0.000
Always	48 (100.0)	0 (0.0)	48 (8.0)	
Sometimes	61 (52.6)	55 (47.4)	116 (19.3)	
Rarely	44 (10.1)	392 (89.9)	436 (72.7)	
Sharing problems with relatives/friends				p=0.000
Always	23 (7.3)	293 (92.7)	316 (52.7)	
Sometimes	41 (27.5)	108 (72.5)	149 (24.8)	
Rarely	89 (65.9)	46 (34.1)	135 (22.5)	

*In addition to spouse and other children

Table 4. The results for the factors associated with depression in logistic regression analysis

Risk Factors	p	OR	%95 CI
Association of individuals at home			
Elementary family			
With spouse's relatives*	0.706	0.779	0.212-2.860
With own relatives*	0.000	3.731	1.881-7.401
Voluntary marriage			
Yes			
No	0.002	5.642	1.879-16.943
Planned pregnancy			
Yes			
No	0.000	6.348	3.207-12.566
Chronic disease			
No			
Yes	0.001	3.310	1.632-6.712
Sharing problems with spouse			
Always/often			
Sometimes	0.000	3.672	1.784-7.556
Rarely/never	0.000	16.708	6.949-40.175
Sharing problems with relatives / friends			
Always/often			
Sometimes	0.008	2.755	1.297-5.855
Rarely/never	0.000	4.445	2.004-9.860

OR: odds ratio; 95%CI: 95% confidence intervals. *In addition to spouse and other children

Depressive mood rates were found to be higher in women living with their spouses' families and depression rates increase as the number of cohabitants increase. In the literature it is indicated that antenatal depression is less frequently observed among pregnant women living with their spouses in a harmonious marriage and that depression frequency increases when there are more cohabitants who are not part of the elementary family [9]. The group with the highest depressive mood risk is pregnant women who live in the same house with their mothers-in-law and who indicate that their relation is uneasy with a non-supportive mother-in-law [19,20]. In our society, living with the spouse's family is quite common, as this factor has a high percentage within the study group as well. Depression frequency does not increase among pregnant women who live with their own families, which could be related to better communication and sharing levels with their own relatives.

A significant correlation was found between existence of a previous antenatal/postnatal depression diagnosis and observed depression. Moreover, having immediate family members diagnosed with depression also increases depression risk. Depression is known to be a disorder with genetic predisposition, and the existence of depression cases within the family increases depression risk; similar to the results we obtained in this study, there are many research studies in the literature reporting an increase in depression among pregnant women who have family members with a depression history [19,20]. In general, these research studies have concluded that diagnosis of depression or any other psychiatric disorder sometime in the past constitutes a risk factor for antenatal depression, similar to our findings in this study.

An association between chronic diseases and psychiatric disorders, especially depression, has been previously reported [21]. Similarly, studies conducted in Brazil with 326 pregnant subjects with chronic diseases and 2398 subjects with chronic high blood pressure revealed high depression rates, consistent with the results of this study [22,23].

Failure in sharing problems with and receiving support of the spouse, close relatives, or friends significantly increases depression scores. Many studies have shown that depression rates are considerably lower among pregnant women who indicate they have a good relationship and can easily share their problems with their spouses, close relatives, or friends [7,12,18]. It is already known that women can adapt to the concept of maternity more easily in marriages where women can comfortably share significant problems with their spouses and where spouses approve of the maternity role. However women are more inclined to depression in marriages with a poor communication level where the husband fails to show interest and care during and after pregnancy [18].

An association between an unplanned pregnancy and depression during pregnancy has been well-documented [8-10,18]. In a study conducted in Australia on 8556 pregnant women during pregnancy and 6 months after pregnancy, observance of antenatal depression was reported to be higher among subjects with unplanned pregnancy. However, depression was regressed during the postnatal follow-up period [24].

Despite a few studies in the literature showing that the increase in number of pregnancies and births is not a risk factor for antenatal depression and that, in fact, multiparity has apositive protective effect [25], the general view is the existence of a positive relation between number of pregnancies and depression during pregnancy, which is also consistent with the results of this study [7,11]. The increase in number of births and living children also increases the burden on women's shoulders andtires them both physically and psychologically and thus may prepare the grounds for antenatal depression.

Despite this high frequency depression levels observed in Turkey and the importance of the issue, no relevant approach has yet to be developed. Depression must be given a high priority and diligently checked during prenatal healthcare services and diagnosis and treatment approaches should be developed accordingly. All risk factors influencing the development and progress of depression should be carefully interpreted, policies versatile in terms of protection should be introduced, and correct messages should be addressed to society. Among preventive approaches countering depression, priority should be given to increasing women's education levels so women will be provided with employment opportunities where they can develop themselves and ensure their economic independence. Also,income levels, a significant determinant of health, should be improved in line with the foregoing and health insurance and social security should be ensured for everyone. Social awareness should be raised against early and involuntary marriages and common traditional perspectives should be corrected.Men particularly-should be educated to improve their approach to and perception of women. Since depression frequency among women increases as the number of pregnancies and births increases,it should be ensured that families have children through conscious choices,

by evaluating the present socio-economic conditions and without neglecting the potential mother's choices and desires. Family planning services should be accessible and approaches that could guide the society in the wrong way should be avoided. Particularly, the negative characteristics of traditional family type which trivializes women should be changed and social awareness should be raised regarding this issue. Depression scanning should be introduced to routine prenatal care programs, it should be possible to make the required interventions, and accessible diagnosis and treatment services should be in place for pregnant women diagnosed with depression.There must be psychiatry units in healthcare centers providing prenatal care programs, due to the fact that the pregnant women, considered to experience depression according to the scale applied in our study, were observed not to apply to relevant healthcare centers for treatment.

The cross-sectional nature of this study and the use of the EPDS screening tool, which is not a diagnostic tool, are limitations of this study in interpreting the results. Large and prospective studies are needed to clarify the risk factors that can cause depression in the antenatal period.

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Competing interests

The authors declare that they have no competing interests

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The effects of silibinin on corporal oxidative stress and antioxidant enzymes in ischemic priapism

Silibininin iskemik priapizmde korporal oksidatif stres ve antioksidan enzimler üzerine etkileri

Silibinin for ischemic priapism

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Öz

Amaç: İskemik priapizm, progresif hipoksi, hiperkapni ve asidozla seyreden ve sonrasında gelişen korporal fibrozisin erektil disfonksiyona yol açabildiği androlojik bir acildir. Silibinin çeşitli hayvan deneylerinde farklı organlar üzerinde antiapoptotik, antilipidemik ve antioksidan etkileri gösterilmiş bir flavonoid derivesidir. Yapılan çalışmalarda silibininin organ koruyucu etkisinin sıklıkla antioksidan etkilerine bağlandığı belirlenmiştir. Buna karşın,literatürde silibininin uzamış priapizm olgularında korporal doku üzerindeki etkilerine ilişkin yayın bulunmamaktadır. Çalışmanın amacı, iskemik priapizm hayvan modelinde silibininin farklı priapizm süreleri sonrasında korporal dokudaki oksidatif stres ve antioksidan enzim düzeyleri üzerine etkisinin incelenmesidir. Gereç ve Yöntem: Otuz adet Wistar-Albino erkek rat 5 eşit gruba bölündü. Bunlar kontrol, 12-saat priapizm+izotonik(Pİ), 12 saat-priapizm+silibinin (PS), 24 saat Pİ ve 24 saat PS grupları olarak belirlendi. Priapizm vakum ereksiyon sonrası penis köküne yerleştirilen konstriktör bant ile sağlandı. 12 ve 24 saatlik priapizm sonrası bantlar çıkarıldı ve ratlar oral gavajla 7 gün boyunca izotonik ya da silibinin ile beslendi. Bir hafta sonunda sıçanlar uyutularak penektomi yapıldı ve dokuda malondialdehit (MDA), superoksit dismutaz (SOD), glutatyon peroksidaz (GPx) and nitrik oksit (NO) düzeyleri değerlendirildi. Bulgular: Korporal MDA düzeyleri priapizm süresi uzadıkça anlamlı arttı. Silibinin tedavisi priapizm gruplarında MDA düşüşü sağladı. Korporal GPx ve SOD değerleri priapizm gruplarında kontrol grubuna oranla belirgin yüksekti. Ancak antioksidan enzim değerlerindeki değişim priapizm süresi ile korelasyon göstermedi. Silibinin ile beslenen ratlarda SOD ve GPx değerleri izotonik gruplarına göre anlamlı azaldı. Nitrik oksit değerleri gruplar arasında anlamlı değişiklik göstermedi. Tartışma: Çalışma sonunda priapizmin korporal dokuda zaman bağımlı olarak oksidatif stresi artırdığı ve silibinin tedavisinin oksidatif stres üzerinde azaltıcı etkisi olduğu gösterildi. Silibinin maddesi priapizm tedavisinde umut vaat eden bir madde olabilir.

Anahtar Kelimeler

Silibinin; Priapizm; Oksidatif Stres; Antioksidan Enzimler

Abstract

Aim: Ischemic priapism is characterised by progressive hypoxia,hypercapnia, and acidosis with subsequent corporal fibrosis which may lead to erectile dysfunction.In various studies, silibinin has been shown to have antiapoptotic,antilipidemic, and antioxidant activities in many organs. However,data is lacking about the effects of silibinin on penile tissues of prolonged priapism cases. The aim of the study was to investigate the possible protective effects of silibinin on oxidative stress and antioxidant enzyme levels in an animal model. Material and Method: Thirty male Wistar-Albino rats were divided into five groups as control,12-hours (h) of priapism+isotonic (PI),12-h priapism+silibinin (PS),24-h PI, and 24-h PS groups,respectively. Priapism was induced by vacuum device and a constrictor rubber band was placed at the base of the erect penis. The rats were fed by isotonic and silibinin with oral gavage for 7 days after corresponding duration of priapic episodes.Then,the rats were anesthesized and penectomies were performed to investigate levels of malondialdehyde (MDA),superoxide dismutase (SOD),glutathione peroxidase (GPx), and nitric oxide (NO). Results: Corporal MDA levels significantly increased as the duration of priapism prolonged.Administration of silibinin insignificantly decreased MDA levels in experimental groups.Corporal GPx and SOD levels were significantly higher in experimental groups than controls.However,increases in antioxidant enzymes were not significant between 12 and 24 hour vehicle groups.Administration of silibinin significantly reduced SOD and GPx levels in 12 and 24 hour priapism groups,respectively. Discussion: This study demonstrated that experimental priapism results in increased oxidative injury in corporal tissues and that treatment with silibinin alleviated those effects.Therefore,it can be extrapolated that silibinin may be used as an antioxidant agent in the treatment of ischemic priapism in future urology practice.

Keywords

Silibinin; Priapism; Oxidative Stres; Antioxidant Enzymes

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Introduction

The term priapism describes an emergent condition with full or partial erection that lasts more than 4 h beyond sexual stimulation and orgasm, or that is unrelated to sexual stimulation [1]. Priapism may be classified into three subtypes as ischaemic (low flow), stuttering (intermittent), and non-ischaemic (high flow) priapism [2,3]. Ischemic priapism(IP) is the most common form, associated with venous outflow obstruction and absence of arterial inflow. Subsequent time-dependent changes including progressive hypoxia, hypercarbia,and acidosis develop and ultimately ischemia and fibrosis in cavernosal smooth muscles may lead to erectile dysfunction [4,5].Since IP is a compartment syndrome, its management re-establishes corporal blood flow, which is associated with reperfusion of ischaemic tissues. Increased corporal oxidative stress may lead to irreversible cellular damage by alterations in cell membranes and the release of reactive oxygen species (ROS) into the systemic circulation [5]. Oxidative damage results in an increase in tissue levels of malondialdehyde (MDA) [6]. Antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) have protective effects against ROS. Previous studies have demonstrated that the levels of ROS increase with the duration of priapism and antioxidant enzymes were found to be elevated in priapic tissue [5,7]. Recently, Kucukdurmaz et al. reported that the oxidative stress and antioxidant enzyme activities increased as the priapic episodes prolonged [8]. Previously, various antioxidant agents have been reported to establish their protective effects in priapism models. Silibinin is the primary active constituent of a crude extract (silymarin) from milk thistle plant (Silybum marianum) seeds [9]. Many studies have reported that it had antioxidant, antiapoptotic, and therefore, cytoprotective effects in various organs. Silibinin exerts its antioxidative effects by direct scavenging of free radicals, preventing free radical formation by inhibiting specific ROS-producing enzymes and decreasing inflammatory responses by inhibiting NF-κB pathways [9]. The antioxidant properties of silibinin are considered to be responsible for its protective actions. Another effect of silibinin is to inhibit the synthesis of nitric oxide synthase (NOS), which is a pro-oxidative enzyme [10-12].

The aim of this study was to investigate the effects of silibinin on corporal oxidative stress, antioxidant enzymes, and nitric oxide levels in an animal model of ischemic priapism.

Material and Method

Animals

The protocol of the experimental study was approved by the local ethics committee. Thirty adult male Wistar-Albino rats (6–10 weeks old) weighing between 250 and 300 g were used for this study. All animals are subject to the ethical treatment in accordance with Guide for the Care and Use of Laboratory Animals. They were placed in plastic cages, three rats per cage, in a constant temperaturecontrolled room on a 12/12-h light/dark cycle. The rats were allowed to eat standard rodent chow and water ad libitum. The rats were divided into five groups of six each. Anesthesia for all procedures was provided by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). Low-flow priapism was created using a vacuum constriction device with a constriction rubber band on the penis [13]. The cap of a 50- mL disposable syringe, holed at the tip, was connected to a syringe using a Foley catheter. After shaving and retracting the prepuce, the hollow tip of the cap was placed firmly over the flaccid penis. Suction was created by gently withdrawing the piston, and after tumescence, a constriction band (cutting 2 mm thickness of a 10 Fr Foley catheter) was placed around the base of the penis using forceps. During the artificially induced priapism, the animals were left undisturbed in their cages. Group 1 served as the control. After 12 h (groups 2,4) and 24 h (groups 3,5) of priapism, the constriction bands were removed and reperfusion was allowed for all rats. Then, rats in groups 2 and 4 were fed with vehicle (0.9% NaCl) and rats in groups 3 and 5 were fed with silibinin 100 mg/kg by oral gavage for 7 days, respectively. At the end of the 7th day, the rats were reanesthesized and penectomies were performed.Sacrificed animals' penile tissues were collected to evaluate the corporal changes in the levels of MDA, NO, and the activities of the SOD and GPx enzymes. Sacrification of animals was performed by cervical dislocation under anesthesia.

Preparation of Corporal Tissue Homogenates

The corporal tissues of the rats were quickly removed, washed, and rinsed with cold 0.9% NaCl, then blotted dry and immediately frozen in liquid nitrogen, to be kept at -80°C until they were analysed. Corporal tissue homogenates (10% w/v) were prepared with ice-cold solution containing 50 mmol/l of Tris–HCl (pH 7.4); 1% Triton X; 150 mmol/l of NaCl; and leupeptin, aprotinin and soya bean trypsin inhibitor (1 lg ml_1 each) at 0–4°C using a polytron homogeniser. In brief, corporal tissue homogenates were centrifuged at 600 9 g for 10 min at 4°C to remove crude fractions. Afterwards, supernatants were centrifuged at 10 000 9 g for 20 min to obtain the post-mitochondrial fraction. Measurement of tissue MDA levels was determined by the Buege & Aust method [14]. MDA reacts with thiobarbituric acid to give a red compound absorbing at 532 nm. The stock reagent (15% w/v trichloroacetic acid, 0.375% w/v thiobarbituric acid, 0.25 mol/l hydrochloric acid, and 0.01% butylated hydroxytoluene) was thoroughly mixed with the sample and heated for 15 min in a boiling water bath. After cooling, the precipitate was removed by centrifugation at 1000 9 g for 10 min and the absorbance of the supernatant was determined at 532 nm against a blank containing all the reagents. The breakdown product of 1,1,3,3-tetraethoxypropane was used as the standard. MDA levels were calculated using 1.56 x 10-5 mol-1 cm-1 as the molar extinction coefficient. MDA levels were expressed as nmol mg-1 protein for corporal tissue. Measurement of antioxidant enzyme activity SOD activity was determined as described by Fridovich [15]. The principle of the method is based on the inhibition of nitro blue tetrazolium chloride (NBT) reduction by the xanthinexanthine oxidase system, a superoxide generator. Xanthine (Sigma-Aldrich) and xanthine oxidase (Sigma-Aldrich) generate superoxide radicals, which react with NBT (SigmaAldrich) to form a red formazan dye. SOD activity was then determined according to the degree of inhibition of this reaction. One unit of SOD was defined as the quantity of enzyme (mg) causing 50% inhibition in the NBT reduction rate. SOD activity was expressed as units of SOD per mg protein. The glutathione peroxidase (GPx) activity assay was based

on the oxidation of nicotine adenosine dinucleotide phosphate (NADPH; Sigma-Aldrich) to NADP + , which is accompanied by a decrease in absorbance at 340 nm. The rate of this decrease is directly proportional to the GPx activity in the sample [16]. Therefore, GPx activity was measured by the enzymatic reaction that was initiated by adding H 2 O2 to a reaction mixture containing reduced glutathione, NADPH, and glutathione reductase (Sigma-Aldrich). The change in the absorbance at 340 nm was monitored using a Shimatzu UV-1601 spectrophotometer (Shimadzu Corp.). Protein levels were estimated as described by Lowry et al. [17] and activity was expressed in units of GPx per mg protein. The determination of concentration levels of nitrite, which is the stable end product of nitric oxide (NO) radicals, was used as a measure of NO production. Nitrite concentration was determined using a classic colorimetric Griess reaction. Briefly, equal volumes of samples and Griess reagent (Sigma-Aldrich) were mixed at room temperature. After 5 min, the absorbance was measured at 540 nm using a spectrophotometer (UV 1601; Shimadzu Scientific Instruments, Inc., Columbia, MD, USA). The concentration of nitrite was determined using a standard curve prepared with sodium nitrite [16].

Statistical Analysis

The distribution of continuous variables was evaluated according to the Kolmogorov– Smirnov normality test. If the distribution was normal, a parametric one-way ANOVA test was used for statistical analysis; if the distribution was not normal, a nonparametric Kruskal–Wallis test was used. Post hoc analysis was performed by Tukey's, Tamhane's, or Dunnett tests. The continuous variables were presented as the mean and standard deviation. A p-value of<0.05 was considered significant. Analyses were performed by using SPSS statistical software (PASW v15 SPSS Inc., Chicago, IL, USA).

Results

Corporal tissue MDA levels for groups 1,2,3,4, and 5 were 5.79±4.82, 11.38±3.45, 8.86±3.11, 21.79±3.72, and 16.24±3.20, respectively. Post-hoc analysis revealed that MDA levelssignificantly increased as the duration of priapism prolonged (p=0.001). In addition, MDA levels were found to be significantly increased with respect to duration of priapism in the groups treated with silibinin. Although administration of silibinin decreased MDA levels when compared to vehicle groups, this decline was not significant for the 12 and 24 hour priapism groups. SOD and GPx activities were also found to be increased with respect to the duration of priapism (p=0.001). Besides, corporal levels of those enzymes were found to be significantly different between groups 2 and 3 (p=0.001) and also between groups 4 and 5 (p=0.001), which means that silibinin may help to decrease antioxidant enzyme activities in priapic tissues. There were no significant changes among groups in terms of NO levels. Corporal tissue oxidative stress parameters and antioxidant enzymes are presented in Table 1. Corporal MDA levels are shown in Figure1.

Discussion

Ischaemic priapism (IP), which has been accepted as a compartment syndrome and thought to be caused by an imbalance between the vasoconstrictor and vasorelaxant mechanisms, represents more than 90% of priapism cases [5]. In IP, time-dependent changes such as progressive hypoxia, hypercapnia, and acidosis may result in corporal fibrosis with subsequent severe ED [18-19].

Ultrastructural changes in corporal microenvironment occur after 12 h in IP, focal necrosis after 24 h, and eventually necrosis and transformation of fibroblast-like cells after 48 h. If priapism is left untreated or treated late (>24 h), necrosis in cavernous smooth muscle, irreversible corporal fibrosis, and permanent erectile dysfunction will occur [19]. The most significant determining factor in the prevention of tissue damage after ischemic priapism is the duration of ischemia, which is directly correlated with reperfusion injury. Previous studies revealed that oxidative stress increased as the duration of priapic episodes prolonged [7,8]. In another study, male rabbits were exposed to a low-oxygen-tension breathing gas to achieve hypoxia within the corpora cavernosa and to decrease systemic oxygen saturation to 60%, and priapism was induced by clamping the base of the penis after pelvic nerve stimulation [5]. After varying durations of ischemia, it was determined that corporal partial oxygen pressure progressively decreased as the duration of priapism increased. Our data also supported the finding that MDA levels significantly increased with respect to time. Anti-

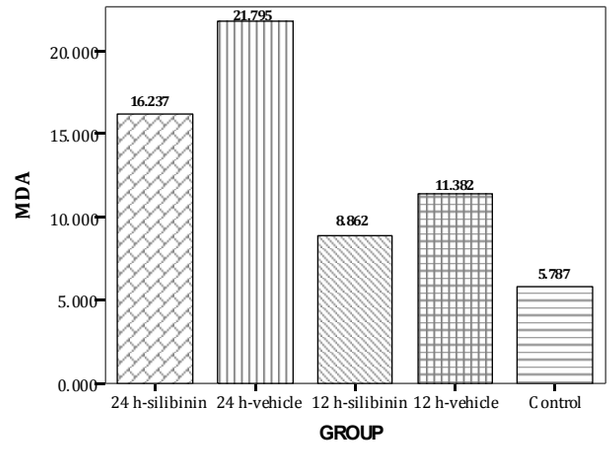


Figure 1. MDA levels among study groups
Significant differences between control and vehicle groups, p<0.001
Significant differences between 12 h and 24 h vehicle and treatment groups, respectively p<0.001

Table 1. Oxidative stress parameters and antioxidant enzyme activities among groups

	Control	12 h vehicle	12 h silibinin	24 h vehicle	24 h silibinin	p
MDA	5.79±4.82	11.38±3.45	8.86±3.11	21.79±3.72	16.24±3.20	0.001 [a,b,e,f]
SOD	0.17±0.10	0.33±0.05	0.20±0.02	0.53±0.15	0.27±0.06	0,001[a,c]
GPx	0.13±0.02	0.20±0.01	0.15±0.01	0.21±0.02	0.16±0.03	0,001[a,c,d]
NO	0.26±0.07	0.16±0.06	0.32±0.23	0.17±0.08	0.27±0.18	0.239

Data were presented as mean±SD,
a,significant difference between control-12 h vehicle and control-24 h vehicle groups
b,significant difference between control and 24 h silibinin groups
c, significant difference between 12 h vehicle and 12 h silibinin groups
d,significant difference between 24 h vehicle and 24 h silibinin groups
e, significant difference between 12 h silibinin and 24 silibinin groups
f, significant difference between 12 h vehicle and 24 h vehicle groups

oxidant enzymes such as SOD and GPx increase in response to increased oxidative stress in many I/R models. They are known to be the major enzymes that counteract the effects of ROS in reproductive organs. However, data about the level of antioxidant enzymes in priapic tissues are limited. An experimental model revealed that the levels of SOD and CAT were found to be higher in priapic tissue when compared to a control group [20]. Kucukdurmaz et al. [8] stated that antioxidant enzyme activities also increased in parallel to oxidative stress as the priapism prolonged. Similar to those reports, our study revealed that antioxidant enzyme activities increased with respect to the duration of priapism.

Silibinin is a pharmacologically active constitute of Silybum marianum. Silibinin possesses marked antioxidative, anticancer, and anti-inflammatory properties [9,21]. It is widely used in treatment due to its safety and lack of adverse effects [9]. Cytoprotective effects of silibinin are generally attributed to its antioxidant properties [9]. Silibinin exerts its antioxidant activities in various ways. These include direct free radical scavenging, inhibition of free radical producing enzymes, and decreasing inflammatory responses by inhibiting NF-κB pathways [22]. Silibinin seems to be a promising protective agent for repairing free-radical induced damage in a variety of pathological conditions [10]. Many studies reported the protective effects of silibinin in various organ systems. It has been shown that silibinin has hepatoprotective activity by its antioxidant and antiinflammatory properties [11,23]. Kalemci et al. reported that silibinin attenuated methotrexate-induced pulmonary injury by relieving oxidative stress(24). Another experimental study revealed that silibinin ameliorated arsenic-induced nephrotoxicity by decreasing oxidative stress and inflammation in kidney tissue [10]. Silibinin was also shown to protect cardiac cells from phenylephrine toxicity via antioxidant mechanisms involving mainly the inhibition of intracellular cell signals [25]. The effects of silibinin on nitric oxide are controversial; however, it is mostly stated that silibinin downregulates nitric oxide synthase and iNOS levels [10-12]. Kan et al. [26] reported that administration of silibinin inhibits tumor promotional triggers and tumorigenesis against experimentally induced skin carcinogenesis and downregulates oxidative stress and inflammation by decreasing mediators such as nitric oxide, iNOS, and interleukin-6.

It was previously mentioned that silibinin exerts its organ protective effects mainly by antioxidant mechanisms. Therefore, this study has been performed to investigate not only the changes in oxidative stress parameters and the antioxidant enzyme activities according to varying durations of priapism but also the effects of silibinin on those parameters in priapic tissues. For this purpose, rats were treated either by vehicle (0.9% NaCl) or silibinin for 7 days after 12 and 24 hours of priapic episodes. When silibinin and vehicle groups were compared, it was found out that silibinin insignificantly decreased MDA levels in both the 12 and 24 hour priapism groups. The decrease in oxidative stress with the administration of silibinin was consistent with the previously mentioned literature. In addition, when silibinin and vehicle groups were compared in terms of antioxidant activity, it was observedthat the levels of antioxidant enzymes were significantly lower in rats treated with silibinin. There were no significant differences among the groups in terms of corporal nitric oxide levels. To our knowledge, this is the first study thatinvestigates the effects of silibinin on corporal oxidative stress and antioxidant enzymes in animal model ischemic priapism. Our results showed that silibinin had beneficial effects to relieve oxidative stress in prolonged priapic episodes. Further research including histopathological investigations in corporal tissues should be conducted to investigate organ-protective effects of silibinin.

Conclusion

This study demonstrated that oxidative injury in cavernosal tissues of rats increased with the duration of priapism, and treatment with silibinin decreased oxidative stress and antioxidant enzyme activities when compared to the vehicle group. From the results of this experimental study, it can be concluded that silibinin may be used as a new antioxidant agent in the treatment of ischemic priapism.

Competing interests

The authors declare that they have no competing interests.

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Do we provide enough nutrition in geriatric patients with percutan endoscopic gastrostomy?

Perkütan endoskopik gastrostomi ile geriatri hastalarında yeterli beslenme sağlayabiliyor muyuz?

Nutrition in geriatric patients with peg

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Öz

Amaç: Oral yoldan beslenemeyen ancak gastrointestinal sistem fonksiyonları normal olan yaşlı hastalarda beslenme sağlanması amaçlı perkütan endoskopik gastrostomi (PEG) işlemi güvenilir olarak sıklıkla kullanılmaktadır.Bu çalışmada amacımız 65 yaş üzerinde PEG takılan hastaların beslenme desteğinin yeterliliğini değerlendirmektir. Gereç ve Yöntem: 2012 Nisan ve 2016 Ocak ayları arasında çekme yöntemi ile yüzeyel anestezi altında PEG yerleştirilen, 65 yaşın üstündeki 97 hastanın; işlem günü, 3. ay ve 6. ay hemogram ve prealbumin değerleri ile antropometrik ölçümleri retrospektif olarak incelendi. PEG endikasyonu 60 olguda serebrovasküler hastalıklar, 21 olguda demans ve 16 olguda diğer nörolojik hastalıklardı. Bulgular: Çalışmamıza 51'i kadın, 46'sı erkek toplam 97 hasta alındı. Yaş ortalaması erkeklerde 76,6(±6,4) yıl ve kadınlarda 74,4 (±8,8) yıl idi. Toplam 10 hastada minör komplikasyon (8 olguda yara enfeksiyonu, 2 olguda hafif sızdırma) görüldü. Hastaların takibinde bazal protein: 6,64 mg/dl, albümin: 2,96 mg/dl, prealbumine: 0,08 mg/dl, hemoglobin: 9,2 mg/dl iken 3. ayda ve 6 ayda bu değerlerde anlamlı değişiklik saptanmamıştır. Erkek hastalarda geliş kol çevresi 26,52 cm ve baldır çevresi 36,9 cm ; kadın hastalarda geliş kol çevresi 25,48 ve baldır çevresi 33,9 cm saptanmıştır. İki grupta da bu değerlerde 3. ayda ve 6. ayda kontrollerde anlamlı değişiklik gözlenmemiştir. Hastaların takip süresi 442 (242- 1102) gün olup işleme ait mortalite saptanmamıştır. Tartışma: PEG, çeşitli nedenlerle oral yoldan beslenemeyen geriatrik olgularda uzun süreli beslenme desteği sağlayan güvenli bir yöntemdir. Hastaların gerekli kalori desteğini alabilmeleri hayat kalitesi açısından önemlidir. Çalışmamıza alınan hastaların zaten bir protein enerji malnutrisyonu mevcuttu ve verilen beslenmenin yeterli desteği sağlayamadığını görmekteyiz. Hastalarımızın kalorisi ve proteini daha yüksek beslenme ürününe ihtiyaç duyduklarını düşünmekteyiz.

Anahtar Kelimeler

Enteral Beslenme; Gastrostomi; Geriatri; Endoskopi; Peruktan Endoskopik Gastrostomi

Abstract

Aim: Percutaneous endoscopic gastrostomy (PEG) is safely and regularly used in elderly patients who have problems with feeding orally but have normal functioning gastrointestinal systems. The aim of this study is to evaluate the nutritional efficiency of PEG in patients over 65 years old. Material and Method: Study was performed between April 2012-January 2016 with 97 patients (51female, 46male). PEG was placed under superficial anesthesia and anthropometric measurements, hemograms and prealbumin levels on the procedure day, at the 3rd month and 6th month were retrospectively analyzed. PEG indications included cerebrovascular disease in 60 patients, dementia in 21 patients and other neurological disorders in 16 patients. Results: Total of 97 patients (51 female, 46 male) were included in the study. Mean age was 76,6(±6,4) for men and 74,4 (±8,8) for women. Minor complications were seen in 10 patients(8 wound infection and 2 slight leakages). Patients mean baseline protein levels were; 6,64 mg / dl, albumin: 2,96 mg / dl, prealbumin: 0,08 mg / dl, hemoglobin: 9,2 mg / dl and there were no significant changes in baseline protein levels of the patients during follow-up at 3 months and 6 months. In male patients, the baseline circumference of the arm was measured 26.52 cm and the baseline circumference of the thigh was measured 36.9 cm and in female patients, the baseline arm circumference was found to be 25.48 and the baseline thigh circumference was found to be 33.9 cm. There were no significant changes during the follow-up period in both groups. The follow-up period of the patients was 442 (242-1102) days and there was no mortality related to the procedure. Discussion: PEG is a safe method of providing long-term nutritional support in geriatric cases that can not be fed orally for various reasons. It is important for quality of life that patients can get the necessary calorie support. Patients included in the study already had a protein energy malnutrition and we can see that provided nutrition did not provide adequate support. We think that our patients need higher calorie and protein products.

Keywords

Gastrostomy; Geriatrics; Endoscopy; Enteral Nutrition; Peruktan Endoskopik Gastrostomi

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Introduction

Ages over 65 are considered as old age and old age is beginning to form a larger part of the population in our country just like rest of the world. One of the effective factors in maintaining health and improving the quality of life is an adequate and balanced diet [1]. In addition to age progression, there are also increasing conditions, mostly neurological, in which oral intake is disturbed.

Nutritional support is often necessary to provide a quality life for such diseases. Nasogastric catheterization, gastrostomy or PEG feeding is performed in patients where oral intake is not possible. The most commonly used method for nutritional status monitoring is body mass index (BMI) measurement based on weight and height. Age-related shortening of the bone height and kyphosis do not have a right assessment technique. Weight measurement can also be difficult in this patient group. The elderly can sit, but if they can not stand, the weight can be measured with portable bed scales or a mobile wheelchair. For bedridden patients, beds with weighing capability are available, but not easily accessible. In these patients, body weight can be calculated as 95% confidence interval using thigh circumference, knee length, arm circumference and subscapular skin layer thickness. While this is not an ideal solution, it can give acceptable results in patients who can not move or be moved. Anthropometry is one of the most important methods for monitoring the health of the elderly [2]. It involves the systematic measurement of the physical parameters of the body, primarily dimensional descriptors of body size and shape, not only in the elderly but across all age groups. The parameters are then compared with the reference values for that age and sex to determine the nutritional and health status.

Another method for monitoring the nutrition is monitoring of blood proteins. Serum albumin level in healthy individuals should be above 4 mg/dl. Albumin is the most common protein found in blood plasma of humans and other mammals. It constitutes 60% of the proteins found in blood and 30-40% of the total albumin in the body is in the blood. Albumin has a half-life of 18-21days. Albumin has proven to be a prognostic factor (1 g / dl increase leads to a 6% reduction in mortality) but there are limiting factors in the use such as; long half-life span, influence from the body fluid state and acute phase reactivity [3]. Prealbuminine has a half-life of 2-3 days and synthesis and degradation are faster than albumin. Therefore, the fall in plasma prealbumin levels (falling below 15 mg / dL) reflects malnutrition and it is a more reliable and sensitive parameter for following the Nutritional support program. In addition, if sufficient nutrition is available, it returns to normal values in a short time (three days). However, prealbumin is affected by inflammatory reactions [4].

Percutaneous endoscopic gastrostomy (PEG) is an alternative method of surgical gastrostomy developed in 1980 for continuing enteral feeding in patients who can not be fed orally for longer than 4 weeks due to underlying diseases [5]. In 1980 and 1981, Gauderer and Ponsky used this method for the first time, respectively. Whatever the underlying disease is, it is an enteral feeding route that can be used for sustained or transient long-term nutrition when the patient has no gastrointestinal disturbance [6]. Often applied to neurological patients who are not able to receive oral nutrition after cerebrovascular accident, it is also applied to patients with severe dysphagia secondary to operations, high risk of aspiration pneumonia, long-term intubation and external or internal esophagus compresssşions which can not provide food passage.

Operation related major complications are; peritonitis, organ perforation, hemorrhage, gastrocolic fistula, aspiration pneumonia, buried buffer syndrome and minor complications are; infection, leakage and transient vomiting. Surgical gastrostomy, which is an alternative to PEG, has higher mortality and morbidity compared with PEG due to the need for general anesthesia, difficulty in care and increased risk of leakage. Therefore, PEG is now a safer gastrostomic method for patients with nutritional problems of all ages [7]. In this study, we aimed to evaluate whether we can give enough calories to provide adequate nutrition by PEG in elderly patients with normal gastrointestinal system function who can not be fed orally.

Material and Method

This study was conducted between April 2012 and January 2016. Informed consent was obtained from all patients. 97 cases who received PEG were enrolled in our study above the age of 65 who had a life expectancy of 6 months and predicted to not be able to be fed orally due to underlying diseases for a period of 4 weeks. Patients with severe infection and a catabolic disease such as underlying malignancy were not included in the study. In addition, lesion on the anterior wall of the abdomen and epigastrium, past operation, gastro-duodenal ulcer which is not suitable for endoscopy, intestinal obstruction or ascites were judged to be contraindicated for PEG and they didn't receive PEG. Preoperative coagulation tests, hemoglobin and platelet counts were evaluated in all patients. The procedure was not performed in patients with bleeding and coagulation disorders. All patients, except patients taking antibiotics for their underlying disease, were treated with 2 g of Cephazolin sodium prophylactic antibiotic intravenously 2 hours before the procedure. Patients' oxygen saturation measurements and cardiac monitoring were performed during all PEG procedures. All patients were sedated with midazolam. The endoscopic and percutaneous intervention of all patients was performed by the same physician. Diagnostic gastroscopy was performed with the aim of eliminating any condition that could prevent PEG insertion in all patients before the procedure. Gastrostomy tubes were implanted using abdominal PEG kit (Shocare-PEG set 18 CH, Nutricia Healthcare S.A. CH-1618 Chatel-St-Denis, Switzerland) with the help of gastroscopy light. All procedures were performed in the endoscopy unit in conjunction with the Fujinon EG 450 WL5 and Pentax EG-2980 K video gastroscopy devices with a pull method following a 12-hour fasting. After checking that there was no leakage from the edge of the PEG catheter by 20-30 cc of water, the liquid food was fed by increasing the amount as the patient could tolerate 2 hours after the procedure.

Hemogram, total protein, albumin and prealbumin values of the patients before and 3 to 6 months after PEG insertion were retrospectively found in the hospital archive or home care unit. Arm circumference and thigh circumference measurements on the first day and in the 3rd and 6th month were also obtained

from the records. The patient was turned from the supine position to the right or left side, with palms facing upwards and both arms extended on the body. Patients elbow was supported and the midpoint between the elbow and shoulder ledge was marked and the arm circumference measured at that the level of the mark. In the measurement of the thigh circumference of patients using a wheelchair, an angle of 90 ° C is provided for the ankle and the knee to support the leg and in bedridden patients, the leg is bent 90 ° C from the knee and the foot is pressed on a hard and flat floor. The widest part of the thigh was measured. As the patients with PEG do not have the ability to move too much, daily nutrient intake is calculated as 1500-2000 kcal, 60-80 grams of protein, 50-68 grams of fat.

Statistical analyses were performed using the SPSS 21.0 program (version 14.0; SPSS Inc., Chicago, IL).Data on demographic and clinical characteristics of the patients are presented as mean ± standard deviation (SD) or median and frequency (%) values. Parametric data were analyzed using the Student's t-test and nonparametric data using the Mann-Whitney U test. P< 0.05 was considered statistically significant. The study protocol was conducted in accordance with the ethical principle stated in the Declaration of Helsinki and was approved by the local Research Institutional Ethics Committee (no, 75/5, 10/03/2016).

Results

In our study, 51 patients (52.6%) were female and 46 patients (47.4%) were male. The mean age was 76.6 (± 6.4) in males and 74.4 (± 8.8) in females. Cerebrovascular diseases were detected in 60 (61.5%), dementia in 16 (16.5%) and other neurological diseases in 21 (22%) cases as PEG indications (Table 1). The mean duration of the procedure was measured as 8,6 (± 1,6) minutes. The follow-up period of the patients was 442 (242-1102) days and there was no mortality related to the procedure. In our series 8 (8,2%) cases of wound infection requiring antibiotic treatment and 2 (2.1%) cases showed slight leakage from the edge of the catheter. 49 (50.5%) cases were followed by 224 (68- 660) days of follow-up as of the end of the study (January 2016).

Table 1. Demographics of the Patients

	Male	Female	Total
Age years (mean± SD)	76,6 ± 6,4	74,4 ± 8,8	
Number	46	51	91
Type of Neurological Disorder	Number	Percent (%)	
Ischemic cerebrovascular disease	60	61,5	
Dementia	21	22	
Parkinson's disease	7	7,5	
Others	9	9,2	
Total	97	100	
Follow-up period	442 (242- 1102) day		

Blood glucose, albumin, prealbumin values and upper arm, thigh circumference measurements during hospitalization were not statistically different when compared to 3rd and 6th months controls. The baseline protein value was 8,1 ± 1,12 mg/dl, albumin level was 2,96 ± 0,70 mg/dl and hemoglobin was 9,2 ± 1,02 mg/dl at the time of hospitalization and no significant change was detected in these values at 3 months and 6 months controls (Table 2). In male patients, the basal arm circumference was 26.52 ± 4.02 cm and the thigh circumference was 36.9 ± 5.7 cm and in female patients, the arm circumference was 25.48 ± 4.4 cm and the thigh circumference was 33.9 ± 6.42 cm. There was no significant change in controls in both groups (Table 3).

The total minor complication rate was determined as 10.2%, but no major complication and procedural mortality were observed. No patients PEG catheter was removed for oral feeding during the follow-up period.

Table 2. Results of analysis with biochemical analysis

	Total protein g/dl	Albumin g/dl	Hemoglobin mg/dl
During PEG procedure	6,64 ±1,12 (6,2-7,6)	2,96±0,70 (1,9-4,4)	9,2 ± 1,02 (7,6-10,4)
3. month	6,98 ±1,09 (6,4-8)	3,06±0,64 (2,1-4,7)	10,2 ± 1,12 (8,3-11,4)
6. month	7,04 ±1,1 (6,4-8,1)	3,1±0,68 (2,3-4,8)	11,4 ± 1,2 (9,6-12,6)

p > 0,05: there were no significant changes in these values.

Table 3. Anthropometric measurements in elderly patients

	Arm circumference (cm)		Thigh circumference (cm)	
	Male	Female	Male	Female
During PEG procedure	26,5	25,4	36,9	33,9
3. month	26,6	25,7	37,0	34,1
6. month	27,0	26,0	37,1	34,0

Discussion

Although institutional practices may vary in different centers, PEG is generally used to continue enteral feeding in patients who have normal digestive function and a minimum life expectancy of 3-6 months. Such patients often belong to the geriatric age group. This approach is often considered acceptable by patients who are unable to feed orally, especially due to neurological diseases, but who are able to continue an active life [8]. It is preferred instead of feeding with nasogastric tube because it has lower risk of aspiration, patient and relative compliance is better and the possibility of occlusion and displacement is less. Compared to total parenteral nutrition, it is an important advantage that general infection complications are low, central venous route is not required, it is cheaper and patient compliance is better [9-10]. Although it is mostly used in patients with neurological impaired ability for oral intake, it is equally applicable to patients with physical obstruction to passage of food (e.g., cancer), prolonged intubation and those at high risk of aspiration pneumonia [11]. All our patients had neurological disorders.

41.2% of our patients were in intensive care unit when PEG was attached. Some of these patients were on prolonged ventilation and the majority were cerebral ischemia or hemorrhage. The proportion of patients in need of home-based care was reported to be 40% and most of these patients were with neurological problems in accordance with the literature. In some of the studies performed, the mean duration of the procedure was 34 minutes from the beginning of the anesthesia, whereas the

mean duration of the procedure in our study was calculated as 8,6 ± 1,6 minutes (6-13 minutes).

Complications associated with the PEG procedure during or after the procedure can be seen. These may develop due to many factors such as age, underlying disease, obesity, size and material of the PEG catheter, and experience of the performing team. Complications that may occur during the procedure are abdominal wall hemorrhage, pneumoperitoneum, colon or small bowel injury, liver or spleen laceration, intra or retroperitoneal hemorrhage. None of these complications seen as major complications developed in our cases. Complications following the procedure are peristomal pain, wound infection (which may require catheter removal), aspiration and diarrhea. These are seen as major complications and most common ones are wound infections and catheter leakage. In our study, infection is the most common complication. In our study 2 (2.1%) patients had leakage from the side of the tube and 8 (8.2%) patients had local wound infection which was controlled by simple antibiotic treatment.

A prospective study of antibiotic prophylaxis revealed 33.6% of peristomal infections occurred when no prophylaxis was performed [11]. We applied antibiotic prophylaxis with 2 g Cefazolin 2 hours before the procedure to each patient who did not receive antibiotic treatment in the clinic. In patients with leaking, the edge of the PEG catheter was fixed with a suture and after the procedure leakage stopped in both patients.

Anthropometric measurements are often used to assess nutritional status. For this purpose, absolute weight (body weight) and BMI are the most commonly used measures. Due to osteoporosis-related short stature in the elderly, it can lead to high BMI results even in patients whose weight is below normal [12, 13]. It is also very difficult to measure height and weight in elderly and bedridden patients. For these reasons, other measures that can give more accurate results in the elderly are; arm circumference, thigh circumference and triceps skin thickness (subjective and high error margin) are used. Measurement of the thigh circumference is a more sensitive and valid method of measurement of muscle mass than the circumference of the arm. The reason is that it points to change in the lean muscle mass and the decrease in activity with age [14]. We evaluated arm and thigh circumference measurements in our patients, which are more objective indicators. The measurement of triceps skin thickness was not made because of high error margin and subjective. Arm and thigh circumference values of our patients at the time of PEG insertion and at 3 and 6 months were compared based on the baseline and initial values. Although there was an increase in the baseline value and the 6th month value, it was not statistically significant. According to these results, we think that we can not protect our patient's muscle mass and we can not provide enough calories and protein support. However, considering that the majority of our patients were bedridden, we evaluated our bedridden and non-bedridden patients separately. In the bedridden group, 1500 kcal, 60 grams of protein, 50 grams of fat were given daily. In the non-bedridden group 2000 kcal, 80 grams of protein and 68 grams of fat was provided.

Perhaps this nutritional insufficiency may be overlooked since patients with PEGs are in fact a group of patients with very limited activity and often only able to maintain their vital functions. However, sufficient protein support in the elderly in the geriatric group prolongs life and provides cognitive function stability.

Serum protein levels are also significant in evaluating nutritional status. An ideal protein indicator is required to have a short half-life, be rapidly affected by the protein deficiency in the diet, resulting in a decrease in blood levels, a low reserve, a rapid synthesis, a very stable metabolic rate, and sensitivity to protein and energy restriction only [14]. We are deprived of the indicators that contain all these ideal conditions. Protein markers commonly used in clinical chemistry are total protein, albumin, transferrin, prealbumin and retinol-binding protein.

Albumin is a complex, high molecular weighted protein produced in the liver. Due to its long half-life (18-21 days) the deposition of albumin deposits may be about 2 weeks. It is often used in nutritional assessment as it can be easily and widely measured. Decreased albumin levels have been shown to be associated with increased morbidity and mortality in hospitalized patients. For this reason, it is frequently used as a prognostic indicator. Although the albumin is referred to as an indicator of nutritional assessment, there are serious doubts about its sensitivity. Serum albumin level does not response to or respond poorly to nutritional support in sepsis or stress. If there is no significant stress effect on the presence of protein malnutrition, nutritional support may provide rapid response. However, hypoalbuminemia is not specific for malnutrition and can be observed in many diseases in inflammatory conditions, independent of nutritional status. In the elderly living in their own community hypoalbuminemia may be indicative of protein energy malnutrition. However, changes in serum protein levels in the elderly in the hospital are thought to be indicative of acute-phase reaction and inflammation other than malnutrition. The decrease in serum albumin level is also seen in congestive heart failure or in renal diseases with increased plasma volume. In addition, advanced liver failure, enteropathy leading to protein loss and advanced renal failure causes severe albumin loss, limiting the use of albumin in the evaluation of malnutrition [15]. Given this situation, we also did not include patients with enteropathy, infection or malignancy, advanced heart failure and renal insufficiency within the patient group of choice. In our study, we did our follow-ups at 3rd and 6th months to exceed the least 2 weeks required to fill the deposits, due to the long half-life of albumin, eliminates the limitations of the albumin use.

In the follow-up of our patients, liver or chronic kidney disease did not occur. There was no statistically significant change in our patient's baseline total protein, albumin and prealbumin values measured on the first day of PEG insertion compared to the 3rd and 6th months ($p > 0.05$). Our patients were malnourished as of the first day but serum albumin and prealbumin values were not changed after nutritional support. Nutritional support does not provide for laboratory improvement that's why we need to give a higher calorie and protein supplement.

In conclusion, PEG is a reliable feeding method that can be applied in a short time and provide long-term and optimal nutritional support in cases that can not be fed orally for various reasons. Daily intake of sufficient calories and protein is especially important during childhood and geriatric age. It is difficult

to detect nutritional deficiency in the elderly. There is no gold standard method for clinical evaluation, so it is not ideal to use single measurements. It should not be forgotten that early detection of malnutrition will ensure successful intervention. Daily food supplementation is often inadequate in the elderly. It is recommended to carry out researches to develop nutritional assessment tools to detect specific malnutrition risks on elderly individuals.

Animal and Human Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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Vancomycin resistant enterococci colonization in a neonatal intensive care unit: case-control study

Yenidoğan yoğun bakım ünitesi'nde vankomisin dirençli enterokok kolonizasyonu: vaka-kontrol çalışması

Vancomycin resistant enterococci in neonates

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Öz

Amaç: Vankomisin dirençli enterok (VDE), hastane kaynaklı ve yoğun bakım hastalarıyla ilişkili bir mikroorganizmadır. Bu çalışmanın amacı, yenidoğan yoğun bakım ünitesinde, VDE kolonizasyonuna etki eden risk faktörlerini, salgını kontrol etmeye yönelik önlemleri ve VDE kolonizasyonunda Lactobacillus reuteri'nin etkisini incelemektir. Gereç ve Yöntem: Çalışma Aralık 2012-Haziran 2013 arasında 39 vaka ve 78 kontrol ile yapılan bir vaka-kontrol çalışmasıydı. Çalışmada birincil olarak, VDE kolonizasyonuna etki eden risk faktörlerinin belirlenmesi hedeflendi. İkincil amaç da VDE eliminasyonunda Lactobacillus reuteri'nin etkisini belirlemekti. Bulgular: İkiyüz yetmiş iki yenidoğanın 39'u (%14.3) VDE ile kolonize idi. Çok değişkenli analizlere göre VDE kolonizasyonu için risk faktörleri gebelik yaşı, ortak ultrasonografi kullanımı ve metisilin dirençli antistafilokokal antibiotik kullanımı olarak bulunmuştur. VDE pozitif olan hastaların 26'sı Lactobacillus reuteri aldı. 26 hastanın 11'i (%42.3) probiyotik kullanımından sonra negatifleşti. VDE'nin negatifleşme süresi 9.61 ± 5.53 gün idi. Tartışma: Vankomisin dirençli enterokok kolonizasyonunda, düşük gebelik haftası, ultrasonografi cihazının ortak kullanılması ve metisilin dirençli antistafilokokal ilaç kullanımı bağımsız risk faktörleri idi. Ünite içinde yayılımı engellemek için etkin enfeksiyon kontrol programı uygulanmalıdır. VDE kolonizasyonunda probiotiklerin etkinliğini belirlemek için ise ileri randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

Vankomisin Dirençli Enterokok; Yenidoğan; Laktobasillus Reuteri; Probiyotik

Abstract

Aim: Vancomycin-resistant enterococcus (VRE) is a concerning microorganism among hospitalized and intensive care patients. The aim of this study was to report the outbreak characteristics, the risk factors, and the outbreak control of VRE colonization in a neonatal intensive care unit and the effect of Lactobacillus reuteri on VRE colonization. Material and Method: Thirty- nine cases and seventy-eight controls were included in the case-control study between December 2012- June 2013. The primary outcome variable was the risk factors of VRE colonization. The secondary outcome was the effect of Lactobacillus reuteri on elimination of VRE. Results: Of 272 neonates, 39 (14.3%) were colonized with VRE. Multivariate analysis suggested that gestational age, shared use of ultrasonography, and receiving anti-methicillin resistant staphylococcus aureus drugs were the risk factors of VRE colonization. Twenty-six of the 39 VRE positive patients received Lactobacillus reuteri. Eleven (42.3%) of 26 patients became negative after the use of probiotics. The clearance time of VRE was 9.61 ± 5.53 days. Discussion: Low gestational age, shared ultrasonography, and anti- methicillin resistant staphylococcus aureus drug exposure are major independent risk factors for VRE colonization. An effective infection control programme should be implemented. To determine the effectiveness of probiotics in VRE colonization, further randomized controlled trials must be conducted.

Keywords

Vancomycin-Resistant Enterococci; Neonate; Lactobacillus Reuteri; Probiotic

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Introduction

Vancomycin-resistant enterococcus (VRE) is a concerning microorganism among hospitalized and intensive care patients. The US Centers for Disease Control and Prevention reported VRE as having a 28.5% prevalence rate in intensive care units [1]. Morbidity, mortality, and hospital costs are increased due to VRE infections. The patients who are exposed to healthcare settings have an increased risk of VRE. It is already known that VRE transmission occurs primarily by ward staff members [2].

There have been inadequate studies about outbreaks of VRE in neonatal intensive care units (NICU). We described here outbreak characteristics, the risk factors for VRE colonization, and the outbreak control of VRE colonization in the NICU. We also evaluated the effect of Lactobacillus reuteri (L.reuteri) to eliminate the VRE colonization.

Material and Method

This was a retrospective, case-control study of VRE colonization at a university hospital in Istanbul, Turkey, a referral hospital providing tertiary care in NICU. Approximately 500 patients are admitted to the NICU annually.

Population

Records were obtained from the database of NICU patients for December 2012 through June 2013. The surveillance for VRE in NICU was started in December 2012 after the detection of the first patient colonized with VRE in urine culture.

Case definition

The index case was admitted from the emergency room and was born in a private hospital. He was 12 days old on admission and hospitalized for insufficient breastfeeding. He had also the phenotype of Down syndrome. VRE was detected in the urine culture which was taken on admission. Subsequently VRE surveillance was started by the Infection Control Section in the NICU. Rectal swabs were obtained from every baby on admission to the NICU and every Monday during the hospitalization period.

Case-control study

Based on the finding of the first VRE colonized case, a case-control study was initiated. Thirty-nine patients who had VRE colonization were enrolled into the study. Seventy-eight controls were randomly matched 1:2 from the NICU admission list during the same surveillance time. The controls consisted of patients whose rectal swabs were negative of VRE.

This study had two steps. First, we evaluated the risk factors of VRE colonization and second, we explored the effect of L. reuteri on elimination of VRE. The patients received L. reuteri after informed consent was obtained from the parents. We wanted to give a probiotic (L. reuteri) to all babies who were colonized with VRE but some parents refused the use of L. reuteri. Therefore, 26 of 39 patients received L. reuteri with a dose of 5 drops/day (108 cfu) after the detection of VRE until a negative result was seen.

During the study period, surface cultures from the incubators, infusion pumps, ventilators, and computer keyboards were obtained but we could not detect VRE in the environmental spaces.

Outbreak control measures

We have revised the methods of infection control as follows:

a. The staff were re-educated on hand hygiene.

b. The nursing staff were assigned to different nurse groups according to the babies who were VRE negative and VRE positive.

c. The babies who had VRE positive swabs were housed in the same room (isolation precaution).

d. All the staff who took care of these babies used gloves and gowns.

e. Extensive cleaning of the environmental surfaces was done throughout the outbreak with Minudes (Ecolab GmbH &Co. OHG) and Cavicide TM.

f. The rounds started from the babies whose swabs were negative of VRE.

g. Shared medical equipment was disinfected before being brought into the NICU.

h. Plastic bags were used to cover the ultrasonography (USG) probes.

i. Each incubator had its own equipment, such as a stethoscope and hand disinfectant.

Microbiology

Rectal swabs for VRE cultures were first inoculated onto 5% sheep-blood agar and VRE chrome agar (Salubris, Inc., Istanbul, Turkey) for 18-24 hours. Following 24 hours of incubation, a definite spot of growth or more than one colony indicates that the Enterococci may be a VRE. The catalase test was used and if the sample was catalase negative, L-pyrolidonyl beta naphthylamid (PYR) was done. Identification (E. faecalis/ E. faecium) was confirmed by the Vitek®2 (Biomeriux, France) fully automated microbiological system. Susceptibility testing was done by the same system.

Statistical analysis

Data were entered into a database using SPSS 10.0 for Windows (SPSS Inc, Chicago, USA). The X2 test and the independent samples t-test were used for categorical and continuous variables, respectively. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. A stepwise multivariate logistic regression was conducted to examine the association of risk factors controlling potential confounders. The logistic model included all variables for which a p value of <0.05 was obtained in the multivariate analysis. A p value of <0.05 was considered significant.

Results: In a retrospective approach, 272 neonates were identified in the surveillance population, of whom 39 (14.3%) were colonized with VRE. The duration of VRE colonization was 14.5±24.69 (min 0-max 150) days.

The main epidemiological characteristics of cases and controls are shown in Table 1. The mean gestational ages and weights of cases were lower than in the controls (p<0.001).

Multivariate analysis suggested that gestational age, use of shared USG, and receiving anti-methicillin-resistant staphylococcus aureus (MRSA) drugs (vancomycin-teicoplanin) were the risk factors of VRE colonization in the NICU (Table 2).

Twenty-six of the 39 VRE positive patients received L. reuteri. Eleven (42.3%) of 26 patients became negative after the use of probiotics. The clearance time of VRE was 9.61 ± 5.53 (min

5-max 26) days. Only two (15.4%) of 13 patients who did not receive L. reuteri had clearance of VRE. There was no VRE infection during the surveillance period. All VRE were identified as E. faecium. Molecular tests could not be done to show the clonal relationship due to financial difficulties.

Table 1. Characteristics of case and control patients

Feature	Cases (n=39)	Controls (n=78)	p value
Sex, male	24	51	0.68
Gestational age, weeks, mean±SD	34.18±3.82	37.65±2.02	<0.001
Gestational weight, g, mean±SD Range, g	2172.18±891.97 (510-3900)	3057.77±672.22 (1840-4440)	0.0001
Born in study hospital	35	59	0.07
Delivery mode, C/S	29	43	0.04
Respiratory distress, Mechanical ventilation	17	6	0.0001
TPN, duration, days (median)	14.42±9.70	4.92±3.20	0.002
Nasogastric tube,n	22	11	0.0001
USG, n	34	28	0.0001
Central lines (CVC, UVC)	12	6	0.002
Antimicrobial agents			
Vancomycin,n	10	0	0.0001
Teicoplanin,n	5	1	0.008
Meropenem,n	17	3	0.0001
Ampicillin,n	24	29	0.01
Duration of hospitalization	27.02±30.51	5.42±4.18	0.0001

p<0. 05 is statistically significant

Table 2. Multivariate odds ratios of potential risk factors for VRE colonization

Risk factors	OR (95%CI)	p
Gestational age	0.78 (0.62-0.97)	0.027
Anti-MRSA drug	9.17 (1.01=83.06)	0.049
USG	4.43 (1.35-14.47)	0.014

p<0.05 is statistically significant

Subtitles:
C/S: Cesarean section
CVC: Central venous catheter
MRSA: Methicillin-resistant staphylococcus aureus
USG: Ultrasonography
UVC: Umbilical venous catheter
TPN: Total parenteral nutrition
VRE: Vancomycin- resistant enterococcus

Discussion

Our study demonstrated that gestational age, anti-MRSA drug exposure, and the use of shared USG are major independent risk factors for VRE colonization. We could not determine the effect of L. reuteri on clearance of VRE statistically, but the clearance was much higher in babies who received L. reuteri. The colonization rate of VRE was 14.3% in our NICU during the seven month period. The data about the colonization rate of VRE in NICUs in Turkey is limited. A study by Akturk et al. reported it as 12% [3].

Intrahospital transfer, hemodialysis, receiving antimicrobial drugs, and malignancies have been reported as risk factors for VRE colonization. Low birth weight was previously reported as a risk factor for VRE colonization in the literature [1-4-5-6]. Tapering off vancomycin use was also mentioned as an important factor to keep an outbreak of VRE under control. Prior use of antimicrobial therapy, including vancomycin and cephalosporin, has been shown to be associated with acquisition of VRE [5-7-8)]. In a study by Askarian et al. [7], this factor was also significant and increased the risk for VRE colonization 3-fold.

It was reported that VRE colonization is more frequently seen in units where patients were hospitalized longer [3-5-9]. It is also seen more frequently in neonates requiring prolonged mechanical ventilation, use of vascular catheters, prolonged total parenteral nutrition, prolonged duration of hospitalization, and frequent exposure to antibiotics, especially anti-MRSA [3]. Askarian et al. [7], mentioned that all VRE positive patients were VRE negative on admission and 80% of these patients were colonized early in the first week of hospitalization.

Shared personnel and/or medical equipment may be responsible for the transmission of VRE [10]. It has been reported that ultrasound nebulizer use increased VRE colonization [11]. Rapid spread of VRE can be seen among neonates in NICUs [10]. Staff should be further educated to improve standard precautions and contact precautions and the appropriate selection of antibiotics should be promoted to avoid the spread of VRE in the hospital environment [5-8-10-11]. Strict infection control measures can decrease the rate of VRE colonization among neonates.

Therapeutic options for VRE infections are limited. Oral bacitracin with or without gentamycin was ineffective for the clearance of VRE [12]. It is important to consider that colonized babies have a large occult reservoir for transmission of VRE [3-13]. Surveillance studies could prevent the development of such a reservoir. In many reports it was mentioned that contact isolation, cohorting of patients, and strict and proper decontamination of surfaces may control the transmission of VRE [3-12-14].

Probiotics are the agents that have been used in several studies to improve the intestinal microbial balance [15]. There is no conclusive evidence about the effect of probiotics in eradicating or preventing VRE. There are few studies in which probiotics were used in VRE colonized patients; also, the proper dose of probiotics has not been researched in any study [16]. In our study, the sample is small so the statistical analysis is not significant. To evaluate the effectiveness of L. reuteri in elimination of VRE, large, prospective studies are needed. Also, the effective dose of probiotics should be investigated.

The present study has some limitations. First, it is a retrospective study; however, we matched the patients well according to the surveillance period. Second, the number of cases who received L. reuteri was small. If the number of cases had been higher, a significant effect of L. reuteri treatment may have been determined. Third, while the study was retrospective we could not research the effective dose of L. reuteri due to infant's weight or use of antibiotics.

There is an urgent need to restrict the unjustified use of anti-MRSA drugs as much as possible. Just as important, transmission of VRE is the best indicator for measuring the compliance with hand hygiene protocols and also for decontamination of environment. We have to evaluate the most effective infection control programs for stopping the spread of VRE in the NICU and the hospital.

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Competing interests

The authors declare that they have no competing interests.

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Asymmetric dimethylarginine and M30 concentrations in heart failure

Kalp yetmezliğinde asimetrik dimetilarjinin ve M30 düzeyleri

Heart failure, adma and M30

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Öz

Amaç: Kardiyovasküler hastalıkların gelişiminde apoptozun önemi vurgulanmaktadır. Caspase cleaved cytokeratin 18 (M30) apoptotik hücre ölümü sırasında salınan bir biyobelirteçtir. Bu çalışmada M30'un kalp yetmezliği hastalarındaki düzeyinin belirlenmesi ve M30'un asimetrik dimetilarjinin (ADMA) ile olan korelasyonun değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Çalışmaya 30 kalp yetmezliği hastası ve 30 sağlıklı kontrol dahil edildi ve çalışma populasyonundaki bireylerin serum M30 ve ADMA düzeyleri ölçüldü. Bulgular: Hastalardaki M30 (p=0.01) ve ADMA (p = 0.012) düzeyleri sağlıklı kontrol grubundan daha yüksek bulundu. Hastalarda M30 konsantrasyonu ile ADMA düzeyi arasında pozitif korelasyon saptandı (p < 0.001, r= 0.627) ancak M30 düzeyi ile N terminal pro brain natriuretic peptide (NT-pro-BNP) düzeyi arasında herhangi korelasyon saptanmadı. Tartışma: Çalışmamızdan elde edilen bulgular kalp yetmezliği hastalarında M30'un apoptotik serum biyobelirteci olabileceğini göstermektedir. Ayrıca hastalarda artan ADMA düzeyinin aktive ettiği apoptotik kaskadın kalp yetmezliğinin oluşum mekanizmasında rol oynadığı düşünülmektedir.

Anahtar Kelimeler

Asimetrik Dimetilarjinin; M30; Sitokereatin-18 Peptid; Kalp Yetmezliği; Apoptoz

Abstract

Aim: Apoptosis has been implicated in the development of various cardiovascular diseases. Caspase-cleaved cytokeratin 18 (M30) is released during apoptotic cell death. The concentrations of M30 and the correlation with asymmetric dimethylarginine (ADMA) in heart failure (HF) are not known. The objectives of this study were to determine the possible association between M30 and ADMA and the potential use of M30 as an apoptotic marker in patients with HF. Material and Method: In this study M30 and ADMA concentrations were evaluated in 30 patients with heart failure and 30 healthy control subjects. Results: Increased M30 (p=0.01) and ADMA (p = 0.012) concentrations were found in the patients and a positive correlation was determined between ADMA and M30 in the patient group (p < 0.001, r= 0.627). No correlation was determined between M30, N terminal pro brain natriuretic peptide (NT-pro-BNP), and ejection fraction. Discussion: These results demonstrate that M30 can be used as a novel apoptotic serum marker in patients with heart failure. The apoptotic cascade activated by increased ADMA concentrations can be considered to contribute to the molecular mechanism of HF.

Keywords

Asymmetric Dimethylarginine; M30; Cytokeratin-18 Peptide; Heart Failure; Apoptosis

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Introduction

Cardiovascular diseases are the leading cause of death in developing countries [1]. Heart failure (HF) is a systemic disease in which the heart cannot pump enough blood to meet the body's requirement [2]. The prevalence of the disease is on the rise, with approximately two million new cases of HF diagnosed per year worldwide [3]. Different pathophysiological mechanisms such as oxidative stress, neurohormonal changes, and inflammatory activation lead to myocyte death by promoting apoptosis, necrosis, and autophagic cell death in HF [4,5]. Cytokeratin 18 (CK-18) is an intermediate filament of epithelial cells. CK 18 fragments such as caspase cleaved cytokeratin 18 (M30) are released into the extracellular space due to caspase digestion during apoptosis and serve as markers of apoptosis [6]. The elevation of plasma M30 level is involved in different diseases including colon cancer [7], sepsis [8], and chronic hepatitis B [9]. To the best of our knowledge, no previous study has investigated the changes of M30 concentrations in heart failure.

Asymmetric dimethylarginine (ADMA) is one of three circulating endogenous analogues of L-arginine derived by methylation of arginine residues catalyzed by a family of proteins known as protein arginine methyltransferases [10]. ADMA is an endogenous competitive inhibitor of NO synthase and is eliminated from the body by a combination of renal excretion and metabolism by the dimethylarginine dimethylaminohydrolase (DDAH) enzymes [10,11]. Increased levels of ADMA have been found to be associated with atherosclerosis [12], coronary artery disease [9], peripheral arterial occlusive disease, hypertension [13], and HF [14]. However, the role of ADMA in heart failure has not been well investigated.

The hypothesis of our study is that increased serum ADMA concentrations may trigger the apoptotic process in HF. Therefore, an assessment was made of the ADMA and M30 concentrations and the possible association between these biomarkers in patients with HF. The potential use of M30 as an apoptotic marker in patients with HF was also investigated. This study provided an important opportunity to advance the understanding of the role of ADMA in HF.

Material and Method

Patients and controls

The study included 30 consecutive patients [17 males and 13 females; mean age: 68 ± 12 years (range, 24-83 years)] with chronic HF with reduced ejection fraction (HFrEF) who were hospitalized for acute decompensated HF and 30 healthy control subjects [10 males and 20 females; mean age: 65 ± 13 years (range, 28-78 years)]. HF had been diagnosed in the patients group at least 12 months previously. Data was collected from the patients' records in the Cumhuriyet University Medical Faculty Hospital laboratory information system, including age, gender, levels of CK-MB, triglyceride (TG), total cholesterol (TCHOL), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), N terminal pro brain natriuretic peptide (NT-pro-BNP), prothrombin time (PT), activated partial thrombin time (aPTT), and international normalized ratio (INR). These laboratory values were taken within the admission period. Patients with moderate to severe aortic stenosis, anticipated cardiac transplantation, chronic dialysis, malignancy, high-output HF, age <18 years, or concomitant use of an investigational product or device were excluded from study. For the control group, the exclusion criteria included clinical suspicion of infections (body temperature out of the range 36°C - 38 °C, heart rate > 90 bpm, respiratory rate > 20/minute, white blood count > 12 x 103 mcL or < 4 x 103 mcL), presence of abnormal ejection fraction, liver disease, kidney disease, rheumatic disease, malignancy, pregnancy, and smoking. The HF patients were referred by physicians from Cumhuriyet University Medical Faculty, Department of Cardiology. Overnight fasting blood samples were collected from all participants into red top tubes (Becton Dickinson, UK) during the admission. The serum samples were allowed to clot before centrifugation. After centrifugation at 4°C for 15 minutes at 3500 rpm, the serum was aliquoted and immediately frozen at -20°C. The study protocol was approved by the Ethics Committee of Cumhuriyet University Medical Faculty (Approval number: 2016-04/06).

Biochemical analysis

Caspase cleaved cytokeratin 18 and ADMA concentrations were determined using commercially available ELISA kits. The Complete Blood Count analysis was performed using a hematology system (Mindray BC 6800, China). CK-MB, TG, TCHOL, HDL-C, and LDL-C concentrations were determined by the enzymatic colorimetric method (Beckman Coulter AU5800, USA). Serum NT-pro-BNP was measured using immunoassay (AQT90 flex Radiomater, Denmark). PT and aPTT concentrations were determined using a coagulation system (ACL TOP 700, Italy). Troponın I values were determined using immunochemical method (Beckman Coulter AU5800, USA). Estimated glomerular filtration rate (eGFR) values were calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Echocardiographic examination

Echocardiographic examinations were performed by experienced operators. Patients were imaged in the left lateral decubitus position with commercially available systems (Vivid systems, GE Healthcare, Wauwatosa, USA). Left ventricular dimensions, volumes, and ejection fraction (EF) [by modified Simpson's method] were measured according to the European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE) recommendations [15]. LV diastolic functions were evaluated according to EAE/ASE standards [16]. The diagnoses of HFrEF were made according to guidelines [17].

Statistical analysis

Sample size was determined as 30 observations for each group, based on α=0.05and β=0.10. The power of the actual performed test was calculated as 90%. Analyses were conducted using PASS 11.0 (Power Analysis Statistical System) software. The Shapiro-Wilk test was used to determine the distribution characteristics of the variables. The Student t test and Mann-Whitney U test were applied to compare the differences of the parametric and nonparametric variables between the groups, respectively. Spearman correlation coefficients were calculated to evaluate the relationship between M30, ADMA, NT-pro BNP,

ejection fraction (EF), white blood cell count, eGFR, and creatinine. The results were expressed as mean ± SD and median (25th – 75th percentile). A value of $p < 0.05$ was considered statistically significant.

Results

A summary of the laboratory parameters of the patient and control groups is shown in Table 1. Mean NT-pro BNP, troponin I, and CK-MB levels were 2110 (1088.75 – 8095.50) pg/mL, 0.03 (0.01-0.04) ng/mL, and 18.30 (6.67 – 24.25) U/L in the patient group, respectively. The eGFR values were <60 ml/min/1,73 m2 in 9 patients. The median M30 levels were 178.42 (147.2400 to 222.15) and 236.84 (185.78 – 278.51) IU/L in the control and patient groups, respectively (p = 0.01). The median ADMA levels were 14.72 ± 4.67 and 20.03 ± 10.23 µg/L in the control and patient groups, respectively (p = 0.012). The results were given within a 95% confidence interval (CI). A positive correlation was determined between M30 and ADMA in the patient group ($p < 0.001$, r= 0.627) (Figure 1). No statistically significant correlation was determined between M30, creatinine (p = 0.327, r = - 0.18), eGFR (p = 0.851, r = - 0.03), NT-pro-BNP (p= 0.404, r= 0.157), troponin I (p = 0.638, r = 0.241), WBC (p = 0.805, r = 0.04), and ejection fraction (EF) (p= 0.861, r= 0.032). No statistically significant correlation was determined between ADMA, creatinine (p = 0.710, r = -0.07), WBC (p = 0.690, r = 0.07), EF (p = 0.144, r= 0.322), eGFR (p = 0.780, r = -0.053), NT- pro-BNP (p = 0.775, r = -0.054), and troponin I (p = 0.341, r = 0.064) in patients. The clinical features of the patients are given in Table 2.

Discussion

Recent evidence suggests that apoptosis is involved at multiple points in HF, although the molecular biology and biochemistry of the apoptotic death machinery are far from being completely resolved in HF [5]. In this study, M30 concentrations were found to be higher in patients than in the healthy control group. There have been few studies conducted on the concentrations of M30 in cardiovascular disease [18-19]. It has been revealed that cardiac lipofuscin-laden lysosomes obtained from patients with ischemic, congestive, and hypertrophic cardiomyopathy contain M30 [19]. Adlbrecht et al. [18] reported elevated levels of M30 in patients with acute myocardial infarction. Recent evidence has suggested that caspases, which are a group of cysteine proteases, play a crucial role in the apoptosis of myocyte and the formation of M30 and thereby have a crucial role in HF [20,21]. In previous research of sheep fitted with variable aortic constriction devices, it was indicated that activated cardiomyocyte caspase enzymes play an important role during the transition to heart failure [20]. Merkle et al. [21] demonstrated the upregulation of myocardial caspase-1 in a murine heart failure model. In a study by Narula J et al. [22], increased caspase 3 activation was reported in patients with heart failure. The reason for increased M30 concentrations can be assumed to be associated with increased caspases activation. M30 can therefore be considered a biomarker in the monitoring of myocardial damage associated with apoptosis in patients with heart failure.

In the present study, no associations were found between the concentrations of NT-pro-BNP, EF, troponin I, and M30. Natri-

Table 1. Laboratory parameters of patients and controls

Characteristics	Patients (n: 30)	Control (n:30)	P value
AST (IU/L)	25.68 ± 9.79	23.97 ± 5.94	0.556
ALT (IU/L)	22 ± 14.26	22.97 ± 14.02	0.360
HDL-C (mg/dL)	34.72 ± 10.16	44.89 ± 9.34	< 0.001
LDL-C (mg/dL)	96.66 ± 32.21	86.20 ± 15.15	0.116
TCHOL (mg/dL)	157.10 ± 49.50	140.55 ± 20.82	0.100
TG (mg/dL)	108.60 ± 49.17	99.55 ± 40.58	0.445
eGFR (ml/min/1,73 m2)	73.41 ± 30.49	99 ± 9.57	0.014
Creatinine (mg/dL)	1.08 ± 0.85	0.93 ± 0.17	0.457
PT (sec)	11.78 ± 0.69	11.3 ± 0.32	0.392
aPTT (sec)	29 ± 2.81	31 ± 1.25	0.283
INR	1.02 ± 0.5	1.03 ± 0.2	0.427
Na (mEq/L)	134.50 ± 4.50	136 ± 2	0.642
K (mEq/L)	3.79 ± 0.65	4.07 ± 0.30	0.846
WBC (10^3 mcL)	7.70 ± 1.65	8.10 ± 1.5	0.153

aPTT: activated partial thromboplastin time, ALT: Alanin aminotransferase, AST: Aspartat aminotransferase, HDL-C: High density lipoprotein cholesterol, INR: International normalized ratio, K: Potassium, LDL-C: Low density lipoprotein cholesterol, Na: Sodium, PT: prothrombin time, TCHOL: total cholesterol, TG: Triglyceride TSH: Thyroid stimulant hormone, WBC: White blood cell. Results were given as mean ± SD and with 95% confidence intervals.

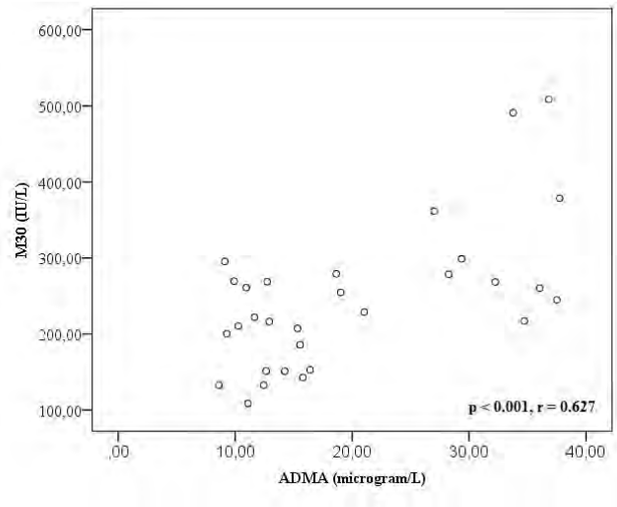


Figure 1. A scatterplot matrix with Pearson correlation to demonstrate the association between M30 and ADMA

Table 2. Clinical features of heart failure patients (n=30)

Clinical features	Values
NYHA functional class III/IV	24/6
Diabetes mellitus (yes/no)	11/19
Hypertension (yes/no)	22/8
Hyperlipidemia (yes/no)	6/24
Obesity (yes/no)	11/19
COPD (yes/no)	7/23
CEID (yes/no)	9/21
Chronic kidney disease (yes/no)	6/24
Ischemic/non-ischemic etiology	12/18
SPAP (mm/Hg)	39 ± 16
EF (%)	27 ± 3
Concomitant right ventricular systolic dysfunction (yes/no)	10/20

EF: Ejection fraction, CEID: Cardiac implantable electrical devices, COPD: Chronic obstructive pulmonary disease, SPAP: Systolic pulmonary artery pressure, TR: Tricuspid regurgitation, NYHA: New York Heart Association

uretic peptides including BNP and NT-pro-BNP, an amino-terminal propeptide equivalent to BNP, are reliable biomarkers for the diagnosis, prognosis determination, and treatment of heart failure [23]. From the results of the current study, it was concluded that M30 may not be used for the diagnosis and prognosis determination of HF as there was no correlation between M30 and NT-pro-BNP and EF. However, caution must be applied in the evaluation of this conclusion because of the low sample size. Further studies are required with larger sample sizes to evaluate the diagnostic performance of M30 in patients with HF.

Although an association has been reported in literature between ADMA concentrations and heart failure [14], the role of ADMA has not been completely defined. The ADMA concentrations were found to be higher in the patients than in the control group in the present study. Previous studies have reported elevated ADMA concentrations in patients with heart failure [24-27]. The findings of the current study are in accordance with these previous studies. A positive correlation between ADMA and M30 concentrations was determined in the current study. It is a well-known fact that there is an association between ADMA and apoptosis. Different molecular mechanisms such as the p38MAPK-dependent signaling pathway, accumulation of cytochrome c, and activation of endoplasmic reticulum stress have been described in ADMA-related apoptotic processes in different conditions [22,28,29]. The current study results suggest that increased concentrations of ADMA trigger the caspases activation in HF. Small sample size was major limitation of our study.

In conclusion, M30 can be used as an apoptotic serum marker in patients with heart failure. In addition, the activated apoptotic cascade caused by increased ADMA concentrations can contribute to the molecular mechanism of the formation and progression of HF. Therefore, further studies are warranted with respect to the potential therapeutic utility of the regulating of ADMA concentrations and caspase inhibition with potential DDAH activity and caspase inhibitors and its improved delivery system to the heart in patients with HF.

Competing interests

The authors declare that they have no competing interests.

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Evaluation of validity-reliability of Turkish version of the household food security survey short form

Hane halkı besine ulaşılabilirlik ölçeğinin Türkçe geçerlilik ve güvenilirliğinin değerlendirilmesi

Turkish version of the household food security survey

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Öz

Amaç: Çalışmada, Hane Halkı Besine Ulaşılabilirlik Ölçeği-Kısa Formu'nun Türkçe sürümünün kültürel uyumu ile birlikte geçerlilik ve güvenilirlik çalışmasını yapmak ve Mevsimlik Tarım İşçileri'nin besine ulaşabilme sorununun boyutunu yerle halkla karşılaştırmak amaçlandı. Gereç ve Yöntem: Çalışma, 2012 yılı tarım mevsiminde yürütülen metodolojik bir araştırmadır. Çalışma grubu, Eskişehir ili Mevsimlik Tarım İşçileri'nden ve onların yaşadığı kamp bölgelerine en yakın kırsal bölgedeki yerleşik halktan oluştu. Kullanılan anket formunun birinci bölümü hane katılımcısının sosyo-demografik özelliklerini, ikinci bölüm ise Hane Halkı Besine Ulaşılabilirlik Ölçeği-Kısa Formu'nu içermekteydi. Çalışmada yapı geçerliliği için açımlayıcı faktör analizi, iç ölçüt geçerliliği için Mevsimlik Tarım İşçileri ile yerel halk karşılaştırıldı. Güvenilirlik analizleri için madde toplam korelasyon ve Cronbach alpha katsayıları hesaplandı. Bulgular: Açımlayıcı faktör analizi sonuçlarına göre maddeler tek faktör altında toplanmakta olup, varyansın %68.38'ini açıklamaktadır. Maddelerin faktör yükleri 0.82 ila 0.90 arasında değişmekteydi. Toplam puanın %27'lik alt ve üst gruplar arasında fark anlamlı olup (p<0.001), Mevsimlik Tarım İşçileri'nin aldıkları puan yerel halkın puanından daha yüksekti (p<0.001). Ölçekte yer alan maddelerin madde-toplam korelasyon katsayılarının 0.65 ile 0.84 arasında değişmekte olup içtutarlılık katsayısı 0.904 idi. Mevsimlik Tarım İşçileri'nin hanelerinden %90.4'ü besine ulaşmada riskli iken yerleşik olarak yaşayan hanelerin %36.6'sının besine ulaşmada riskli olduğu saptandı (p<0.001). Tartışma: Hane Halkı Besine Ulaşılabilirlik Ölçeği-Kısa Formu'nun Türkçe uyarlaması Türk toplumunda uygulanabilir, besine ulaşmayı değerlendiren geçerli ve güvenilir bir ölçektir. Mevsimlik Tarım İşçileri'nde besine ulaşılabilirlik önemli bir sorundur.

Anahtar Kelimeler

Hane Halkı Besine Ulaşılabilirlik Ölçeği-Kısa Formu; Mevsimlik Tarım İşçileri; Geçerlilik

Abstract

Aim: This study aimed to assess the validity and reliability of the Turkish version of the Household Food Security Survey Module-Short Form Scale with cultural adaptation and to compare the size of the problem of food accessibility of seasonal farmworkers with locals. Material and Method: This study is a methodological research executed in the 2012 agricultural season. The study group was composed of seasonal farmworkers in Eskisehir and residents located in rural areas next to the camp sites of seasonal farmworkers. The first part of the survey included socio-demographic characteristics of the household and the second part contained the Short Form of Household Food Security Survey Module. Exploratory factor analysis was conducted for construct validity and for internal criterion validity scores of seasonal farmworkers and locals. For reliability analysis, item total correlation and Cronbach alpha coefficients were measured. Results: Results of exploratory factor analysis indicated that the items are collected under one factor and explain 68.38% of the variance. Factor loadings of the items varied between 0.82 and 0.90. The difference between the upper and lower groups was significant (p <0.001), and the score of seasonal farmworkers was higher than that of the local population (p <0.001). The internal consistency coefficient was 0.904. It was found that 90.4% of the households of seasonal farmworkers were at risk of accessing food, while 36.6% of the local residents were at risk of accessing food (p <0.001). Discussion: The Turkish version of the Household Food Security Survey Module-Short Form is a valid and reliable measure evaluating nutritional access that can be applied in Turkish society. Food accessibility of seasonal farmworkers is a critical problem.

Keywords

Household Food Security Survey Module-Short Form; Seasonal Agricultural Labors; Validity

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Introduction

Food accessibility is defined as "convenient, accessible, and affordable food for all people at all times" [1]. Food safety is defined as accessibility of people to safe, adequate, and nutritious food meeting nutritional requirements and food choices in order for people to live active and healthy lives, and containing three key elements related to availability [2,3]. Food accessibility, one of the basic elements of food safety, is a critical human problem and its consequence is also an important public health problem.

A report issued by the United States (US) Department of Agriculture found that 11.1% of households had risk of accessing food. It was reported that in communities known as being at risk, such as those of agricultural laborers, the risk of accessing food is seven times higher than that of the normal population [4]. The Global Food Insecurity report published by the World Health Organization (WHO), World Food Program, and the International Agricultural Development Fund reported that 870 million people (12.5% of the world population and 14.9% of the population in developing countries) were undernourished and could not reach the energy needed [5]. Nutritional deficiencies and microelement deficiencies contribute significantly to the global disease burden. In addition to the increased incidence and severity of infectious diseases, deficiencies also play roles in increasing chronic diseases, such as food insufficiency, obesity, diabetes, and cardiovascular diseases. Consequently, they increase the economic burden on the health system [6].

Many organizations and countries are striving to augment food accessibility and prevent hunger. In order for these efforts to be successful, there is a need to identify the groups experiencing food accessibility and hunger problems. Seasonal Farmworkers (SFW) ranks first in Turkey among risk groups with food accessibility and hunger problems. SFW have food accessibility problems because of difficult working and living conditions.

A low cost easy-to-use measurement instrument to evaluate food accessibility can be a guide for governments and organizations by demonstrating both where and how much of a risk exists [7]. In this context, the U.S. Household Food Security Survey Module (HFSSM) developed in the US in 1995 with 18 items, contains metrics for the availability of food to households [8]. In 1999, Blumberg et al. developed a shorter and faster-to-administer form by selecting 6 items from these 18 items [9]. The Household Food Security Survey Module- Short Form (HFSSM-SF) assesses food security according to whether it is accompanied by hunger or not.

In this study, since there is not yet a Turkish version of HFSSM-SF, we primarily aimed to implement validity and reliability research with cultural adapation and to evaluate the size of the problem of SFW food security compared with that of local residents.

Material and Method

Study Group

This study is a methodological research applied in the 2012 agricultural season that aimed to implement validity and reliability analysis of the HFSSM-SF in Turkey. In order to implement the study, approval of the ethics commitee was obtained. Verbal approvals of the participants were obtained. In addition, necessary permissions were received from Provincial Public Health Directorate, local administrative and health managers, and informal managers of the SFW campground.

This study was executed with SFW settled in the rural region of Eskişehir (located in the Central Anatolian Region of Turkey) and local residents living in rural areas close to the camping zones. SFW were camping and settling next to their working areas. Tents were built on the ground and most were covered with nylon or tarpaulins. Only 19% of the tents had electricity accessibility. Many tents had no space for a kitchen, bedroom, toilet, or bathroom. There was no water supply in the tents and drinking water needed to be carried from a common tusk to the tents. People living in tents were facing many health problems due to their living conditions.

In line with the purpose of the study, since there were no records of SFW, 52 households from the largest camp site and 186 households from the nearest settlement half-rural area (Alpu), totaling 238 households, were randomly selected and included in the research. Field work of the study was conducted by a research team and intern doctors. All the researchers took theoretical training before the field study began. Each tent in the camp site was considered a household and they were visited by researchers one by one. When the head of the household was not in the tent, a person aged 18 or over was considered as householder. After explaining the purpose of the study, the questionnaire form was applied by the researchers using a face-to-face interview technique. SFW who did not know Turkish were interviewed via people they selected who knew Turkish. Sampled participants from the Alpu district center were also visited in their houses and the same questionnaire form was applied through the face-to-face interview technique by the same research group.

Data Collection Tools

The questionnaire used in the survey contained two parts. The first part included socio-demographic characteristics of the participants and the second part embodied HFSSM-SF. HFSSM-SF consisted of 6 items questioning sufficiency of food intake in the previous 12 months, attainment of balanced meals, and occurrence of skipping meals despite being hungry because of economic deficiency [9]. Participants were asked to answer the questions from the options: 'Often True', 'Sometimes True', 'Never True', 'Do not know' or 'Refused' for items 1, 2 and 4 and 'Yes', 'No' or ' I don't know' for items 3, 5, and 6. If the participant marked 'Often True' for the items 1, 2 , 4 and 'Yes' for the items '3, 5, and 6', it was scored 1 point and for other options it was scored '0'. The score from the scale ranged from 0 to 6. If the score was '0' it was interpreted as 'high food security'; if the score was '1', it was interpreted as 'marginal food security (there was a risk for accessibility to food)'; if the score was '2-4' it was interpreted as 'low food security (no access to food, but this situation was not accompanied by hunger)'; and if the score was '5-6' it was interpreted as 'very low food security (food was not attainable and this was accompanied by moderate hunger)'. Interpretations of the scores collected from the HFSSM-SF are in Table 1.

Table 1. Meaning of the scores taken from HHFSSM-SF

HHBUÖ-KF Score	Meaning
0 point	High food security
1 point	Marginal food security (there is risk to access food)
2-4 point	Low food security (not accessing food but not accompanied by hunger)
5-6 point	Very low food security (not attaining food and accompanied by moderate hunger)

Validity Analysis

In order to provide the language validity of the scale, first the scale items were translated from English to Turkish, and later by different people they were translated from Turkish to English again. In addition, linguistic and cultural adaptation was ensured to avoid changes in meaning. In terms of scope validity, expert opinions were received from seven people and the suggestions were incorporated into the revised form. Later, the scale items were pre-tested with 15 people and all items appeared to be clear and understandable.

In order to test construct concept validity, Exploratory Factor Analysis (EFA) was implemented. In order to test the internal criterion validity, by structuring the hypothesis that HFSSM-SF scores of agricultural labors were higher than the resident locals, scores obtained from the scale were compared. Moreover, the scores were ranked and observed as to whether there was a difference between the medians of the highest three-tier slice and the lowest three-tier slice.

Reliability Analysis

For reliability analysis of HFSSM-SF descriptive statistics of the items and for total correlation coefficient, Pearson Moments Multiples were determined. Items with correlation coefficients higher than 0.20 were considered reliable. Cronbach alpha coefficient was calculated in order to determine the internal consistency.

Evaluation of data

Data collected from the scale was evaluated via IBM SPSS (version 20) package programme. Descriptive statistics were utilized for demographic characteristics of the study group. Suitability of the scores taken from HFSSM-SF to normal distribution was observed via Shapiro-Wilk Test. Non-parametric tests were used because of the absence of normal dispersion. In the comparison of the two groups, Mann Whitney U was used for the quantitative data and Chi-square analysis was used for the qualitative data.

Results

The study was executed with 238 households composed of 56 SFW and 186 locals. In the SFW group, the average age of the people that provided information was higher than in the local group. In addition, the average number of people and children per household was higher in the SFW group. The general characteristics of participant households are provided in Table 2.

Validity Analysis Results of HFSSM-SF

The construct validity of the HFSSM-SF was examined by EFA method. Kaiser-Meyer-Olkin (KMO) coefficient was 0.837 and

Table 2. General Characteristics of participant Households

Properties	SFW n=52	Local residents n=186	Statistical Analysis p
Age of the person received information) Avarage (SD)	37.9 (10.4)	33.3 (6.2)	< 0.001
Average number of people in the house Median (min-max)	8.1 (2.0-18.0)	4.5 (3.0-9.0)	< 0.001
Number of children Median (min-max)	6.0 (1.0-13.0)	2.0 (1.6-6.0)	< 0.001

Barlett's Test was observed to be significant (X2 =1201.73, p<0.001). The KMO coefficient and Barlett'sTest indicated that the data and sample size was appropriate for the selected analysis. When the structure of the scale was examined using the EFA method, only 1 factor was identified with an eigenvalue higher than 1. The eigenvalue of this factor was 3.69 and accounted for 68.38% of the variance. Factor loads ranged from 0.75 to 0.90. Factor loads are shown in Table 3.

Table 3. Factor loads of HHFSSM-SF, item total correlations and Cronbach alpha coefficients when the item is removed

HHFSSM-SF	Factor Loads	Item total Correlation	Scale Cronbach Alpha Values when the item is removed
Insufficiency of nutrition intaken	0.90	0.77	0.88
Not accessing balanced meal	0.87	0.65	0.90
Reducing size of the meal because of economic inadequacy	0.84	0.84	0.87
Frequency of reducing size of meal because of economic inadequacy	0.82	0.79	0.88
Eating less because of economic inadequacy)	0.78	0.73	0.88
Could not eat even he/she is hungry because of economic inadequacy	0.75	0.68	0.89
Explained variances: %68.38()	Cronbach alfa:0.904		

In order to assess the internal criterion validity of the scale, scores of households from scale items were ranged from low to high. The distribution was found to be significant (z = 11.476, p <0.001), with 27% subgroup median (min-max) value 0 (0-0) and 27% upper group mean value 5 (2-6).

The hypothesis that HFSSM-SF scores of SFW would be found to be higher than the scores of the resident households was refuted. While the median (min-max) value of SFW from the scale was 5 (0-6), the median value of the locals was determined to be 0 (0-6). HFSSM-SF scores of SFW were found to be higher than local residents (z=9.081, p<0.001).

Reliability Analysis Results of HFSSM-SF

One of the reliability indicators was corrected item-total correlation coefficient. According to existing results, item-total correlation coefficient of the items in the scale varied between 0.65 and 0.84. For a valid and reliable scale, the lower limit of alpha coefficient was considered to be 0.70 [10]. When any of the items in the scale were excluded, it was determined that the Cronbach alpha coefficient did not change significantly.

The Cronbach's alpha coefficient of HFSSM-SF, consisting of six items, was 0.904; in the SFW group it was 0.883 and in the local residents group it was 0.849. Results of reliability analysis of HFSSM-SF are reported in Table 3.

Comparison of Scale Results in the Study Groups

The distribution of the responses of the study groups to HFSSM-SF items is indicated in Table 4.

While 90.4% of SFW were at risk of access to food, 36.6% of the local residents were found to be at risk of accessing food (p <0.001).

Table 4. Distribution of answers that study groups gave to HHFSSM-SF items

HHBUÖ-KF	SFW n (%)	Local residents (%)	Statistical Analysis p
Insuficiency of nutrition intaken	39 (75.0)	39 (21.0)	<0.001
Not accessing balanced meal	44 (84.6)	47 (25.3)	<0.001
Reducing size of the meal because of economic inadequacy	33 (63.5)	29(15.6)	<0.001
Frequency of reducing size of meal because of economic inadequacy	30 (57.7)	18 (9.7)	<0.001
Eating less because of economic inadequacy	35 (67.3)	37 (19.9)	<0.001
Could not eat even he/she is hungry because of economic inadequacy	26 (50.0)	16 (8.6)	<0.001

Discussion

Although food insecurity is widespread in developing countries, who these people are and to what extent they are affected is unclear. In order to determine the frequency and extent of food insecurity, reliable and valid measurement tools are required. After a comprehensive literature review it was observed that there was no scale utilized in community-based studies in Turkey; therefore we aimed to undertake reliablity and validity studies of the HFSSM-SF.

In the validity analysis of EFA, a one-dimensional structure was established and total variance of the one-dimensional structure was revealed to be 68.38%. It is advantageous that the variance is above 50%. The higher the variance, the better the measurement can be made. Explanation of 30% of total variance in scale adaptation studies and factor loads of scale items of at least 0.40 were reported to be an adequate value [11]. Findings suggests that the Turkish version of the HFSSM-SF is similar to the structure of the original scale.

The scores obtained for criterion validity are intended to distinguish the measured feature with its characteristics whether to possess the feature demanded or not [12]. For criterion validity, the study was evaluated in two different ways with the internal criterion. First, the difference between the lower and upper group point averages were observed to be significant (p <0.001). Therefore, the Turkish version of HFSSM-SF was demonstrated to be capable of distinguishing between those who have the studied feature and those who do not.

Corrected item total correlation coefficient was calculated to determine contribution of items to conceptual structure of the scale and to identify whether the scale measures the desired feature. Items having corrected item total score correlation greater than 0.40 are considered highly distinctive, coefficients between 0.21 and 0.40 are considered to be distinctive at the moderate/acceptable level, and coefficients lower than 0.20 are identified as low level distinctive [13]. Correlation coefficient of every item in the scale was higher than 0.65 and the items all had good levels of distinctiveness.

At a reliable scale, the Cronbach alpha value is required to be at least 0.70 [10]. In this study, the Cronbach alpha coefficient varied between 0.87-0.90 among the study groups and it was 0.90 in the whole group. When any of the items in the scale were removed, it was observed that the Cronbach alpha coefficient did not increase significantly.

When the responses of the study groups to the items of the HFSSM-SF were evaluated, it was observed that SFW were receiving insufficient food compared with local residents, they were unable to access a balanced meal, and they reduced the size of their meal because of economic inadequacy. One of the most dramatic results of the study is that half of the SFW could not eat when they were hungry because of their economic inadequacies. When these results were evaluated, it was determined that the SFW were at risk for access to food compared with the local people and, as a terrifying consequence of this, they were hungry. Studies conducted in the US also asserted that SFW were found to be riskier in terms of nutrient availability than local populations in line with the results of the present study [14,15]. There are many studies in the literature reporting that SFW are risky groups in terms of nutritional accessibility and that they are starving to various degrees [16-18].

This study has similar results with other studies in the literature. SFW were observed to be a risky group in terms of nutritional accessibility in our country similar to the world population. Especially, this group's level of hunger indicates the seriousness of the problem. Therefore more comprehensive solutions need to be implemented rather than local solutions in order for this problem to be solved.

This is the first study of the validity and reliability of the HFSSM-SF in Turkey. A new scale to assess household accessibility, particularly in disadvantaged groups, has been added to the literature. Communication difficulties caused by language problems of SFW and the impossibility of performing test-retest for the reliability of the scale due to working hours are significant limitations.

Consequently, in light of the analysis conducted, the Turkish version of the HFSSM-SF is a valid, reliable, and applicable scale evaluating food security in society. Moreover, using this scale demostrated that food accessibility of SFW is extremely inadequate. In addition, urgent solutions at a national level are needed to address this problem. Furthermore, by using this scale, research conducted with different large groups will be beneficial and the results of these studies will contribute to scale development.

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Competing interests

The authors declare that they have no competing interests.

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Do ligament-bone attachment angles have any effect on patellar chondromalacia?

Ligament-kemik yapışma açılarının patellar kondromalazi gelişimi üzerine etkisi var mı?

Ligament-bone attachment angles

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Öz

Amaç: Bizim bu çalışmadaki amacımız patella çevresindeki bağların patella ve tibiaya yapışma açıları ile patellar kondromalazi arasındaki ilişkiyi araştırmaktır. Gereç ve Yöntem: Rastgele olarak seçilen 30'u patellar kondromalazili ve 30'u kondromalazi bulunmayan toplam 60 diz MR görüntülemesi çalışmaya dahil edildi. Patellar kondromalazi bulunup bulunmadığının tesbitinde yağ baskılı T2 ağırlıklı fast spin-echo görüntüleri kullanıldı. Qudriseps tendonu ile patella (Q-P), patella ile patellar tendon (P-PT) ve patellar tendon ile tibia (PT-T) arasındaki yapışma açıları ölçüldü. Bulgular: Hastaların ortalama yaşı kondromalazili grupta 45,1 ± 14,9; kondromalazisiz grupta ise 37,2 ± 11,9 olarak hesaplandı. Ortalama Q-P açısı kondromalazili grupta 42,4 ± 9,2 derece; kondromalazisiz grupta ise 46,1 ± 6,9 derece olarak hesaplandı (p=0.083). Ortalama P-PT açısı kondromalazili grupta 113,9 ± 11,1 derece; kondromalazisiz grupta ise 112,9 ± 11,7 derece olarak hesaplandı (p=0.727). Ortalama PT-T açısı kondromalazili grupta 29,9 ± 5,9 derece; kondromalazisiz grupta ise 28,9 ± 7,6 derece olarak hesaplandı (p=0.608). Tartışma: Bu çalışma patella çevresindeki bağların patella ve tibiaya yapışma açıları ile patellar kondromalazi gelişimi arasında ilişki olmadığı ortaya koymuştur.

Anahtar Kelimeler

Kondromalazi; Manyetik Rezonans Görüntüleme; Diz; Patella

Abstract

Aim: The aim of this study was to evaluate the relationship between the ligament to bone attachments and patellar chondromalacia. Material and Method: This study included a total of 60 knee magnetic resonance imagings of 60 patients (30 with patellar chondromalacia, and 30 without patellar chondromalacia) which were selected randomly from our hospital's picture archiving and communication system records. T2 weighted fast spin-echo images with fat-saturation were used to detect the presence or absence of chondromalacia patella. The angles between quadriceps tendon and patella (Q-P), patella and patellar tendon (P-PT), and patellar tendon and tibia (PT-T) were measured separately. Results: The mean ages of the patients were 45.1 ± 14.9 for the patellar chondromalacia group and 37.2 ± 11.9 for the non-chondromalacia group. The mean value of the Q-P angle was 42.4 ± 9.2 degrees in the chondromacia group and 46.1 ± 6.9 degrees in the non-chondromalacia group (p=0.083). The mean value of the P-PT angle was 113.9 ± 11.1 degrees in the chondromacia group and 112.9 ± 11.7 degrees in the non-chondromalacia group (p=0.727). Finally, the mean value of the PT-T angle was 29.9 ± 5.9 degrees in the chondromacia group and 28.9 ± 7.6 degrees in the non-chondromalacia group (p=0.608). Discussion: This is the first study that focused on the ligament-bone attachments around the patella. This study revealed that there is no relationship between the attachment angles of the ligamentous structures around the patella and the presence of chondromalacia.

Keywords

Chondromalacia; Magnetic Resonance Imaging; Knee; Patella

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Introduction

Chondromalacia of the patella has a wide course starting from the softening of articular cartilage to total destruction of the cartilage. It is the most frequently diagnosed cartilage lesion in the knee joint. Although chondromalacia of the patella is a common phenomenon, its etiology is unclear. Many factors such as mechanical factors, body mass index, infrapatellar fat pad volume, and proteoglycan depletion have been implicated [1-3]. The mechanism is considered to be the breakdown of articular cartilage and damage to superficial chondrocytes resulting in release of proteolytic lysosomal enzymes [4].

The attachment of quadriceps to patella, of patellar tendon to patella, and of patellar tendon to tibia differ from person to person. The aim of this study was to evaluate the relationship between the ligament to bone attachments and patellar chondromalacia.

Material and Method

This retrospective study was approved by the Institutional Review Board. This study included a total of 60 knee magnetic resonance imagings (MRI) of 60 patients (30 with patellar chondromalacia and 30 without patellar chondromalacia) which were selected randomly from our hospital's picture archiving and communication system (PACS) records. All MRIs were obtained with a 1.5-T MR (Gyroscan Intera, Philips, Best, The Netherlands) system equipped with a QD knee coil. Patients with patella alta, patella baja, patellar tilt, patellar subluxation, previous knee surgery, and effusion were excluded. T2 weighted fast spin-echo images with fat-saturation were used to detect the presence or absence of chondromalacia patella. The presence of surface irregularity and subtle signal changes, areas of hyperintensity, subchondral reactive bone marrow oedema pattern, and secondary changes of osteoarthritis at the patella in MRI were accepted as patellar chondromalacia. The angles between quadriceps tendon and patella (Q-P), patella and patellar tendon (P-PT), and patellar tendon and tibia (PT-T) were measured separately. All the measurements were done digitally by one experienced orthopaedic surgeon at two different times, and the mean values were calculated.

Statistical Analyses

The IBM SPSS statistical software package (SPSS, version 23 for Windows; SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. The distribution of the data was evaluated with the Kolmogorov Smirnov test. The independent samples t-test was used for the statistical comparison of the normally-distributed parameters. Correlation between measurements was analyzed with interclass correlation analysis. All data were expressed as mean value ± standard deviation. A value of $p < 0.05$ was considered significant in all statistical analyses.

Results

Of the randomly chosen 30 patients with patellar chondromalacia, 16 were males and 14 were females. Among the 30 patients without patellar chondromalacia, 11 were males and 19 were females. The mean age of the patients was 45.1 ± 14.9 for the patellar chondromalacia group and 37.2 ± 11.9 for the non-chondromalacia group. There was no statistically significant difference between the groups in terms of age (p=0.096). The mean value of the Q-P angle was 42.4 ± 9.2 degrees in the chondromacia group and 46.1 ± 6.9 degrees in the non-chondromalacia group. There was no significant difference between the groups (p=0.083). The mean value of the P-PT angle was 113.9 ± 11.1 degrees in the chondromacia group and 112.9 ± 11.7 degrees in the non-chondromalacia group. There was no significant difference between the groups (p=0.727). Finally, the mean value of the PT-T angle was 29.9 ± 5.9 degrees in the chondromacia group and 28.9 ± 7.6 degrees in the non-chondromalacia group. There was no significant difference between the groups (p=0.608) (Figure 1). Intra-observer agreements were 0.78 (95% confidence interval [CI], 0.63–0.87) for Q-P, 0.73 (95% CI, 0.54–0.84) for P-PT, and 0.79 (95% CI, 0.65–0.88) for PT-T. There were perfect correlations between two measurements for Q-P and PT-T, and there was a good correlation for P-PT.

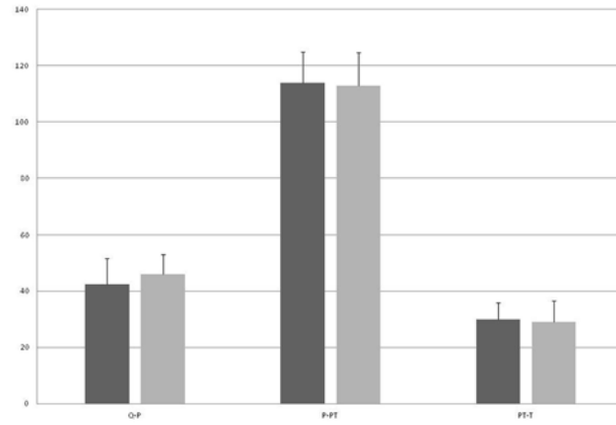


Figure 1. The mean values and standart deviations for Q-P, P-PT, and PT-T angles. (The bold columns show the chondromalacia groups.)

Discussion

Chondromalacia patella tend to progress starting from fibrillation with loss of healthy cartilage, osteoarthritis, and ensuing pain and disability. Some medical and surgical treatment options such as pain management and use of chondroprotective pharmacological agents, joint lavage, and mechanical debridement have been performed. However, none has been proven to be effective [5]. Therefore, the most effective treatment against chondromalacia patella is trying to prevent it before it starts. That increases the importance of the studies on understanding the etiology and the mechanisms that cause patellar chondromalacia. This study focused on one of the mechanical factors that may cause chondromalacia.

Although arthroscopy is considered to be the gold standard for the diagnosis of chondromalacia, MRI is an important method for evaluating chondral lesions in the patella because it is non-invasive [6]. Proton-density weighted images and the T2 weighted fast spin-echo images with or without fat-saturation, the gradient-echo sequence such as the fat-suppressed spoiled gradient-echo images, and the fat-suppressed fast low angle shot images are frequently used sequences for evaluating the knee [7]. Hyaline cartilage shows low signal intensity in T1-weighted images (WI). However, T1-WIs do not provide good contrast between joint effusion and the cartilage surface, a

shortcoming that limits their usefulness in the assessment of focal cartilaginous defects. Hyaline cartilage shows high signal intensity in T2-WIs. T2-WIs evaluate the subchondral bone and the interface between the cartilage and the synovial fluid, with less distinction between changes in the intrinsic signal of the hyaline cartilage. The articular cartilage appears hyperintense on T2 weighted fast spin-echo sequences. It provides excellent morphological detail of articular cartilage. Also, the other structures of knee joint can be identified. Therefore, in this study we used T2 weighted fast spin-echo images with fat-saturation to detect the precence or absence of chondromalacia patella.

Aksahin et al. researched the sagittal plane tilting deformity of the patellofemoral joint and showed the mean P-PT angle was significantly lower in the chondromalacia group than in the control group [8]. We found no difference in P-PT angle between groups with and without patellar chondromalacia.

Kusnezov et al. reported that increasing chronological age, female sex, black race, and physical activity significantly correlated with an increased risk for chondromalacia patellae in an active population [9]. Also, it was revealed that patellofemoral joint morphology has a relationship to chondromalacia patella [10]. Edama et al. found that posterior attachment of the patellar tendon to the patella related to shorter patellar tendon, suggesting the possibility of strong tensile stress on the tendon fibers of the posterior facet of the inferior patellar pole [11]. A high ratio of trochlear sulcus angle to trochlear depth was identified as an independent risk factor for chondromalacia patella [12]. Our study focused on ligamentous parameters without evaluating any bony development, but we found no relationship between the ligamentous structures around the patella and chondromalacia.

The relationship between the attachment of quadriceps tendon to patellar superior pole and the development of patellar chondromalacia has not been investigated yet. However, the importance of quadriceps muscle exercises for pain relief in patients with chondromalacia patella is well known [13]. On the other hand, although physical activity improved the quadriceps muscle, Zhang reported that it also increased the prevalence of chondromalacia patella [14]. This study investigated and revealed that the attachment angle of quadriceps tendon to the superior pole of the patella had no significant relationship to the presence of chondromalacia patella.

This is the first study to focus on the ligament-bone attachments around the patella, and it revealed some novel information. However, the small number of patients and the lack of information about their complaints and their clinical symptoms were the limitations for this study. Prospective randomized trials with larger case series will help us better understand the etiology of the development of chondromalacia patella.

Competing interests

The authors declare that they have no competing interests.

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Awareness of human papillomavirus and acceptability of human papillomavirus vaccine: A survey of Turkish university students

Human papilloma virüsü hakkında farkındalık ve human papilloma virüs aşısının kabul edilebilirliği: Türk üniversite öğrencileri araştırması

Human papillomavirus vaccine survey university students Turkey

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Öz

Amaç: Türk üniversite öğrencilerinin Human Papilloma Virüsü (HPV) hakkında farkındalıklarını ve HPV aşısının yaptırılmasını etkileyen faktörlerin değerlendirilmesini amaçladık. Gereç ve Yöntem: Bu kesitsel çalışmada, Ankara, Türkiye'de 158'i iletişim fakültesi ve 129'u Tıp fakültesi olmak üzere, toplam 287 öğrenciye 33 sorudan oluşan bir anket uygulandı. Bulgular: HPV aşısının olası yan etkileri, HPV aşısının kanserden ve genital siğilden koruyucu etkileri, HPV enfeksiyonun seksüel yolla geçişi öğrencilerin aşılanma isteğini etkileyen faktörler idi. HPV aşısının kanserden koruyucu etkisinin farkındalığı (7,7-odds) HPV aşısı yaptırmada en güçlü faktör olarak bulundu. Tartışma: Türk üniversite öğrencilerinin HPV için aşılanma oranlarını arttırmak için HPV aşısının kanserden koruyucu etkisinin iyi açıklanmasına ihtiyaç vardır.

Anahtar Kelimeler

Farkındalık; Human Papillomavirüs; Human Papillomavirüs Aşısı; Türk Üniversite Öğrencileri; Servikal Kanser

Abstract

Aim: We aimed to assay the awareness of Human Papilloma Virus (HPV) and factors affecting willingness of HPV vaccination among Turkish university students. Material and Method: A total of 287 students (158 from the department of communication and 129 from the department of medicine) received a survey including 33 questions in this cross-sectional study in Ankara, Turkey. Results: The probable adverse effects of HPV vaccine, protective effects from cancer and genital wart of HPV vaccine, sexually transmission risk of HPV infection were the significantly different factors among students which affect willingness of vaccination. Awareness of HPV vaccination about its protective effect from cancer was found the most powerful factor (7.7-odds) for HPV vaccine administration. Discussion: The protective effect of the HPV vaccine from cancer needs to be well described to increase the HPV vaccination among Turkish university students.

Keywords

Awareness; Human Papillomavirus; Human Papillomavirus Vaccine; Turkish University Students; Cervical Cancer

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Introduction

Cervical cancer is the most common gynecological cancer all over the world [1] approximately 500,000 cases per year are diagnosed and 80% of those cases occur in developing countries [2,3]. Differences in prevalence of cervical cancer between developed and developing countries are associated with the generally successful use of the screening programs in developed countries.

After the proven association between Human Papilloma Virus (HPV) and HPV-related diseases, research to prevent HPV transmission, in particular HPV vaccination, was encouraged by the investigators. HPV vaccination can prevent HPV-related diseases, including genital warts, vaginal, anal and cervical cancer [4]. Since the United States Food and Drug Administration (FDA) had approved of the first HPV vaccination in 2006, HPV vaccination became widespread, particularly in developed countries. HPV vaccination was introduced in national vaccination programs in at least 66 countries.

Turkey is a country located in middle-east, and neighbors the European Union. 99.2 % of the citizens in Turkey are Muslim. The HPV vaccination rate in Turkey is not evident. We may figure out approximate HPV vaccination rates through selling reports of companies. In total, 188,402 box HPV vaccine had been sought from 2007 until August 2016, in Turkey. This data points that approximately 60, 000 women (0.17 % of total women population) had HPV vaccination in 9 years. The estimated rate is considered to be very low compared to those of developed countries. By 2010, the rates of HPV vaccination reached 37.6 % and 32 % in USA and in Austria, respectively [2,3].

The Ministry of Health of Republic of Turkey consider to add HPV vaccination to the national vaccination program. In a developing country as Turkey, although HPV vaccination is introduced free of charge as part of national HPV vaccination; the implementation of HPV vaccine may be lower than expected because of some superstitions and religious reasons which may arise due to the lack of knowledge about HPV and its vaccination. Therefore, it carries quite importance to know the awareness, attitudes and factors affecting HPV vaccination among young citizens lived in a Muslim country as Turkey, so we conducted this study assay the awareness and factors affecting acceptability of HPV vaccine among Turkish university students.

Material and Method

This is a cross-sectional study assaying awareness and factors affecting acceptability of HPV vaccination between January and April 2015 in Ankara, Turkey. A total of 287 undergraduate students at Ankara University; 158 from the department of communication (DoC) and 129 from the department of medicine (DoM), received a self-administered survey including 33 questions.

The survey was designed to evaluate the awareness and knowledge about HPV infection and vaccine. The survey was divided into 3 main parts and contained 33 questions in total. The first part of the survey explored demographics and non-identifying information such as age, gender, smoking status, sexual experience, current vaccination status, knowledge and awareness about HPV infection and HPV vaccine. The second part explored acceptability of HPV vaccine and factors that affect this decision. There were 5 questions in this part. Each of those 5 factors were in a 4-point Likert scale, from 1 to 4; 4-point scale (strongly non-important, not-important, important, strongly important) on the participants' attitudes regarding having HPV vaccine. The evaluated factors were the price of the HPV vaccine, likely adverse effects of the HPV vaccine, belief on low risk to transmission of HPV infection to themselves, preventive effect of HPV vaccine from cervical cancer and protective effect of HPV vaccine from genital warts. The mean points were determined for each factor. The third part of the survey aimed to evaluate the knowledge about HPV infection and HPV vaccine. This part had a scale comprised of 19 ''True or False'' questions. In the third part, the total knowledge score was calculated on a 0-100 scale, based on the fraction of correct answers to the questions.

The normality of the variables was analyzed by the Kolmogorov–Smirnov test. Student's t test or the Mann–Whitney U test were used to compare the categorical and continuous variables. Chi-square or Fisher's exact test were performed for nonparametric variables between groups. Odds ratios and 95% confidence intervals (CIs) for factors affecting acceptability of HPV vaccine were calculated via a logistic regression model. Two-sided p values were considered statistically significant at $p < 0.05$. Statistical analyses were carried out using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

This project received ethical approval from the Ankara University Institutional Review Board and the Ethics Committee.

Results

The socio-demographic characteristics, attitudes and knowledge of the students of the DoC and the DoM groups about HPV infection and HPV vaccine were shown in Table 1. There were statistical significant differences between DoC and DoM groups in terms of average ages; 22.4 ± 1.9 years vs 24.1± 0.8 years, smoking status; 44.9 % vs 24.8 %, sexual intercourse; 46.2 % vs 22.5 %. The willingness of HPV vaccination; 48.7 %

Table 1. Social-demographic characteristics of the participated students

Variables	Students of the DoC n=158	Students of the DoM n=129	p value
Age (years)	22.4 ± 1.9	24.1± 0.8	< 0.001
Number of the participants who recommend HPV vaccine	99 (62.7)	123 (95.3)	< 0.001
Gender Male Female	 79 (50.0) 79 (50.0))	 73 (56.6) 56 (43.4)	 0.266
Being in a relationship	65 (41.1)	50 (38.8)	0.682
Smoking	71 (44.9)	32 (24.8)	< 0.001
Sexual intercourse	73 (46.2)	29 (22.5)	< 0.001
Number of the participants who had HPV vaccine before survey	0 (0)	3 (2.3)	0.091
Willingness of HPV vaccination	77 (48.7)	81 (62.8)	0.017
Number of the participants who had heard HPV vaccine	22 (13.9)	117 (90.6)	< 0.001
[a] Total knowledge (for HPV infection and vaccine) (%)	10.5 (0-89.4)	68.5 (0-100)	< 0.001

Values are given as mean ± SD, median (min-max) and number (percentage), HPV: human papilloma virus, DoC: Department of Communication, DoS: Department of Medicine, [a]: The knowledge percentile about HPV infection and cervical cancer, *p<0.05 is considered statistically significant

vs 62.8 %, the number of the participants who had heard HPV vaccine; 13.9 % vs 90.6 % and total knowledge for HPV infection and vaccine 10.5 % vs 68.5 % were significantly higher in DoC group than DoM group.

The comparison of willingness HPV vaccination among students was shown in Table 2. The willingness of HPV vaccination was significantly higher in female students than male students (p< 0.001) and the students of the DoM have higher significantly willingness of HPV vaccination than the students of the DOC, p=0.017.

Table 2. Comparison of willingness HPV vaccination among students

Variables	Willingness n=158	Non-willingness n=129	p value
Gender			
Male	68 (44.7)	84 (55.3)	< 0.001
Female	90 (66.6)	45 (33.4)	
Students of the DOC	77 (48.7)	81 (51.3)	
Students of the DoM	81 (62.8)	48 (37.2)	0.017
Being in a relationship	63 (39.9)	52 (40.3)	0.940
Smoking	58 (36.7)	45 (34.9)	0.748

Values are given as number (percentage) , DoC: Department of Communication, DoS: Department of Medicine, HPV: human papilloma virus, *p<0.05 is considered statistically significant

Four of the 5 variables; including likely adverse effects of HPV vaccine point (p< 0.001), sexually transmission risk of HPV infection point (p< 0.001), protective effect of HPV vaccine from cancer point (p< 0.001) and protective effect of HPV vaccine from genital wart point (p<0.001), were found to be statistically significant among students compared willingness versus non-willingness HPV vaccination groups (Table 3).

Table 3. Comparison of the factors affecting willingness HPV vaccination among students

[a] Variables	Willingness n=108	Non-willingness n=39	p value
Cost of the HPV vaccine	1.1 ± 1.0	0.9 ± 0.8	0.649
Adverse effects of HPV vaccine	2.5 ± 0.6	1.8 ± 1.0	< 0.001
Transmission risk of HPV	2.5 ± 0.6	1.6 ± 1.1	< 0.001
Protective effect of HPV vaccine from cancer	2.7 ± 0.6	1.0 ± 0.6	< 0.001
Protective effect of HPV vaccine from genital wards	2.5 ± 0.7	1.0 ± 0.7	< 0.001

[a] Each of those variables were in a 4-point Likert scale, from 1 to 4; 4-point scale (strongly important, important, not-important, strongly non-important) on the participants' attitudes regarding having HPV vaccine, Statistical analysis were performed through the numeric value of the points. Values are given as mean ± SD, median (min-max), HPV: human papilloma virus, *p<0.05 is considered statistically significant

When we performed logistic regression analysis of independent risk factors' point by using a cut-off score level ≥3 to identify the most important factors for willingness of having HPV vaccination among students, we found the protection from cancer score ≥3 was merely the significantly statistical factor which affected the willingness of having HPV vaccine (OR: 7.7, CI: (3.4-17.6), p< 0.001), (Table 4).

Table 4. Logistic regression analysis of independent risk factors' point for willingness of having HPV vaccination among students (n= 158).

Variables	OR (95% CI)	P value
Price point ≥3*	0.5 (0,2-1.1)	0.104
Adverse effects point ≥3*	0.5 (0.2-1.1)	0.099
Transmission risk point ≥3*	1.4 (0.7-2.9)	0.312
Protection from cancer point ≥3*	7.7 (3.4-17.6)	< 0.001
Protection from genital ward point ≥3*	1.2 (0.6-2.6)	0.485

OR: Odds Ratio, CI: Confidence Interval, *p<0.05 is considered statistically significant, Price point: price of the HPV vaccine point, Adverse effects point: likely adverse effects of HPV vaccine point, Transmission risk point: sexually transmitted risk of HPV infection point, Protection from cancer point: protective effect of HPV vaccine from cancer points, Protection from ward point: protective effect of HPV vaccine from genital wart point.
*: Each of those 5 factors were scored from 1 to 4; 4-point scale (strongly non-important, not-important, important, strongly important) on the participants' attitudes regarding having HPV vaccine.

Discussion

We evaluated the university students (students of the department of communication vs students of the department of medicine) by the same self-administered survey including questionnaires aimed to assess the awareness and factors affecting acceptability of HPV vaccine. The awareness, total knowledge and willingness of the students of the department of medicine regarding HPV vaccine was higher than of the students of the department of communication. The likely adverse effects of HPV vaccine, sexually transmitted risk of HPV infection, protective effect of HPV vaccine from cancer, protective effect of HPV vaccine from genital wart were the factors that affect the willingness of HPV vaccination among the university students. When compared with other factors, the protective effect of HPV vaccine from cancer was the only factor that increased the willingness of HPV vaccination by 7.7-fold.

We found that the acceptance of the HPV vaccine among students from DoM were 62.8 %. The corresponding values were found as 48.7 % among students of the DoC. In a study by Pandey et al. [5], the acceptance of the HPV vaccine among medical students was found to be 67.8 %. This ratio was similar to the findings of the current study for students from DoM. In current study, we found that the increased awareness concerning HPV infection and vaccine was associated with high willingness of having HPV vaccine as it was indicated in previous studies [6-8]. Education about diseases may also be considered as one of the important parameters to struggle with those diseases. In a study, investigating the cervical cancer knowledge, education about the disease resulted in improvements [9].

The gender may be considered as an important factor concerning acceptance of HPV vaccine. In current study, 44.7% of the male participants and 66.6% of the female participants were amenable for HPV vaccination. In a recent study conducted among young males aged 14-24 in Italy, 54.9% of the participants reported that they had heard of HPV infection, and after being explained about HPV infection and vaccine, 58.2% of the participants reported that they would be willingness HPV vaccination [10]. In the current study, the rates of willingness HPV vaccination were found to be significantly lower in male students than in female students (44.7% vs. 66.6%). This finding actually may have similar viewpoints with the first HPV vaccination policy which was considered the target population as girls only. However, more recent data and vaccination policy include adolescent boys for HPV vaccination anymore [11,12].

In the current study, only 13.9% of students of the DoC have heard of HPV infection. This percentage was comparably lower than in western countries; such as Denmark, in which the rates of hearing HPV infection was 78%; respectively [13]. Unfortunately, in current study; we could reach those high levels of awareness (79.1%) only among students of Medicine University. In several studies, it has been shown that the acceptance of the HPV vaccine increased after explanation of HPV vaccine and its benefits [11-13]. Current study has showed that the willingness of the HPV vaccine depended on the high awareness and knowledge of the HPV infection and vaccine. The likely adverse effects of the vaccine, transmission risk of HPV infection, protective effect of HPV vaccine from cancer and protective effect of the HPV vaccine from genital ward were the significantly important factor that affect the willingness of HPV vaccination of the students. In particular, being aware of the protective effect of HPV vaccine from cancer was the most important factor and was found to be associated with higher willingness rate of having HPV vaccine; it increased the acceptability of HPV vaccine 7-folds among students.

In total, 188,402 box HPV vaccine had been sought from 2007 until August 2016, in Turkey. This data points that approximately 60, 000 women (0.17 % of total women population) had HPV vaccination in 9 years. The estimated rate is considered to be very low compared to those of developed countries. By 2010, the rates of HPV vaccination reached 37.6 % and 32 % in USA and in Austria, respectively [4]. Islam is the largest religion in Turkey with 99.2 % of the population being recognized as Muslim according to the survey which was done by Republic of Turkey Presidency of Religious Affairs. It may be more difficult to explain the benefits of a vaccine that prevents diseases mostly related with sexual relation in a country which most of the citizens were Muslim. Additionally, in some conservative cultures, virginity is considered as a high moral standing, and a woman who had extramarital sex or polygamy may suffer from various social or familial problems [14,15]. In Muslim countries and in conservative cultures, a negative campaign against vaccination may be arranged easily with speculations that the vaccination leads the people to extramarital sex or polygamy which the religion had banned. Although all those negative thoughts, in the local meetings with the representatives of the Ministry of Health of Republic of Turkey; it was mentioned that they consider the HPV vaccination to add to the national vaccination program. However, there is a lack of knowledge about awareness and attitude of Turkish young population about HPV infection and its vaccine. Therefore, studies about HPV vaccination from Turkey should be encouraged and the policies which increase the awareness and knowledge about HPV and its vaccination should be supported.

In conclusion, current study showed that the awareness of HPV vaccination about its protective effect from cancer was the most powerful factor for HPV vaccine administration among Turkish university students. The protective effect of the HPV vaccine from cancer needs to be well described to increase the HPV vaccination among Turkish university students.

Statement of Human and Animal Rights: The authors undersign, certificate that the procedures and the experiments. The authors have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000, as well as the national law.

Competing interests

The authors declare that they have no competing interests.

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The frequency of occult HBV infection in Eskisehir region of turkey between 2001-2015

Eskişehir bölgesinde okült HBV enfeksiyonu sıklığının 2001-2015 yılları arasında dağılımı

Occult HBV, frequency

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Öz

Amaç: Okült HBV enfeksiyonu (OBİ), HBs Ag negatif kişilerde, serumda, immün sistem hücrelerinde ve/veya karaciğerde düşük titrede HBV-DNA pozitifliği ile karakterize bir enfeksiyondur. Görülme sıklığı; test edilen hasta popülasyonuna, laboratuvar tanıda kullanılan yöntemlerin duyarlılığına bağlı olarak değişir. Ayrıca OBİ organ ve kan donörlerında virüs kontaminasyonu için kaynak olabilir. Bu çalışmada, viral hepatit B ön tanılı hastalarda, okült HBV enfeksiyon sıklığı değerlendırılmıştır. Gereç ve Yöntem: Bölgemizde 2001- 2015 yılları arasında gönderilen HBV enfeksiyonu ön tanılı hastalara ait serum örneklerınde HBV-DNA, gerçek zamanlı PZR (Qiagen); HBV, HCV ve HDV serolojik işaretleri ise, EIA (Axsym ve Architect i2000SR) yöntemi ile çalışılmıştır. Ayrıca HBsAg negatif, HBV-DNA pozitif serumların alanin aminotransferaz (ALT) ve aspartat aminotransferaz (AST) düzeyleri araştırılmıştır. Bulgular: HBV DNA'sı pozitif olan 4036 hastanın 105'inde (%2.6) HBsAg negatifliği saptanmıştır. Minimum ve maksimum DNA düzeyleri ise $1x10^1$-$1.7x10^8$ kopya/mL olarak belirlenmiştir. Okült HBV enfeksiyonu ön tanılı bu 105 hastanın tamamında Anti HBc IgM negatif ,31'inde (%29.5) tek başına anti-HBc (+), 3'ünde (%2.8) tek başına anti-HBs (+), 16'sında (%15.2) anti-HBs ve anti-HBc birlikte (+), 13'ünde (%12.3) ise tüm HBV serolojik işaretleri negatif olarak bulunmuştur. Beş hastada ise anti-HCV pozitif olup, tüm hastalarda anti HDV negatiftir. Ondokuz (%18) hasta immün düşkün konak özelliği taşımaktadır. Tartışma: OBİ, transplantasyon veya kan transfüzyonu yolu ile bulaşmasını takiben, tipik HBV enfeksiyonuna neden olabilmesi, özellikle immün süpresyon koşullarında reaktivasyonu ve karaciğer hastalığı varlığında progresyon veya hepatoselüler karsinomdaki rolü açısından önem taşımaktadır.

Anahtar Kelimeler

Hepatit B Enfeksiyonu; Görülme Sıklığı; PZR

Abstract

Aim: Occult HBV infection (OBI) is characterized by the detection of HBV DNA in low levels in serum and peripheral blood mononuclear cells and/or in the liver, in the absence of detectable hepatitis B surface antigen (HBsAg). The prevalence of OBI varies among patient populations tested and the sensitivity of the assay employed. Also OBI can be a source of virus contamination in both blood and organ donations. In this study, we evaluated the presence of occult HBV infection in patients diagnosed with viral hepatitis B infection. Material and Method: All samples were investigated for serological markers of HBV, HCV, and HDV by ELISA (AxSYM and Architect i2000SR, Abbott, USA) and also examined for the presence of HBV DNA by Real-time PCR in the clinical microbiology laboratory between 2001-2015. Also, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were evaluated. Results: We detected HBsAg negativity in the sera of 105 (2.6%) of 4036 patients having positive HBV DNA. The minimum and maximum DNA levels were $1x10^1$-$1.7x10^8$ copies/mL. Among the 105 patients, 31 (29.5%) were positive for only anti-HBc total, 3 (2.8%) were positive for anti-HBs, and 16 (15.2%) were positive for both anti-HBs and anti-HBc. Thirteen (12.3%) of the 105 patients were negative for serological markers of HBV infection. Nineteen (18%) patients were immunocompromised individuals. Discussion: Especially in immunocompromised individuals, occult HBV infection can reactivate and cause liver damage. Also OBI should be carefully assessed in particular clinical contexts: HBV infection transmission, liver disease progression, hepatocellular carcinoma onset, and HBV reactivation.

Keywords

Frequency; Hepatitis B Infection; PCR

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Introduction

The existence of occult HBV infection has been a matter of debate for years, but its existence and clinical relevance is now supported by many publications [1]. Occult HBV infection is characterized by the detection of HBV DNA in low levels in serum and peripheral blood mononuclear cells and/or in the liver in the absence of detectable hepatitis B surface antigen (HBsAg) with or without antibodies to hepatitis B core antigen (anti-HBc) or hepatitis B surface antigen outside the pre-seroconversion window period [2-5].

The gold standard for OBI diagnosis is liver tissue biopsy, although this is not usually feasible and standardization of this assay is not established. Therefore, most often OBI diagnosis is based on the results of a blood test. It is important to determine the optimal method to quantify HBsAg and HBV DNA. It is critical to use a very delicate and specific assay because OBI is usually associated with low levels of HBV DNA. An international consensus has suggested a cut-off value to detect HBV DNA by molecular assays (<200 IU/mL) [6].

The prevalence of occult HBV infection varies among patient populations tested, but also depends on the assay employed in routine serological or nucleic acid test screening [4,7]. Detection of HBV DNA in the absence of HBsAg has been increased with the improvements in the sensitivity of genomic amplification assays. Improvement in molecular diagnostic methods and in particular the development of increasingly sensitive PCRs has favored the recognition of occult HBV infections in an increasing number of clinical settings and geographical areas [1]. Recent technologies (nested-PCR, real-time PCR, and transcription based mediated amplification) have reduced the lower detection limit to >5 copies/mL and improved sensitivity. Prevalence of occult HBV has been found higher in seropositive persons, particularly those who are positive for anti-HBc only, than in seronegative individuals [8].

The prevalence of OBI in blood donors depends on the rate of HBV in the population. In developed countries this rates is under 1%, while in less developed and developing countries it is as high as 17%, reported rates in anti-HCV-positive blood donors range from 0-15%, and from 0-89% in HIV-infected individuals [1-6, 9,10]. OBI rates are reported as 45% and 51% in intravenous drug addicts and hemophilic patients, respectively [10].

OBI has been reported in 0.1-2.4% of HBsAg-negative, anti-HBc positive (anti-HBs positive or negative) blood donors in Western countries such as the United States, where only 5% of the population has prior exposure to HBV. In contrast, OBI has been reported in up to 6% of a similar cohort of donors (HBsAg-negative, anti-HBc positive) who reside in HBV endemic areas where 70-90% of the population has been exposed to HBV. When only anti-HBc data is evaluated (anti-HBe positive or negative), the rates range from 0% to 15% (median of 1.1%) [4]. Prevalence may also vary depending on the nature of biological material tested, with a higher proportion for the liver compared to serum specimen [1]. Occult HBV infection may follow recovery from disease, displaying antibody to hepatitis B surface antigen (anti-HBs) and persistent low-level viraemia, escape mutants undetected by the HBsAg assays, or healthy carriage with antibodies to anti-HBe and anti-HBc. All forms have been shown to be infectious in immunocompromised individuals, such as organ or bone marrow transplant recipients [6]. In several studies, occult HBV infection prevalence is high in immuncompromised situations. There are some studies which show that occult HBV infection was reactivated and caused liver damage and liver failure in 20% of immunocompromised cases such as anti-HIV positive patients, hematopoietic stem cell or solid organ transplant recipients, or patients treated with monoclonal antibody, anti-TNF antibody, or chemotherapy regimens because of rheumatological disorders [11-14].

In this study, we aimed to evaluate the presence of occult HBV infection in patients diagnosed with viral hepatitis B infection.

Material and Method

All samples were investigated for serological markers of HBV, HCV, and HDV by ELISA (AxSYM and Architect i2000SR, Abbott, USA) and also examined for the presence of HBV DNA by Real-time PCR in the clinical microbiology laboratory. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of HBV DNA-positive sera were evaluated.

Serological markers. Tests for HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc total, anti-HBc IgM, anti-HCV, and anti-HDV were done with commercially available kits (AxSYM and Architect i2000SR, Abbott, USA).

Detection of HBV DNA. Serum samples were assayed for HBV DNA by using Artus HBV RG PCR kit (Qiagen, USA) between 2001-2010, Cobas TaqMan (Roche, Germany) between 2011-2013, and RTA HBV Real-time PCR kit (RTA, Turkey) after 2013. Total DNA extraction of HBV DNA and real-time PCR were performed according to the manufacturers' instructions. The limit of detection of Artus HBV RG PCR was 20 IU/mL, Cobas TaqMan HBV test was 20 IU/mL, and RTA HBV real-time PCR was 24 IU/mL.

Statistical analysis

Analysis was performed using the SPSS Version 20.0 (SPSS Inc., Chicago, IL, USA) software. The associations between baseline patient characteristics and the assay results were analysed using one-way ANOVA and Fisher's exact test. P value of <0.05 was considered statistically significant.

Results

In this study, 16,853 sera of 4036 patients who were considered as having HBV infection were tested in Eskisehir Osmangazi University Medical Faculty, Medical Microbiology Laboratory between 2001-2015. One hundred and five (2.6%) of the patients positive for HBV DNA were HBsAg negative. These 105 patients were from the following clinics: 36 (34.2%) Gastroenterology, 34 (32.3%) Infectious Disease, 15 (14.2%) Hematology, 8 Internal Medicine, 6 General Surgery, 5 Pediatrics, and 2 Gynecology and Obstetrics. The minimum and maximum DNA levels were $1x10^{1}$-$.7x10^{8}$ copies/mL.

Anti-HBc IgM was negative in all of the patients. Among 105 patients, 31 (29.5%) were only positive for anti-HBc total, 3 (2.8%) were positive for anti-HBs, and 16 (15.2%) were positive for both anti-HBs and anti-HBc total in their sera. Thirteen (12.3%) of all patients were negative for serological markers of HBV infection. The sera of 5 patients were anti-HCV positive. All of the patients positive for anti-HCV were also only anti-HBc

total positive. All of the patients were negative for anti-HDV.

The liver function test results were all in normal range, except that ALT and AST levels were abnormal in 40 (38%) and 38 (36.1%) patients, respectively. Both ALT and AST levels were abnormal in 21 patients (20.0%). The mean levels of ALT and AST were 79.58 and 72.78 IU/L, respectively. Nineteen patients (18%) were immunocompromised.

In the occult HBV group, the viral load was < 2x10 copies/ mL in 42 of 105 patients, and in non occult HBsAg positive group, in 16 patients the level was < 2x10 copies/ mL. We found statistically significant difference between the occult and nonoccult groups according to their viral loads ($p<0.05$). In terms of HBeAg positivity, Anti HBc positivity, Anti HBs positivity and Anti HBc-HBeAg positivity, the differences among the two groups were highly significant (Table 1).

Table 1. Characteristics and antibody status of occult and non occult hepatitis B (HBs Ag Positive) patients.

	Occult HBV (n:105)	Non occult HBsAg positive group (n: 114)	P value*
Mean age	48.31	43.85	0.019
Sex (male/female)	61/44	71/43	0.527
Mean viral load (copies/mL)	$2.1x10^4$(10-$1.7x10^8$)	$2.4x10^5$(10-$8.6x10^7$)	0.006
HBeAg positive	6 (5.7 %)	21 (18.4%)	0.004
Anti HBc positive	89 (84.7 %)	111 (97.3%)	0.001
Anti HBs positive	41 (39.0%)	9 (7.8%)	<0.0001
Anti HBc and Anti HBs positive	16 (15.2%)	7 (6.1 %)	0.088
Anti HBc and HBeAg positive	1 (0.9 %)	20 (17.5%)	<0.0001
Anti HBc, AntiHBs and HBeAg positive	1 (0.9 %)	1 (0.8%)	0.953

*P value <0.05 is statistically significant.

Discussion

Occult hepatitis B is defined by the presence of HBV DNA in the serum or liver of patients who are negative for HBsAg. The clinical significance of occult HBV infection remains largely unknown. This clinical entity has been reported in healthy blood donors, patients with chronic liver disease, and patients with hepatocellular carcinoma [4]. There is a clear association between occult HBV infection and liver diseases in the absence of other causes, such as HCV infection or excessive alcohol intake [15].

OBI in particular has a high prevalence, particularly in chronic HCV infection, cryptogenic, chronic and fulminant hepatitis patients [16]. Studies have suggested that, similar to HBV infection, OBI's obvious protooncogenic activity contributes to the development of cirrhosis or HCC [17-18]. In addition, non-Hodgkin's lymphoma and malignancies such as intrahepatic cholangiocarcinoma show a noteworthy relationship between HBV infection and OBI [19].

Occult HBV has also been detected in chronic HCV infection with or without antibody markers of HBV [20]. In our study, the rate of occult HBV was found as 2.6%. The rate of occult HBV infection in our study correlated with other studies in Turkey. Among 935 HBsAg-negative patients, occult HBV infection rate was found as 5.77% in a study of Akduman et al. in the Manisa region of Turkey [21]. In different studies from Turkey, among HBsAg negative patients 3.4%-19% OBI rates reported [22]. In Pakistan, Bhatti et al. selected 966 donors for testing of anti-HBc and HBV markers and detected HBV DNA in 5 blood donors who were negative for HBsAg [23]. O'Brien et al. tested 493,344 donors who made donations otherwise eligible for transfusion, and among them, 5,585 (1.13%) were detected as reactive for anti-HBc. Of these, 29 donors tested positive for the presence of HBV DNA but were negative for the presence of HBsAg (0.52% of all anti-HBc-reactive donors) [9]. Recently, Olotu et al. reported OBI prevalence of 5.4 % among anti-HBc positive blood donors in Ile-Ife, Nigeria. This means that after HBsAg screening, about 1 in 20 to 1 in 25 blood donations still have HBV DNA [24].

In our study, 3 (2.8%) patients were only anti-HBc total positive and 16 (15.2%) were positive for both anti-HBc total and anti-HBs. Recent data shows that about 20% of occult hepatitis B sera are negative for all serological markers of HBV infection except HBV DNA, 50% are positive for hepatitis B core antibody (± anti-HBs), and 35% are positive for hepatitis B surface antibody (± anti-HBc) [2,4]. Overall, the prevalence of occult HBV infection is higher in anti-HBc positive patients than in anti-HBc negative patients. The HBV DNA detection rate is greater in subjects who are anti-HBc positive but anti-HBs negative, and the infectivity of blood donations containing anti-HBc as the only marker of HBV infection has been known for several decades [4,5]. Blood products with these very low HBV viral loads are potentially infectious, as shown in recent reports [25].

Data on the rate of OBI in the general population is generally insufficient. In one study of seropositive and seronegative groups, the HBV DNA positivity rate was 18% and 8%, respectively. Other studies have reported an OBI rate of 15.3% for hematopoietic stem cell donors who were HBV/HCV negative, 16% in a group with normal serum transaminase values, and 8% in a group of individuals who were HBsAg negative and with a chronic family history of HBV infection [26-28].

When we looked at the rate (29.5%) of only anti-HBc total positive patients in our study, it was considered that anti-HBc screening of blood donors could identify most of the occult HBV infections.

In our study, 19 (18%) of patients were immunocompromised individuals and it is known that occult HBV infection can reactivate and cause liver damage in these patients. All forms of occult HBV infection have been shown to be infectious in immunocompromised individuals [6].

The limitation of our study is that we collected the data of the patients retrospectively and therefore we could not follow up the serological markers, viral loads, and clinical outcomes of the patients.

OBI has a variety of clinical impacts. The possible transmission of the infection (via blood transfusion, solid organ transplantation, hemodialysis, and also by close contact as has been reported recently), the contribution to liver disease progression, the development of hepatocellular carcinoma (HCC), and the risk of reactivation of HBV are the most relevant contexts [17,29]. Furthermore, detection of HBV DNA with highly sensitive PCR techniques should be routinely performed on blood

donations to minimize the occult HBV transmission risk.

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Competing interests

The authors declare that they have no competing interests.

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The prevalence of postpartum depression and associated factors: a hospital-based descriptive study

Postpartum depresyon prevalansı ve ilişkili faktörler: hastane bazlı tanımlayıcı çalışma

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Öz

Amaç: Postpartum depresyon (PPD), ciddi olumsuz sonuçları ile annelerin yanında, bebeklerini ve ailelerini etkileyen önemli bir sorundur. Bu çalışmada, annelerde PPD prevalansı ve ilişkili olabilecek risk faktörlerinin belirlenmesi amaçlandı. Gereç ve Yöntem: Tanımlayıcı tipteki bu çalışma Ağustos-Ekim 2015 tarihleri arasında, Kütahya da herhangi bir nedenle hastaneye başvuran 0-12 aylık bebeği olan annelerde gerçekleştirildi. Çalışmaya katılmayı kabul eden 302 anne ile görüşme yapılarak, Edinburgh Postpartum Depresyon Ölçeği (EPDÖ) ve sosyodemografik bilgilerin yer aldığı anket formu uygulandı. Verilerin değerlendirmesinde Ki kare testi, logistic regression ve ANOVA testi kullanıldı. Bulgular: Annelerde PPD prevalansı %32.1 bulundu. PPD sıklığı; kiralık evlerde, kalabalık ailelerde yaşayan ve yaşadıkları yerden memnun olmayanlarda daha yüksek bulundu. Gebeliğinde sigara içen annelerde, daha önceden depresyon öyküsü olanlarda, gebeliğinde fazla kilo alanlarda, istenmeyen gebeliği takiben doğum yapan ve prematür bebeği olan annelerde PPD sıklığı daha yüksek bulundu. Annenin yaşı, öğrenim durumu, çalışma durumu ve gelir düzeyi ile PPD sıklığı arasında ise bir fark bulunamadı. 1 aylık bebeği olan annelerin ölçek puan ortalamasının diğer aylara göre daha yüksek olduğu ve bebek ayı arttıkça ölçek puan ortalamasının azaldığı saptandı. Tartışma: PPD üzerine etkili faktörler, yaşadıkları yerden memnun olmama, kiralık evde yaşama, istenmeyen gebelik, daha önceden depresyon öyküsü olması, gebeliğinde sigara içme ve fazla kilo alma ve doğumdan sonraki ilk aylar bulundu. Bu çalışmada saptanan risk faktörleri, özellikle spesifik risk grupları için bölgesel sağlık hizmetlerinin planlanmasında rehberlik edebilir.

Anahtar Kelimeler

Postpartum Depresyon; Risk Faktörleri; Tanımlayıcı Çalışma

Abstract

Aim: Postpartum depression (PPD) is a significant public health concern which could adversely affect mothers as well as their babies and families. This study aimed to identify the prevalence of PPD and its risk factors. Material and Method: This descriptive study included 302 mothers with babies 0-12 months old who presented to the hospital for varying reasons in Kütahya, Turkey, between October and August 2015. Consenting mothers were given the Edinburgh Postpartum Depression Scale (EPDS) and a form including items on postpartum risk factors, reproductive characteristics, and sociodemographic variables. Data were analyzed using Chi-square tests, logistic regression, and ANOVA test analyses. Results: The prevalence of PPD was 32.1%. The rates were higher among those who live in rental homes, in crowded families, and who were not satisfied about where they have been living. PPD was more prevalent among mothers who smoked cigarettes, gained more weight during pregnancy, experienced prior depressive episodes, those with premature babies, and those who gave birth following unintended pregnancy. There were no relationships between mothers' educational, working, or income status and prevalence rates. Mothers of one-month old babies had higher scores on the PPD scale compared to others and the average scores on the scale decreased as babies got older. Discussion: Dissatisfaction with where they live, living in a rented dwelling, an unintended pregnancy, a past experience of depression, smoking, and excessive weight gain during pregnancy, giving birth to an underweight baby, and first months following birth are the risk factors that have a significant effect on PPD. The risk factors identified in this study can guide planning regional health services for specific risk groups.

Keywords

Postpartum Depression; Risk Factors; Descriptive Study

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Introduction

Epidemiological studies across the world show that depression is twice as common in women as in men and is more likely to be seen during the reproductive period. About 80% of women are faced with mood swings, particularly during pregnancy, birth, and the postnatal period; PPD is one such mood disorder [1-4].

Given the diagnostic classification systems used in psychiatry today, DSM-IV and DSM-V criteria define PPD under the category of "mood disorders" and "depression disorders" while ICD-10 codes list PPD among "behavioural syndromes associated with physiological disturbances and physical factors" [2-4].

The symptoms of PPD are not different from depression symptoms seen in periods other than the postpartum period. The symptoms are likely to develop at any time during the first year following childbirth and may even extend into two years [1,2].

The prevalence of PPD is reported to range between 11.0% and 60.0% in Asian countries and lower in European countries [5,6]. The studies conducted in Turkey have reported that the frequency of PPD is between 14.0% and 41.4% [7-10].

Among the PPD risk factors defined in studies are prenatal depression, low self-esteem, weak family ties, an experience of previous depression, a baby with a difficult temperament, family conflicts, insufficient social support, young age of the mother, and gaining too much or too little weight in pregnancy [9,12].

PPD, with its severe consequences, is a public health problem that affects not only mothers but also their babies and families worldwide [7, 12]. It is of particular importance, especially for public health interventions, to perform PPD screening and to identify associated risk factors in primary healthcare services. The data collected at this stage is essential to plan regional mental health services and to enable early diagnosis and treatment of disorders [12]. The results of this study may be used to plan regional healthcare services in Kütahya and to take preventive measures for the mental health of women.

This study aimed to identify the prevalence of PPD in mothers and its risk factors.

Material and Method

Study population

The study population comprised mothers who presented to the polyclinics of the Family Medicine and Children's Health and Diseases at Kütahya Evliya Çelebi Education and Research Hospital, Turkey, between October and August 2015. Permission was received from the hospital administration and ratification was received from the Board of Ethics for this study.

Based on sample volume calculation, we planned to conduct the study with 384 participants, considering the prevalence rate was 50% with 95% confidence interval and 5% margin of error. The questionnaire was administered to 387 mother who consented to participate in the study. However, participants who did not reply to at least 90% of the questions and who did not match the participation criteria were excluded from the study. As a result, the data from 302 mothers was evaluated in the study. The main criterion for participating in the study was having a baby aged 0-12 months.

Data collecting tool

The questionnaire consisted of two parts. The first part comprised questions about the sociodemographic characteristics of the mothers (i.e. age, level of education, occupational status, level of income, information about house, and number of people living in house), reproductive characteristics (age at first birth, number of living children, number of pregnancies and miscarriages, type of delivery, factors affecting pregnancy), and risk factors (whether it was an intended pregnancy, weight and height, presence of any physician-diagnosed chronic diseases, any past experience of depression, smoking during pregnancy, baby's birth weight, sex of baby, and nutrition for baby). The questionnaire also included questions related to mothers' height, weight before and after delivery, and how much weight they gained during pregnancy.

For the purpose of this study, the weight gained during pregnancy was evaluated based on the ideal criteria suggested by Institute of Medicine (Gestational Weight Gain Recommendations) (i.e. 12.5-18 kg for women with BMI <19.8 kg/m², 11.5-16 kg for women with BMI: 19.8-26.0 kg/m², 7-11.5 kg for women with BMI: 26-29.0 kg/m², and 7-11 kg for women with BMI >29.0 kg/m² before pregnancy) [13]. The BMI of the participants before pregnancy was calculated and organized according to the weight they gained during pregnancy. The women who gained weight less than the suggested weight for each BMI category were categorized as little weight gain, more than the suggested weight were categorized as much weight gain, and the remaining participants were categorized as normal weight gain.

The second part of the questionnaire comprised the 10-question EPDS [14]. In the EPDS the lowest score is 0 and the highest is 30; the four choices for each question are scored from 0 to 3. As the score result increases, the likelihood of depression increases. The EPDS was adapted into Turkish by Aydın et al., who determined the cutoff score to be 13. Validity of EPDS was 75.5% for sensitivity and 71.5% for specificity; Chronbach's alpha was 0.72 [15]. In this study, the participants who received a score of 13 and over were accepted as having depression risk.

Data analysis

Variables were investigated using the Kolmogorov-Smirnov test to determine normal distribution ($p>0.05$). Chi-squared test and one-way analysis of variance-ANOVA (Tukey test) were used for the analysis of data in the SPSS 21.0 statistical software. In one-variable analysis, a logistic regression model was developed with independent variables with the value of $p<0.10$. The dependent variable was "depression status". p value of ≤0.05 was accepted as statistically significant.

Results

The average age of the 302 mothers who participated in the study was 28.05±4.33 (18-41) and 8.6% of the mothers were aged over 35. In the group, 57% of the mothers had a primary school degree, 30.5% secondary school degree, and 12.6% higher education/university degree. 74.5% of the mothers and 3.3% of spouses were unemployed. 15.9% of the participants reported having a monthly household income below 1000 Turkish lira (TL) and 13.9% of the participants over 3000 TL.

18.5% of the participants mentioned that they were not satisfied with where they lived, 43.4% reported they were living in a rented dwelling, and 31.8% stated that the number of household members was over 4.

The prevalence of PPD was 32.1% (n: 97) among the participants. With regard to household characteristics, the frequency of PPD was higher in participants who lived in a rented dwelling (p:0.020), were not satisfied with where they lived (p:0.003), or lived in a house where the number of household members was over 4 (p:0.05). There was no relationship between other sociodemographic characteristics and the frequency of PPD (p>0.05). According to results of a multiple regression model, the factors of living in a rented dwelling, dissatisfaction with where they lived, and living with over 4 household members each double the PPD risk. As independent factors such as mother's age, occupational status, and educational level had p>0.10 in one-variable analyses, they were not included in the model (Table 1).

Furthermore, 11.6% of the mothers reported they had smoked during pregnancy and 11.3% had a chronic disease. It was found that 16.6% of the participants had past experience of depression. With respect to pregnancy weight gain, the results show that 14.2% of the mothers gained little weight, 58.6% normal weight, and 27.2% much weight. The results further revealed that 79.1% of the mothers had an intended pregnancy, 43.4% of the babies were female, 40.4% of the mothers had vaginal delivery, the birth weight was under 2500 g in 37% of the babies, and 58.6% of the babies were only breastfed in the first six months (Table 2) .

The frequency of PPD was higher in mothers who smoked during pregnancy (p:0.000), had a past experience of depression (p:0.000), gained much weight during pregnancy (p:0.006), had an unintended pregnancy (p:0.000), or had a baby with a birth weight less than 2500 g (p:0.010). There was no relationship between other characteristics related to the mother and baby and the frequency of PPD (p>0.05). According to results of the multiple regression model, smoking during pregnancy, past experience of depression, and too much weight gain during pregnancy were the factors that almost doubled the PPD risk, while intended pregnancy was a protective factor against PPD. No significant relationship was found between PPD and the sex of the baby, the number of living children. As independent factors such as history of a chronic disease, type of delivery, and type of feeding calculated as p>0.10 in one-variable analyses, they were not included in the model (Table 2).

Table 1. The evaluation of the relationship between mother's sociodemographic characteristics and the frequency of PPD

Risk Factors	Total (N:302)	PPD (N:97)	Statistically evaluation	
	N (%)	n (%)	p value*	OR (confidence interval %95)**
Age of mother				
<25	82(27.2)	26 (26.8)	0.548	
25-35	194(64.2)	62 (63.9)		
>35	26(8.6)	9 (9.3)		
Occupational status of mother				
Employed	77(25.4)	20 (26.0)	0.181	
Unemployed	225(74.6)	77 (34.2)		
Level of education				
Primary	172(57.0))	59 (34.3)	0.442	
Secondary	92(30.5)	29 (31.5)		
High school	38(12.6)	9 (23.7)		
Level of income (TL)				
<1000	48(15.9)	16 (33.3)	0.066	1
1000-2000	120(39.7)	48 (40.0)		1.52 (0.72-3.21)
2000-3000	92 (30.5)	24 (26.1)		0.79 (0.35-1.78)
>3000	42 (13.9)	9 (21.4)		0.77 (0.27-2.14)
Status of house				
Owner of house	171(56.6)	45 (26.6)	0.020	1
Rented	131(43.4)	52 (39.4)		1.91 (1.11-3.29)
Satisfaction from the place of residence				
Satisfied	246(81.5)	70 (28.5)	0.004	1
Not satisfied	56(18.5)	27 (48.2)		1.92 (1.02-3.66)
Number of people living in the house				
≤4	206(68.2)	59 (28.6)	0.051	1
>4	96(31.8)	38 (39.6)		1.87 (1.07-3.29)

*Results of Chi-squared test

**In one-variable analysis, a logistic regression model results were developed with independent variables with the value of p<0.10

Tablo 2. The comparison of some characteristics related to the mother and baby with frequency of PPD

Risk Factors	Total (N:302)	PPD (N:97)	Statistically evaluation	
	N(%)	n (%)	p value*	OR (confidence interval %95)**
Smoked during pregnancy				
No	267 (88.4)	76 (28.5)	0.000	1
Yes	35 (11.6)	21 (60.0)		2.63 (1.18-5.91)
Past experience of depression				
No	252(83.4)	69 (27.4)		1
Yes	50(16.6)	28 (56.0)	0.000	2.93 (1.14-5.90)
Weight gained during pregnancy				
Little weight gain	43 (14.2)	12 (27.9)	0.006	1
Normal weight gain	177 (58.6)	47 (26.6)		0.93 (0.44-1.96)
Much weight gain	82 (27.2)	38 (46.3)		2.23 (1.10-4.94)
Intended pregnancy				
No	63(20.9)	39 (60.3)	0.000	1
Yes	239(79.1)	58 (24.3)		0.22 (0.11-0.42)
Diagnosed chronic diseases				
Yes	34 (11.3)	84 (37.1)	0.498	
No	268 (88.7)	13 (31.5)		
Type of delivery				
Normal	122(40.4)	39 (32.8)	0.759	
Section	180(59.6)	58 (31.1)		
Sex of baby				
Male	171 (56.6)	48 (28.1)	0.085	1
Female	131 (43.4)	49 (37.4)		1.57 (0.91-2.70)
Number of children living				
≤2	251(83.1)	75 (29.9)	0.065	0.98 (0.92-1.05)
2 üzeri	51(16.9)	22 (43.1)		1
Baby's birthweight				
≤2500gr	111 (37.0)	46 (41.1)	0.011	1
>2500gr	191 (63.0)	51 (26.8)		0.63 (0.37-1.09)
Baby's nutritional status				
Breastfed	177 (58.6)	54 (30.5)	0.411	
Mom	43 (14.2)	12 (27.9)		
breastfed +mom	82 (27.2)	31 (37.8)		

*Results of Chi-squared test

**In one-variable analysis, a logistic regression model results were developed with independent variables with the value of p<0.10

The mothers' EPDS scores were also evaluated by the age of the baby, where it was found that the average score was higher in mothers with a one-month baby (11.8±5.7) compared to the others, and that the average score decreased as the age of the baby increased (F:3.63 p:0.003) (Figure 1) .

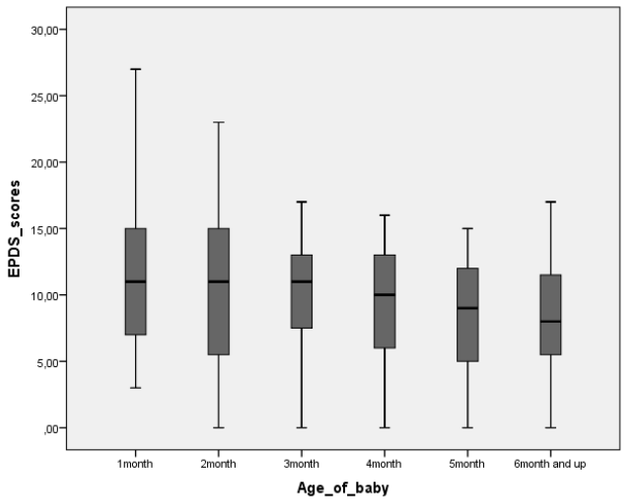


Figure 1. The mothers' average score in EPDS and confidence interval by the age of baby (F:3.63 p:0.003)

Discussion

This study focused on the prevalence of PPD and associated risk factors in mothers with a baby aged 0-12 months, who presented to pediatrics and family medicine polyclinics of the hospital for any reason. The PPD prevalence was 32.1% in the study, where EPDS was used (Tables 1,2). Several cross-sectional studies conducted with this scale worldwide provide the following results with regard to PPD prevalence: 63.1% in Pakistan, 36.5% in South Africa, 36.1% in Korea, 34.5% in Taiwan, 32.4% in India, 11% in Israel, 13% in Canada, 22.5% in Ireland, 13.9% in Japan, 38.1% in Italy, 17.1% in Germany, 17.4% in Spain, 12.8% in the UK, 10.1% in New Zealand, 9.3% in Norway, 9% in Australia, and 8.5% in France [5]. The cross-sectional studies conducted in Turkey indicate that the prevalence ranges between 14.0% and 41.4% [7-9].

The PPD prevalence is likely to vary according to cultural differences and use of different scales for diagnosis [16]. In this study, comparisons were made with studies in which the EPDS was used. However, it should be noted that different cutoff scores determined in different studies may cause variations in prevalence values.

The prevalence rate found in this study is close to the rates in developing countries (considering the rates across the world), and similar to the prevalence rates found in Turkey. Nevertheless, the PPD prevalence is higher in Kütahya than other values reported for western provinces of Turkey. No other study was conducted in Kütahya related to PPD prevalence. However, the fact that this is a hospital-based study may play a role in the higher PPD prevalence. Thus, the result cannot be generalized to the whole population. Most prevalence studies cover a period shorter than one year after birth [5,8,9]. However, the literature suggests that PPD is likely to develop at any time during the year following delivery [2-4]. Thus, we believe that the involvement of mothers with a baby aged 0 to 12 months is one of the strengths of our study.

Among the potential sociodemographic risk factors that are associated with PPD are economic hardship, being a housewife, being an immigrant, having an unemployed or uneducated spouse, polygamy, domestic violence, and dissatisfaction with life conditions [7-11]. Some studies report that the PPD risk is higher among economically disadvantaged women [8-10]. A high economic status causes people to have less anxiety about the future. Furthermore, a living area with desired characteristics improves the quality of life and decreases negative thoughts about life. On the other hand, a low economic status is more likely to bring about depression [10,16]. In the present study, the level of income may explain the increased PPD risk in women who were unsatisfied with where they lived or who lived in a rented dwelling. It was noted that the PPD risk lowered as the level of income increased, although no statistically significant relationship was found between them.

Mothers' level of education is a factor that affects cognitive and behavioral development of children in infancy and later in their lives. The awareness about infant development is expected to be higher as the level of education increases. It was reported that there is a negative correlation between PPD and the educational level of mothers [5,17]. In the case of working mothers, stress at work and the anxiety of not spending enough time with baby are the factors that trigger PPD. However, this study has not presented any statistically significant relationship between PPD and the educational level or occupational status of mothers.

Rituals based on traditions, e.g. support of the elder in family and mothers' taking time to rest, have positive impacts on the mood of mothers expecting affection and care after delivery [18]. A study conducted in the United Arab Emirates reported that domestic problems and hence higher PPD prevalence were present in women living in crowded households. However, the same study also noted that a multiparous mother became happier after each birth and the mother's importance in the family increased as the number of children increased [18]. In Nepal where there are many socially and financially disadvantaged families, a study reported that each child was perceived as a burden and this triggered PPD in mothers [19].

In the present study, we found that the PPD risk was higher in women living in crowded families. The PPD prevalence was higher in mothers who had more than two children; however, the difference was not statistically significant. As the number of family members and children at home increases, the workload of mothers increases too; with the removal from the nuclear family, the effect of cultural factors becomes more tangible. Both factors are likely to trigger depression in women.

Smoking during pregnancy may result from several factors, including low socioeconomic status, low educational level, non-presence of spouse, unintended pregnancy, disregard of the baby's health, and living with smoking family members [20,21]. Although quitting smoking is not easy, many studies have shown that over half of women quit smoking after learning that they are pregnant [20-22]. Miyazaki et al. reported that there was a positive correlation between smoking and depression symptoms [21].

In this study, 11.6% of the mothers reported that they smoked during pregnancy, and it was found that the PPD risk was twice as high in smoking mothers as in non-smoking mothers. Many factors that cause smoking during pregnancy are also likely to be factors that cause depression. It should nevertheless be noted that because details related to smoking were not questioned in the survey, some factors cannot be explained clearly.

There are several studies suggesting that the risk of developing PPD is higher in women with a past experience of depression. Past psychological problems may be an obvious predictor of postnatal depression [19-23].

The results related to the relationship between history of depression and PPD in this study support findings in the literature. The fact that about 17% of the mothers had a prior experience of depression is a significant finding. However, because the past experience of depression was determined based on self-reports of participants, it is not clear whether the depression diagnosis was precise.

The adverse effect of unintended pregnancy on mothers may be explained by social and psychological unpreparedness. An unwanted baby is likely to affect the whole life and career plans of a mother and trigger PPD [24,25]. Thus, it is not surprising that PPD prevalence was higher in this study among mothers that had an unintended pregnancy.

A meta-analysis reported that approximately 40% of mothers with a premature baby showed postnatal depression symptoms [26] and that there was a positive correlation between low birth weight and PPD [27].

We found in this study that the PPD prevalence was higher in the mothers of babies with birth weight less than 2500 g. Low birth weight is likely to cause mothers to feel anxiety for the baby and to feel that she has failed to meet the baby's needs during pregnancy. The inclination for depression may be greater in this group because the above factors increase stress in mothers.

Some studies showed that lack of breastfeeding was a potential risk factor for PPD. The ties between mother and baby get stronger physiologically and psychologically with breastfeeding and the feeling of guilt and insufficiency may have negative effects on the mental health of non-breastfeeding mothers [28-30]. The present study did not show any relationship between breastfeeding and PPD.

The sex of the baby is a hidden PPD risk factor for mothers. It was reported that male children are always preferred in the cultures of countries, such as Arabic countries, Iran, India, China, Japan, Taiwan, and Korea [16,31]. Male children are involved in family business, provide economic support to the family, and continue the family's lineage. Female children are tied to their husband's family after marriage and may not have strong bonds with their own family. The perceptions related to the sex of the baby are similar in Turkey to the above-mentioned countries. However, this study did not show any relationship between the sex of the baby and PPD.

Several studies note that depression risk is higher at the beginning of the postpartum period compared to in the following months [10-13,16]. In this study, the higher rate of depression in the first months after delivery may be explained by the characteristics of the postnatal period. The postnatal period, starting from the first month after delivery, is the period when mother and baby get used to each other and when sleep and adaptation problems are likely to have negative psychological effects on mother.

The frequency of depression increases in teenage women. Yet, there are different viewpoints about PPD and age. In this study we found no correlation between mother's age and PPD while some studies reported that young age or adolescent pregnancy was a factor increasing depression [8,10,11,30]. Some other studies showed that there was no relationship between gestational age and PPD [7,9]. There are studies reporting that excessive or insufficient weight gain in pregnancy may have physiological and psychological negative effects on the mother and that these effects are likely to continue after birth [29-32]. The same studies showed that mothers who gained weight over 16kg during their pregnancy were more depressive, and that there was a positive correlation between weight gain and PPD [31,32]. The results of our study support this finding, showing that gaining too much weight during pregnancy doubled the PPD risk.

This research, conducted in the provincial center of Kütahya, is a cross-sectional study, evaluating the mental health of women at reproductive age after childbirth. The study used the EPDS to screen for the presence of PPD in mothers who presented to the secondary healthcare institution for any reason. However, no psychiatric sessions were conducted with mothers and no scale was used for a precise psychiatric diagnosis. A study reported that the EPDS was more sensitive than a clinical interview [33]. However, the EPDS is based on self-reporting and is mostly used for screening purposes. It is targeted at determining the risk rather than diagnosing depression precisely. These factors constitute limitations for our study, just as for many other studies based on this scale.

The National Institute for Care and Health Excellence guidelines emphasize the need for guidance for antenatal and postnatal mental health of women and they make evidence-based recommendations for possible mental health problems faced by women [34]. In consideration of these recommendations, the data collected in this study may be used to plan regional healthcare services and to take preventive measures for the mental health of women. The EPDS may be used to screen PPD among mothers who present to healthcare institutions for pregnancy follow-up visits or for vaccination of babies. This enables healthcare professionals to follow women with PPD risk more closely and to direct them to related departments for precise diagnosis. Thus, early diagnosis and proper recommendations will help to improve the quality of life, not only for the mothers but also for their babies and families.

To conclude, in the present study, dissatisfaction with where they live, living in a rented dwelling, an unintended pregnancy, a past experience of depression, smoking, excessive weight gain during pregnancy, giving birth to an underweight baby, and the first months after birth are the risk factors that have a significant effect on PPD. The risk factors that have been found in this study can help to guide planning regional health services for specific risk groups.

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Competing interests

The authors declare that they have no competing interests.

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The role of hematological and biochemical markers in preeclampsia prediction

Preeklampsi öngörüsünde hematolojik ve biyokimyasal belirteçlerin rolü

Prediction of preeclampsia with analysis of blood tests

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Öz

Giriş: Bu çalışmanın amacı; erken gebelik dönemindeki tam kan sayımı parametrelerinin ve ilk trimester trizomi taraması sırasında bakılan biyokimyasal parametrelerin erken başlangıçlı preeklampsiyi tespit edip etmeyeceğinin araştırılmasıdır. Gereç ve Yöntem: Çalışmadaki 1. Grup, 18-40 yaşındaki tekil gebeliği olan ve 34. gebelik haftasından önce preeklampsi tanısı alıp 37. hafta ve sonrasında doğum yapan 214 hastadan oluşmaktaydı. Kontrol grubunu 2. grup oluşturdu. Yardımcı üreme teknikleriyle gebe kalanlar, vücut kitle indeksi >30kg/m2 olanlar, kromozomal anomalili gebeliğe sahip olanlar, medikal problemi ya da öyküsü olanlar, çoğul gebelikler, antenatal dönemde vajinal kanaması olanlar ve erken doğum öyküsü olanlar çalışma dışı bırakıldı. Preeklampsi, sistolik kan basıncı 140 mmHg ve üstü, diyastolik kan basıncı 90 mmHg ve üstü hesaplanan ve 20. gebelik haftasından sonra proteinürisi olan gebelikleri tanımlamaktaydı. Tam kan sayımı, PAPP-A ve serbest beta-HCG için kan örnekleri 11+0 ile 13+6 gebelik haftaları arasında alındı. Bulgular: Doğumdaki gebelik haftası ve doğum ağırlıkları 1. grupta anlamlı olarak daha düşük bulundu. Nötrofil lenfosit oranı ve trombosit dağılım genişliği preeklamsi grubunda daha yüksek bulundu. Buna karşın lenfosit sayısı ve PAPP-A düzeyi preeklampsi grubunda daha düşüktü. Tartışma: Mevcut gebelikteki, nötrofil lenfosit oranı ve trombosit dağılım genişliğinin yüksek seviyeleri ve lenfosit sayısı ve PAPP-A'nın düşük seviyeleri ile erken başlangıçlı peeklampsi arasında güçlü bir bağlantı olduğu sonucuna ulaştık.

Anahtar Kelimeler

Gebelik; Preeklampsi; Tarama Testleri; Trombosit; Biyokimyasal Sonuçlar

Abstract

Aim: To investigate whether complete blood count parameters of early pregnancy or biochemical markers of first-trimester trisomy screening were related to the prediction of early onset preeclampsia. Material and Method: Group 1 (n=214) was composed of patients between 18-40 years old with a single pregnancy who was diagnosed with preeclampsia at <34 gestational weeks and had delivery at ≥37 weeks of gestation. Group 2 (n=240) was a control. Women who became pregnant by assisted reproductive technologies or had a body mass index (BMI) >30kg/m2, had a history of delivery complicated by chromosomal anomalies, current or previous medical problems, or multiple pregnancies and patients who had vaginal bleeding in the antenatal period or a history of preterm delivery were excluded. Preeclampsia for pregnancy is defined as having a systolic blood pressure ≥140 and diastolic blood pressure ≥90 as well proteinuria after the 20th gestational week. Blood samples for complete blood count, PAPP-A, and free beta-HCG were collected between 11+0 to 13+6 gestational weeks. Results: The mean gestational weeks at delivery and birth weight were significantly lower in Group 1 (preeclampsia) than in Group 2 (control). NRL and PDW were found significantly higher in Group 1. Lymphocyte count was significantly lower in Group 1. PAPP-A was lower in Group 1. Discussion: We found a strong relation between high levels of NLR and PDW, as well as low levels of lymphocyte count and PAPP-A, with early onset preeclampsia development during the current pregnancy.

Keywords

Pregnancy; Preeclampsia; Screening Tests; Platelets; Biochemical Results

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Introduction

Preeclampsia affects approximately 6-8% of pregnancies [1]. It is one of the most fatal events seen during pregnancy, it presents with hypertension (systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90) and proteinuria (≥300 mg/24 hours or 1+persistent by dipstick) that may arise from early weeks of pregnancy (but generally after the 20th gestational week); it has a high morbidity and mortality rate [2]. While numerous factors have been accused as contributors to the disease, still the pathogenesis is not clear, and therefore early prediction is impossible [3]. Pathologic trophoblastic invasion of maternal vessels causes impairments in placental perfusion, thereby damaging the maternal endothelial cells and destroying their functions by the mediators that flow into maternal circulation. This mechanism is suspected for preeclampsia pathogenesis [2]. It is known that more than half of maternal and fetal mortality due to hypertensive diseases can be prevented [4]. However, termination of pregnancy is still the most effective treatment. Therefore, any of the effective determinants may have great importance in prediction and treatment of preeclampsia.

A balance between the coagulation and anti-coagulation system is essential in the formation and continuation of pregnancy. Many biochemical determinants like D-dimer (DD), soluble fms-like tyrosine kinase-1 (sFlt-1), and platelet distribution width (PDW) have been studied [5-7]. Studies have focused on neutrophil/lymphocyte ratio (NLR), and thrombocyte/lymphocyte ratio (TLR) and researchers have shown that the ratio between blood cell subtypes might be promising in diagnosing and determining the prognosis of the diseases related to a chronic low level of inflammation [8-10].

Pregnancy-associated plasma protein-A (PAPP-A) is one of the most frequently studied first-trimester biochemical markers, especially in pregnancies complicated with intrauterine growth retardation and preeclampsia [11]. PAPP-A is related to fetal growth and trophoblastic invasion of deciduas. Its level increases, especially from the 22nd gestational week to term [12]. PAPP-A is a metalloproteinase that proteolyzes the intrinsic growth factor binding protein-4 (IGFBP-4). In-vitro studies showed that PAPP-A plays a role in cellular response to vascular damage and its increased levels in circulation have been determined as a marker of oxidative stress [13].

In this study, we aimed to investigate whether complete blood count parameters of early pregnancy or biochemical markers of first-trimester trisomy screening (PAPP-A, free beta-HCG) were related to prediction of early onset (before the 34th gestational week) preeclampsia.

Material and Method

This was a retrospective case-control study of preeclamptic nulliparous women who gave birth at the Department of Obstetrics and Gynecology in Medipol University, Faculty of Medicine, from January 2013 to December 2016. The study was based on chart review. In total, 12,960 patients were searched. The study group was composed of patients between 18-40 years old with a single pregnancy who were diagnosed with preeclampsia at <34 gestational weeks and had delivery at ≥37 weeks of gestation who were routinely followed up in our hospital beginning from the first antenatal examination and had first-trimester trisomy screening. The study group patients did not have any previous history of chronic diseases. Our control group was composed of 18-40 year-old women with singleton pregnancies without any complications during pregnancy and who gave birth at ≥37 weeks of gestation in the same period. Women who became pregnant by assisted reproductive technologies or had a body mass index (BMI) >30kg/m2, had a history of delivery complicated by chromosomal anomalies, current or previous medical problems, or multiple pregnancies were excluded. Furthermore, patients who had vaginal bleeding during the antenatal period or a history of preterm delivery were excluded.

Preeclampsia for pregnancy is defined as having a systolic blood pressure ≥140 and diastolic blood pressure ≥90 as well proteinuria (300 mg/24 hours or 1+persistant by dipstick) after the 20th gestational week. Blood pressure was measured at least two times within a 6-hour interval, and it was confirmed that the patient had at least 30 minutes of rest before measurement. Gestational age was calculated based on the first day of the last menstruation period and/or crown-rump length measurement of the first-trimester ultrasound. Blood samples for complete blood count, PAPP-A, and free beta-HCG were collected between 11+0 to 13+6 gestational weeks.

Group 1 (study group) consisted of 214 patients who had early onset preeclampsia whereas Group 2 (control group) was formed from 240 patients. The two groups were compared with each other due to their demographic features and obstetric and biochemical results.

Blood sample collection and laboratory methods:

Venous blood samples were collected by vacuum tubes for biochemical analyses. After the blood had coagulated the sample was centrifuged for ten minutes at 3000 RPM. The electro-chemiluminescence immunoassay (ECLIA) method was used for measuring the quantity of free b-HCG and PAPP-A. For this technique, the Immulite 2000 immunoassay system by Siemens was used. Tubes containing K3EDTA were used for CBC investigation. The quantity of CBC parameters were measured by automated hematology analyzer (XT2000i, Sysmex, Osaka, Japan).

Statistical Method

Data were analyzed by using the Statistical Package Social Sciences (SPSS) Version 15.0 (SPPS Inc., Chicago, IL). Descriptive statistics were used for numerical variables and presented as the mean and standard deviation. Kolmogorov-Smirnov test was used for analyzing normally distributed variables and Mann-Whitney U test was used in the comparison of subgroups.

Results

In total 454 patients' data was analyzed. The mean age was similar for the two groups, being 28.7±3.4 for Group 1 and 27.5±3.5 for Group 2. The mean gestational weeks at delivery and birth weight were significantly lower in Group 1 compared to Group 2 (37.6±1.1 vs. 40.5±1.5 weeks, $p<0.01$ and 2845±334 vs. 3320±331 g, $p<0.01$, respectively). Nevertheless, there was no statistically significant difference for gravidity, smoking status, and BMI before the pregnancy between the two groups (Table 1).

Table 1. Demographic and obstetric features of two groups (for the explanation of gravidity, mean and minimum-maximum values were used; for smoking status, the number of patients and their percentages were used).

	Group 1 (n=214)	Group 2 (n=240)	p-value
maternal age (years)	28.7±3.4	27.5±3.5	0.98
gravidity	2(1-3)	1(0-2)	0.13
smoking status	7 (3.2%)	8 (3.4%)	0.90
gestational weeks at delivery (weeks)	37.6±1.1	40.5±1.5	<0.01
BMI (kg/m^2)	22.9±3.2	22.7±3.5	0.09
Birth weight (g)	2845±334	3320±331	<0.01

Table 2. Comparing two groups for hematological and biochemical markers

	Group 1 (n=214)	Group 2 (n=240)	p-value
leukocyte counts (x10^3/mm$^{3)}$	8.7± 1.5	8.5± 1.4	0.57
neutrophil counts (x10^3/mm^3)	6.8±2.1	6.6±1.4	0.54
lymphocyte counts (x10^3/mm^3)	1.8±0.49	2.3± 0.79	<0.01
platelet counts (x10^3/mm^3)	235± 53	238±41	0.13
NLR	3.96± 1.23	3.22± 1.24	0.05
PLR	119± 51	120± 43	0.87
MPV	10.3±0.85	10.4±1.1	0.24
PCT	0.251±0.04	0.248±0.05	0.77
PDW	12.5±2.1	11.6± 1.87	<0.01
PAPP-A (MoM)	0.78±0.3	1.19±0.84	<0.01
free-b-HCG (MoM)	0.99±0.51	1.05±0.47	0.36

NRL and PDW were found significantly higher in Group 1 compared to Group 2 (3.96±1.23 vs. 3.22±1.24, p<0.05 and 12.5±2.1 vs. 11.6±1.87, p<0.01). The lymphocyte count was significantly lower in Group 1 (1.8±0.49 vs. 2.3±0.79 x103/mm3, p<0.01). Furthermore, PAPP-A was found to be lower in Group 1 (0.78±0.3 vs. 1.19±0.84 MoM, p<0.01). Other CBC parameters, as well as free b-HCG, were found to be similar in the two groups.

Discussion

In this study, it was shown that first-trimester biochemical markers such as NLR, PAPP-A, and hematologic parameters might be useful in the early detection of preeclampsia. Despite the fact that many studies have been conducted on early prediction of preeclampsia, none to date has identified any single marker that is simple, quick, non-invasive, reliable, and low-cost [14].

In a retrospective study, uncomplicated pregnancies were compared with pregnancies with severe and moderate preeclampsia, and it was shown that platelet count was negatively related to the severity of preeclampsia [15]. In support of this, another study showed that preeclamptic pregnant women had lower platelet counts compared to non-complicated pregnant women and non-pregnant women [16]. Furthermore, AlSheeha et al. showed lower platelet count in preeclamptic women, but they could not find any relation between the platelet count and severity of preeclampsia [17]. We could not find any statistically significant difference between the study group and the control group for platelet count. Our findings were supported by a previous study that concluded that preeclampsia impaired platelet function in spite of platelet count abnormalities [1].

During pregnancy, platelet turnover increases in maternal circulation. While larger platelets are metabolically and enzymatically much more active, they have increased thrombotic potential. Previous studies from Turkey had conflicting results. While one study showed statistically significant higher levels of MPV in preeclamptic women [18], another study displayed no difference between two groups for CBC and MPV [19].

MPV is a determinant of platelet function and activation. Its level has been shown to increase in conditions that are related to endothelial cell injury, such as preeclampsia [20]. Endothelial cell injury causes microthrombus formation, increased thrombus turnover, and increased the level of younger platelets in circulation and so increases the MPV level. Furthermore, it was shown that the probability of preeclampsia was two times higher in those pregnant women who had a MPV level lower than 8.5 fL in gestational weeks 24-28 [18]. In contrast, we could not find any significant difference in MPV levels between our study and control groups.

Later studies have focused on NLR and PLR, which are two parameters of CBC thought to indicate systemic inflammation due to decreased lymphocyte rate. It has been found that high levels of NLR and PLR were correlated with renal function impairment in diabetic patients and with increased mortality rate in malignancies [21,22]. Despite the fact that NLR was found to be higher in preeclamptic patients [23], there is conflicting evidence about the association between the severity of preeclampsia and NLR [23-25]. In the present study, NLR was found to be significantly higher in the preeclampsia group than in the control group, while there was no significant difference for PLR. In support of our study, another study from our country could not find any difference for PLR in preeclamptic patients [26].

PDW is a well-known parameter of platelet activation and endothelial cell injury [26]. It was thought to be a much more specific marker of platelet activation than MPV since its level was not affected by platelet distention [7]. Although some studies have not found any statistically significant difference for PDW in preeclamptic patients [17,27]. In most studies, PDW was found higher in preeclamptic patients [7,16,28]. In our study, consistent with most studies in the literature, PDW was found higher in the preeclampsia group. Furthermore, regardless of NLR, PDW occurred at different levels when comparing severe and moderate preeclampsia patients [7].

Plateletcrit (PCT) is calculated with platelet count and MPV [29]. A rate of PCT under 0.1% is an indirect sign of platelet transfusion requirement, and it is a more specific determinant than platelet number in thrombocytopenic patients [30]. Although we found a similar rate between our study and control groups, it is clear that more studies are needed in this field.

Preeclamptic women who had chromosomally normal babies were found to have low levels of PAPP-A, but its predictive value was not found to be convincing enough [31]. Despite this, in another study, low levels of PAPP-A were determined as a statistically significant marker of late-onset preeclampsia [32]. In a study of 973 pregnant women, 111 had preeclampsia,

and their PAPP-A level was found between 0.53 to 1.08, with a mean value of 0.8 MoM [33]. Similarly, we found a mean PAPP-A value of 0.78 MoM in the preeclampsia group. Furthermore, a measurement of the PAPP-A level below the 10th percentile was related to an increased preeclampsia rate (OR 1.6, 95% CI: 1.3-2.6) (32). Despite the fact that our findings did not reveal any critical value of PAPP-A level for prediction of preeclampsia, we found it to have a level lower in the preeclampsia group.

In our study, we found a strong relation between high levels of NLR and PDW, as well as low levels of lymphocyte count and PAPP-A, with early onset preeclampsia development during the current pregnancy. While our results need to be confirmed with larger studies, we believe that patients who have similar hematological and biochemical results to our study should be assessed for preeclampsia.

Competing interests

The authors declare that they have no competing interests.

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Reliability of magnetic resonance imaging in rotator cuff and biceps tendon pathologies

Rotator manşet ve biseps uzun başı tendonu patolojilerinde manyetik rezonans görüntülemenin güvenirliği

Magnetic resonance imaging in shoulder tendons

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Öz

Amaç: Biz bu çalışmada omuz ağrısı ve disfonksiyonun en önemli nedenlerinden olan rotator manşet lezyonları ve biseps uzun başı tendonu patolojilerinde, artroskopi ile karşılaştırmalı olarak manyetik rezonans görüntülemenin tanısal performansını incelemeyi amaçladık. Gereç ve Yöntem: Artroskopik cerrahi uygulanmış 180 hasta tespit edildi. Bu hastalardan öncesinde tanısal manyetik rezonans görüntüleme tetkiki olan ve çalışma kriterlere uyan 17'si erkek, 47'si kadın toplam 64 hasta çalışmaya dahil edildi. Artroskopik cerrahi öncesi 6 hafta süre içerisinde çekilen manyetik rezonans görüntüleme bulguları ile artroskopik omuz eklem muayene bulguları retrospektif olarak incelendi. Bulgular: Supraspinatus tendonu tam kat yırtıklarında sensitivite %89.1, spesifisite %94.4, parsiyel yırtıklarda sensitivite % 93.8, spesifisite %87.5, biseps uzun baş tendonu tam kat yırtıklarında sensitivite %33.3, spesifisite %98.4, parsiyel yırtıklarda sensitivite %58.3, spesifisite %80.8 saptandı. Artroskopide 24 (%37.5) hastada, manyetik rezonans görüntülemede 32 (%50) hastada birden fazla tendonda yırtık saptandı. Ayrıca rotator manşet yırtıklarında artroskopide 15 (%23.4), manyetik rezonans görüntülemede 19 (%29.6) hastada biseps uzun başı tendon yırtıklarının birlikteliği tespit edilmiştir. Tartışma: Manyetik rezonans görüntüleme rotator manşet tendonu patolojilerinde, artroskopi ile karşılaştırmalı olarak, özellikle supraspinatus tendonu yırtıklarında yüksek doğruluk, kappa değeri (kappa değeri: 0,78) ile güçlü tutarlılık aralığında sensitivite ve spesifisitesi yüksek bulunmuştur. Ancak biseps uzun başı tendon patolojilerinde sensitivite düşük tespit edilmiştir. Manyetik rezonans görüntüleme günümüzde, omuz tendonu patolojilerinde özellikle rotator manşet tendonu patolojilerinde güvenilir tanı yöntemi olarak yerini korumaktadır.

Anahtar Kelimeler

Rotator Manşet; Biseps Uzun Başı; Tam Kat Yırtık; Parsiyel Yırtık; Manyetik Rezonans Görüntüleme

Abstract

Aim: In the study, we aimed to evaluate the diagnostic performance of magnetic resonance imaging in comparison with arthroscopy in rotator cuff lesions and pathologies of the long head of the biceps tendon, which are one of the most important causes of shoulder pain and dysfunction. Material and Method: 180 patients treated with arthroscopic surgery were identified. Sixty-four patients (17 males, 47 females) who had undergone diagnostic magnetic resonance imaging and met the study criteria were enrolled in the study. The magnetic resonance imaging within the last 6 weeks preoperatively and arthroscopic shoulder joint examination findings during the operation were reviewed retrospectively. Results: Sensitivity was found to be 89.1% and specificity was found to be 94.4% in the full thickness tears, and sensitivity was found to be 93.8% and specificity was found to be 87.5% in the partial tears of the supraspinatus tendon; sensitivity was found to be 33.3% and specificity was found to be 98.4% in the full-thickness tears, and sensitivity was found to be 58.3% and specificity was found to be 80.8% in the partial tears of the long head of the biceps tendon. 24 (37.5%) patients in arthroscopy and 32 (50%) patients in magnetic resonance imaging had more than one tear in the tendon. Furthermore, the combination of the tears of the long head of the biceps tendon was found in the rotator cuff tears' arthroscopy of 15 patients (23.4%) and magnetic resonance imaging of 19 (29.6%) patients. Discussion: In comparison with arthroscopy, magnetic resonance imaging in rotator cuff tendon pathologies, especially in the supraspinatus tendon tears, demonstrated high accuracy, the kappa value (kappa value: 0.78), high sensitivity and specificity in the strong consistency range. However, sensitivity was low in pathologies of the long head of the biceps tendon. Magnetic resonance imaging remains to be a reliable diagnostic method in shoulder tendon pathologies, especially in rotator cuff tendon pathologies.

Keywords

Rotator Cuff; Biceps Long Head; Full Thickness Tear; Partial Tear; Magnetic Resonance Imaging

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Introduction

Shoulder pain is the third most common clinical complaint of the musculoskeletal system, and it is observed in 7-26% of adults [1]. Among the causes of shoulder pain and dysfunction, rotator cuff lesions are among the leading causes according to their prevalence. The rotator cuff tear is observed in 65-70% of cases and its prevalence increases with age [1-2]. Moreover, pathologies of the long head of the biceps tendon are mostly associated with rotator cuff tears and are among the most important causes of anterior shoulder pain [3]. Therefore, it is very important that the rotator cuff and the long head of the biceps show integrity in patients consulting with complaints of shoulder pain and dysfunction [3].

Nowadays, many imaging methods such as ultrasonography, computed tomography (CT), CT-arthrography, Magnetic Resonance Imaging (MRI), and magnetic resonance- arthrography are used for this purpose. In recent years, the fact that intraarticular and periarticular structures can be displayed in more detail with the increased spatial resolution in MRI has made MRI one of the most preferred diagnostic methods in the evaluation of shoulder joint pathologies nowadays [1,2].

In the study, we aimed to examine the diagnostic performance of MRI in comparison with arthroscopy in pathologies of the rotator cuff and the long head of the biceps tendon, which are among the most important causes of shoulder pain and dysfunction.

Material and Method

Study Population and inclusion criteria

180 patients, who had undergone arthroscopic surgery due to shoulder pain, dysfunction, and rotator cuff pathology between January 2014 and November 2016, were retrospectively identified. 64 patients who had undergone the diagnostic MRI examination and matched the criteria were included in the study. Among the patients, 17 were male, 47 were female, the age average was 56.1+9.8 years, the age range was 37-74 years. The MRIs of all the patients taken within 6 weeks before arthroscopic surgery were examined retrospectively. The local ethics committee approval was received before starting the study (Kırıkkale University clinical research ethics committee, decision no: 10/01, date 11.04.2017).

Exclusion Criteria

Furthermore, patients with adhesive capsulitis, who had undergone a surgical operation on the same side of the shoulder, having massive rotator cuff tear with pseudoparalysis, advanced osteoarthritis, large-scale (bigger than 2 cm) retracted tears associated with atrophy in the rotator cuff muscles and fatty degeneration were not included in the study. The MRI taken at the external center, cases whose MRIs had been taken 6 weeks before the arthroscopic surgery, and patients whose MRI records could not be accessed were excluded from the study.

Arthroscopy

The patients were operated under general anesthesia and in the sitting position called the beach chair position. Initially, the acromion, distal clavicle, acromioclavicular joint, coracoid, and portals were marked with a surgical marker. The posterior portal was opened approximately 2 cm medial and 2 cm inferior of the posterolateral corner of the acromion. The anterior portal was opened approximately 2-3 cm anterior of the anterolateral corner of the acromion, and the lateral portal was opened approximately 2-4 cm lateral of the posterior of the acromioclavicular joint. An arthroscopic examination of the glenohumeral joint was performed through the posterior portal. The tendons forming the rotator cuff and the tear in the long head of the biceps tendon were displayed fully, and their sizes and shapes were recorded.

Magnetic resonance imaging protocol and interpretation

MRI was performed with 1.5 Tesla MR device (Philips MRI Systems, Achieva Release 3.2 Level 2013-10-21, Philips Medical Systems Nederland B.V) using the surface shoulder coil. In the examination, T1 weighted; T1-TSE (Turbo Spin-Echo) axial, T1-TSE oblique coronal (780/15; FOV 14 cm; cross-sectional thickness 3.5 mm; intersection gap 0.4 mm; matrix 320 × 256), T2 weighted; T2-FFE (Fast-Field Echo) axial, T2-TSE oblique sagittal, T2 weighted fat-suppressed, T2-SPAIR (spectral attenuated inversion recovery) axial and oblique coronal (3400/50; FOV, 14 cm; cross-sectional thickness 3.5 cm; intersection gap 0.4 mm; matrix, 256 × 256) images were obtained. All MRIs were retrospectively examined by two radiologists experienced in the musculoskeletal subject (MHŞ, MI).

The pathologies of the rotator cuff tendons, partial and full-thickness tears were examined. The absence or discontinuity of the tendon in the supraspinatus muscle was evaluated as a full-thickness tear (Figure 1a,b), and the limited focal defect on the articular or bursal surface of the tendon was evaluated as a partial tear. The absence or discontinuity of the tendon in the subscapularis and infraspinatus muscles was evaluated as a full-thickness tear (Figure 2), and the focal discontinuity, loss of integrity, and fluid increase in the tendon were evaluated as a partial tear. The pathologies in the long head of the biceps tendon, a supporter of the rotator cuff tendons, were evaluated as a full-thickness tear, partial tear, and tendon subluxation. The dislocation of the long head of the biceps tendon was not included in our study because it was not present in our patients. While the discontinuity of the tendon fibers in the long head of the biceps tendon and an empty bicipital groove in the axial and oblique sagittal sections were evaluated as a full-thickness tear, and the thinning, irregularity, fragmentation, signal increase in the tendon and liquid around the tendon and in the bicipital groove were evaluated as a partial tear (Figure 3a,b,c), the displacement of the long head of the biceps tendon from the bicipital groove to the medial was evaluated as a subluxation.

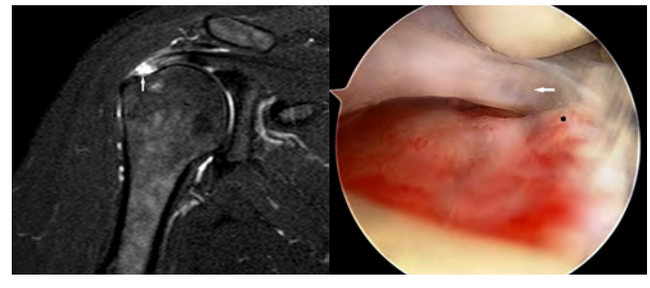


Figure 1. (a) The full-thickness tear in the supraspinatus tendon in oblique coronal T2-SPAIR (spectral attenuated inversion recovery) images in MRI (white arrow), (b) The full-thickness tear in the supraspinatus in the arthroscopy image in the same patient (white arrow), (* Tuberculum majus).

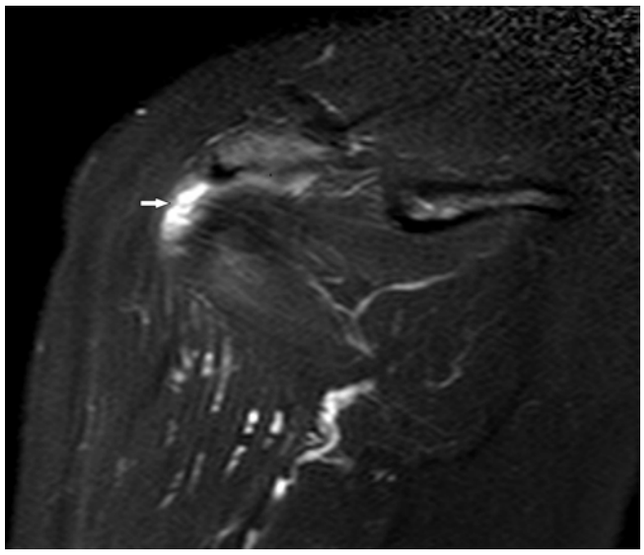


Figure 2. The full-thickness tear in the subscapularis tendon in oblique coronal T2-SPAIR (spectral attenuated inversion recovery) images in MRI (white arrow).

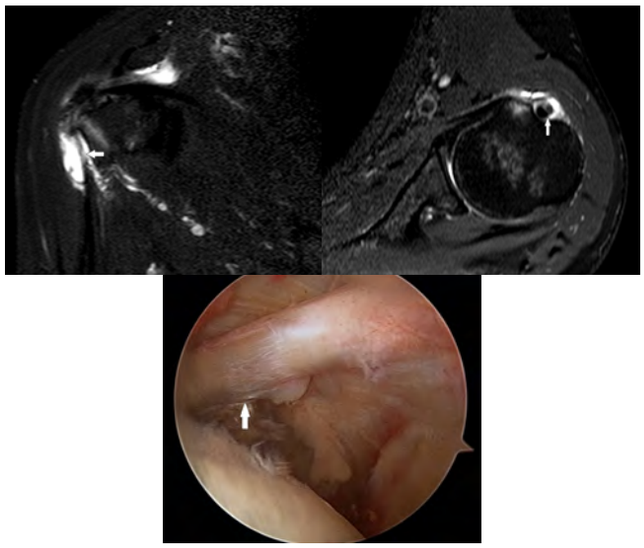


Figure 3. (a, b) The partial tear and the liquid in the tendon circumference in the long head of the biceps tendon in oblique coronal, axial T2-SPAIR (spectral attenuated inversion recovery) images in MRI, (c) The biceps tendon in the arthroscopic image of the same patient (white arrow).

Statistical analysis

The compatibility between the operation and MRI findings of the patients was compared statistically using the IBM SPSS 20.0 program with sensitivity, specificity, positive predictive and negative predictive values, accuracy, p-values, and the kappa analysis test. $p < 0.05$ was considered to be statistically significant. The receiver operating characteristic curves (ROC) were used for the efficacy of full-thickness and partial tear diagnosis of the supraspinatus and the long head of the biceps tendons of MRI.

Results

In arthroscopy, a full-thickness tear of the supraspinatus tendon was detected in 46 patients (71.9%) and a partial tear of the supraspinatus tendon was detected in 16 (25%) patients, and no tear was detected in the supraspinatus tendon in 2 patients (3.1%). There were a full-thickness tear in 4 patients (6.3%) and a partial tear in 6 patients (9.4%) in the subscapularis tendon, a full-thickness tear in 2 patients (3.1%) and a partial tear in 3 patients (4.7%) in the infraspinatus tendon, a full-thickness tear in 3 patients (4.7%) and a partial tear in 12 patients (18.8%) in the long head of the biceps tendon (Table 1). There was no tear in the teres minor tendon. Only full-thickness/partial tear was detected in 39 patients (60%) in the supraspinatus tendon, and no tear was detected in the supraspinatus tendon in 1 patient. Multiple tendon tears were detected in 24 patients (37.5%) (Table 2).

In the MRI examinations, a full-thickness tear of the supraspinatus tendon was detected in 43 (67.2%) patients and a partial tear of the supraspinatus tendon was detected in 20 (31.3%) patients, and no tears were detected in the supraspinatus tendon in 1 patient (1.6%). There were full-thickness tears in 2 patients (3.1%) and partial tears in 8 patients (12.5%) in the subscapularis tendon, full-thickness tears in 2 patients (3.1%) and partial tears in 5 patients (7.8%) in the infraspinatus tendon, full-thickness tears in 2 patients (3.1%) and partial tears in 17 patients (26.6%) in the long head of the biceps tendon, and subluxation in 3 patients (4.7%) (Table 1). No tear was detected in the teres minor tendon. Partial tear was determined in the tendon in the arthroscopy of patients with subluxation in the long head of the biceps tendon in MRI. While only full-thickness/partial tears were determined in 32 patients (50%) in the supraspinatus tendon, tears in other tendons together with

Table 1. The comparison of the sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), accuracy, p-values, and kappa analysis test between the findings of arthroscopy and MRI.

Pathological findings	Arthroscopy(n)	MRI (n)	Sensitivity	Spesificity	PPV	NPV	Kappa values	Accuracy	P values
Full-thickness tears in supraspinatus tendon	46	42	89.1	94.4	97.6	77.3	0.78	90	0
Partial tears in supraspinatus tendon	16	21	93.8	87.5	71.4	97.7	0.73	89	0
Full-thickness tears in subscapularis tendon	4	2	50	100	100	96.8	0.65	96.8	0
Partial tears in subscapularis tendon	6	8	66.7	93.1	50	96.4	0.52	90	0.001
Full-thickness tears in infraspinatus tendon	2	2	100	100	100	96.9	1	100	0
Partial tears in infraspinatus tendon	3	5	100	96.7	60	100	0.73	96.8	0
Full-thickness tears in LHBT	3	2	33.3	98.4	50	96.8	0.37	95.3	0.02
Partial tears in LHBT	12	17	58.3	80.8	41.2	89.4	0.33	76.5	0.06
Subluxation in LHBT	Partial tears	3	-	-	-	-	-	-	-

The Long Head of the Biceps Tendon(LHBT), Magnetic Resonance Imaging (MRI), Negative Predictive Values (NPV), Positive Predictive Values (PPV)

Table 2. The comparison of the association of the pathologies of rotator cuff tendons and the long head of the biceps tendon.

Pathological findings	Arthroscopy (n=64)	MRI (n=64)
Full-thickness/partial tears in supraspinatus tendon	62 (96.8%)	63 (98.4%)
Full-thickness/partial tears in the other rotator cuff tendons	15 (23.4%)	15 (23.4%)
Full-thickness/partial tears in LHBT	15 (23.4%)	19 (29.6%)
Full-thickness/partial tears in supraspinatus tendon + LHBT	14 (21.8%)	17 (26.6%)
Full-thickness/partial tears in supraspinatus tendon + the other rotator cuff tendons	10 (15.6%)	15 (23.4%)
Full-thickness/partial tears in the rotator cuff tendons + LHBT	24 (37.5%)	32 (50%)

The Long Head of the Biceps Tendon(LHBT)
Magnetic Resonance Imaging (MRI)

supraspinatus tendon tears were determined in 32 patients (50%) (Table 2).

In MRI, sensitivity was 89.1% and specificity was 94.4% in full-thickness tears and sensitivity was 93.8% and specificity was 87.5% in partial tears of the supraspinatus tendon; sensitivity was 33.3% and specificity was 98.4% in full-thickness tears and sensitivity was 58.3% and specificity 80.8% in partial tears of the long head of the biceps tendon. The tears of the long head of the biceps tendon were determined to be associated with rotator cuff tears in 19 patients (29%) (Table 2).

The reliability of the rotator cuff tendons in MRI, and the kappa value, especially in the supraspinatus tendon tears (kappa value: 0.78), were found to be high and interpreted within the strong consistency range. Sensitivity was found to be low in the full-thickness/partial tears of the long head of the biceps tendon (Table 1).

In the MRI examinations, the area under the ROC curve was calculated to be 0.918 in the diagnosis of full-thickness tears of the supraspinatus tendon (Figure 4). The area under the ROC curve was calculated to be 0.906 in the diagnosis of partial tears of the supraspinatus tendon. The area under the ROC curve was calculated to be 0.696 in the diagnosis of partial tears of the long head of the biceps tendon (Figure 5).

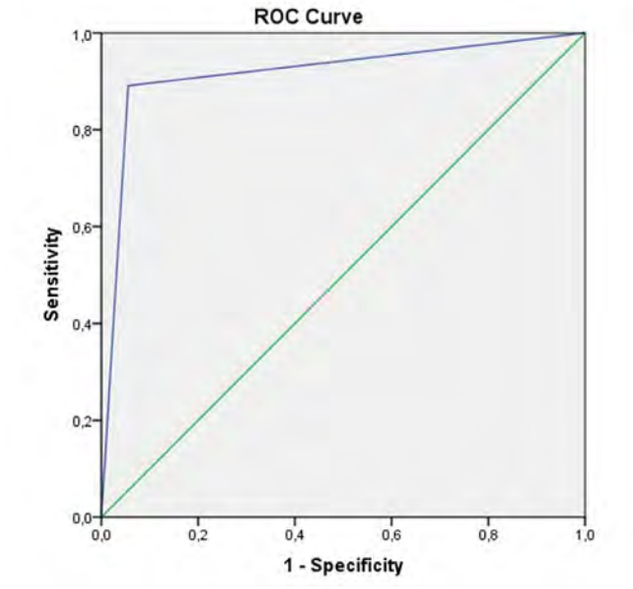


Figure 4. The ROC curve showing the MRI diagnostic performance in the supraspinatus tendon full-thickness tears compared with arthroscopy (The area under the ROC curve in the confidence interval of 0.837-0.999 is 0.918).

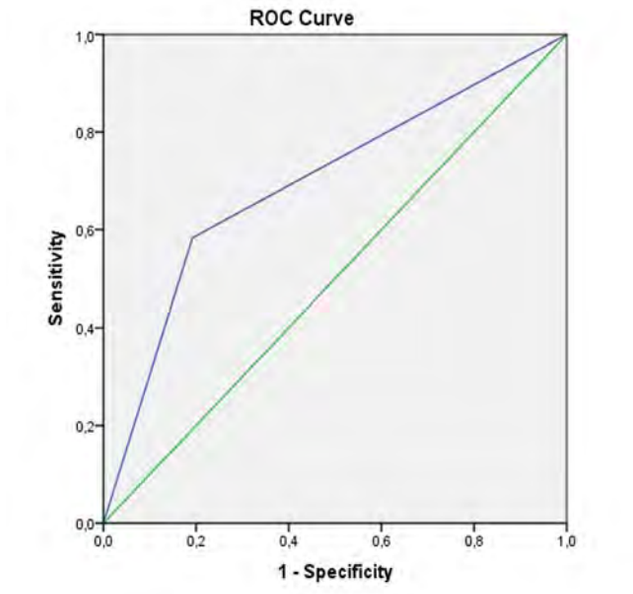


Figure 5. The ROC curve showing the MRI diagnostic performance in the partial tears of the long head of the biceps tendon compared with arthroscopy (The area under the ROC curve in the confidence interval of 0.517-0.874 is 0.696).

Discussion

MRI is an extremely important diagnostic tool in displaying the anatomy and pathologies of the shoulder joint and especially in displaying the rotator cuff lesions [5,6]. Arthroscopy is an invasive method for the diagnosis and treatment that directly shows the internal structures of the shoulder joint [5]. The correct diagnosis of pathologies is necessary to select medical or surgical treatment as well as to plan the specific surgical procedure. Furthermore, preoperative imaging reduces the duration of arthroscopy [6].

The rotator cuff consists of the supraspinatus, infraspinatus, subscapularis, and teres minor tendons. The most common tendon tear is observed in the supraspinatus tendon as it is in our study [1,2]. The tendon tear observed most rarely is the tear of the teres minor tendon, which was not detected in our cases.

In a study conducted by Owen et al. [5] on 31 cases, the accuracy of MRI was found to be 90% without making a distinction between full-thickness and partial tears of the supraspinatus tendon. While Magee et al. [6] determined the sensitivity of MRI to be 100% and specificity to be 87% in the diagnosis of the supraspinatus tendon tear, they determined the sensitivity of MRI to be at a low value of 56% in the detection of partial tears. In our study, the accuracy was found to be 90% in the full-thickness tears and 89% in the partial tears of the supraspinatus tendon, and the sensitivity and specificity values were found to be high.

The second most common rotator cuff tear after the supraspinatus tendon tear is the subscapularis tendon tear. In the study conducted by Malavolta et al. [7], 78% sensitivity and 86% specificity were obtained at 82% accuracy in 93 cases compared with arthroscopy in subscapularis tears. Pfirrmann et al. [8]. reported 91% sensitivity in subscapularis tears. In a

study of Choo et al. [9], 92.5% sensitivity and 64% specificity were found in subscapularis tears. Recent studies have reported 25-80% sensitivity and 91-100% specificity in MRI in the subscapularis tear [10,11]. In our study, the sensitivity and specificity findings in full-thickness/partial tears of the subscapularis tendon were found to be consistent with the literature.

No specific studies have been conducted on other tendons forming the rotator cuff, and studies including all the tendons forming the rotator cuff have been conducted in the literature. In a study conducted by Torstensen et al. [12], sensitivity was found to be 96% and specificity was found to be 49% in 24 cases in the distinction of partial/full-thickness tears of the rotator cuff and sensitivity was found to be 89% and specificity was found to be 41% in the distinction of full-thickness/partial tears of the rotator cuff. Kautzner et al. [13]. reported that the most effective diagnostic tool was MRI and that sensitivity was 92% and specificity was 100% in rotator cuff tears. In a study conducted with 56 patients, Vlychou et al. [14] found that the diagnostic performance of MRI in partial tears was at 97.7% sensitivity, 63.6% specificity, and 91% accuracy. In a study conducted by Bhatnagar et al. [15], 91% sensitivity and 100% specificity were found in the diagnosis of rotator cuff tears, without making a distinction between full-thickness and partial tears.

Among the meta-analysis studies conducted, 73% sensitivity and 74% specificity were found in a meta-analysis study conducted by Roy et al. [16] on the diagnostic accuracy of rotator cuff tears. 84-96% sensitivity and 84-95% specificity were found in full-thickness tears, and 50-82% sensitivity and 88-99% specificity were found in partial tears. De Jesus et al. [17] obtained 85.5% sensitivity and 94.5% specificity in a meta-analysis study conducted on the studies on the MRI's distinction of rotator cuff tears. In another analysis, Smith et al. [18] found 91% sensitivity and 97% specificity of full-thickness tears and 80% sensitivity and 95% specificity of partial tears. MRI is a reliable diagnostic method for full-thickness tears, with quite a high sensitivity of 100% reported [19]. In partial tears, sensitivity is in the range of 35-92% [19,20]. In our study, the sensitivity and specificity values were found to be high, in consistency with the literature.

In a study conducted by Malavolta et al. [21], they found that sensitivity was 67% and specificity was 98% in the diagnosis of the tears of the long head of the biceps tendon with MRI. In a study conducted by Razmjou et al. [22], sensitivity was found to be 54% and specificity was found to be 98% in full-thickness tears of the long head of the biceps tendon and sensitivity was 27% and specificity was 86% in partial tears. Similarly, in the study of Dubrow et al. [23], sensitivity was found to be 56.3% and specificity was found to be 98% in full-thickness tears of the long head of the biceps tendon and sensitivity was found to be 27.7% and specificity was found to be 84.2% in partial tears. Mohtadi et al. [24] found that sensitivity was 100% and specificity was 94% in full-thickness tears of the long head of the biceps tendon and sensitivity was 50% and specificity was 69.82% in partial tears of the long head of the biceps tendon. In a study conducted with 23 patients, Beall et al. [25] determined 79% accuracy, 52% sensitivity, and 86% specificity in full-thickness/partial tears of the long head of the biceps. In our study, sensitivity was found to be low in the tears of the long head of the biceps tendon, especially in partial tears, in a consistent way with the literature. We think that this is due to the fact that the number of full-thickness tears is low and that in partial tears, the fluid in the bicipital groove around the tendon causes mistakes in the interpretation of the partial tear in MRI. Tears of the long head of the biceps tendon accompany rotator cuff tears and serve as supporters of the rotator cuff tendons [25]. Our study supports this, and the partial tears of the long head of the biceps tendon accompany rotator cuff tears.

There are a few limitations in our study. Firstly, arthroscopy was considered to be the reference method in our study. There may be traps and misdiagnoses during arthroscopy. For example, intratendinous tears of the rotator cuff tendons, when the tendons do not contact with any surface, are not visible during arthroscopy [24]. At the same time, it may cause limitations in the distinction between full-thickness and partial tears [24]. Secondly, although arthroscopy was performed blindly, MRI images were taken by the musculoskeletal system radiologist knowing that the study was conducted on tendons. Thirdly, the number of the studies is relatively low, especially in terms of tears other than supraspinatus tendon tears. Finally, our study includes the routine shoulder MRI protocol with a 1.5 Tesla MRI device used retrospectively at our hospital. The specific position for the tendons does not include invasive assessments such as different sequences and MR arthrography. However, we believe that the current study we have conducted can be suitable for the evaluation.

A lot of different studies and meta-analyses have been carried out on the diagnosis of the pathologies of the rotator cuff tendons with MRI. Our study supports this. Differently, in our study, the update of the information was performed together with the evaluation of the pathologies in the long head of the biceps tendon, which is the supporter of the rotator cuff tendons. The association of single tendon or multiple tendon pathologies was compared (Table 2).

Conclusion

In magnetic resonance imaging, high accuracy, high sensitivity and specificity in the strong consistency range with the kappa value (kappa value: 0.78) were found in rotator cuff tendon pathologies, especially in supraspinatus tendon tears. However, sensitivity was determined to be low in the pathologies of the long head of the biceps tendon. These values can be observed at higher levels in studies to be conducted with developing technological MRI techniques and high-resolution (3 tesla) MR devices. Nowadays, MRI remains to be a reliable diagnostic method in shoulder tendon pathologies, especially in rotator cuff tendons.

Competing interests

The authors declare that they have no competing interests.

Ethical Responsibilities

No animal or human studies were carried out by the authors for this article.

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Apelin and fetuin-a may be subclinical inflammation biomarker in familial mediterranean fever: A pilot study

Ailevi akdeniz ateşinde apelin ve fetuin-a subklinik inflamasyonun biyobelirteci olabilir: Bir pilot çalışma

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Öz

Amaç: Pozitif akut faz reaktanları genellikle ailevi Akdeniz ateşinin (AAA) atak döneminde (AD) yükselir ve atak-dışı dönemde (ADD) normal seviyelerine döner. Bazı hastalarda, bu akut faz reaktanlarının seviyesi ADD de düşmez, bu bize ADD de subklinik vasküler inflamasyonun devam ettiğini gösterir. Bu bilgi doğrultusunda, AAA hastalarında ADD de apelin ve fetuin-a'nın inflamatuvar biyobelirteçolarak kullanılıp kullanılamayacağını araştırdık. Gereç ve Yöntem: 30 AAA hastası ADD de ve 30 sağlıklı birey çalışmaya alındı. Serum apelin ve fetuin-a seviyeleri ELİSA yöntemi ile ölçüldü. Bulgular: AAA'lı hastalarda ortanca apelin seviyesi 113.07±15.9 ng/L ve sağlıklı bireylerde 307.82±52.76 ng/L idi (p= 0.002). Ortanca fetuin-a seviyesi AAA grubunda 1352.2±127.61 ng/mL ve kontrol grubunda 843.82±137.66 ng/mL idi (p= 0.009). AAA hastalarında, apelin ve fetuin-a seviyeleri arasında anlamlı bir ilişki saptandı (r = 0.399; p = 0.029). Ayrıca, yaş ve apelin arasında anlamlı ters bir ilişki (r= -0.499; p = 0.005), ve beden kitle indeksi (BKİ) ve apelin arasında pozitif bir ilişki (r = 0.769; p = 0.001) saptandı. İlave olarak, BKİ ve fetuin-a arasında anlamlı ilişki saptandı (r = 0.397; p = 0.030). Tartışma: AAA'lı hastalarda ADD de subklinik vasküler inflamasyonun devam ettiğinin göstergeci olarak, düşük serum apelin seviyeleri ve yüksek fetuin-a seviyeleri sağlıklı bireylere kıyasla gözlendi. AAA'ya bağlı subklinik inflamasyonu göstermede apelin ve fetuin-a'nın rolünü saptamada daha popülasyonlu ve farklı etnik grupları içeren çalışmlara ihtiyaç vardır.

Anahtar Kelimeler

Apelin; Ailevi Akdeniz Ateşi; Biyobelirteç; Fetuin-A; Subklinik İnflamasyon

Abstract

Aim: Positive acute-phase reactants generally increase during the attack period (AP) of familial Mediterranean fever (FMF) and return to normal range in the attack-free period (AFP). In some patients, the level of these acute-phase reactants does not decrease during the AFP, suggesting that subclinical vascular inflammation continues during the AFP. In the context of this information, we tested whether apelin and fetuin-A can be used as inflammatory biomarkers in the AFP of FMF patients. Material and Method: Thirty FMF patients within AFP and thirty healthy subjects were included in this study. Serum apelin and fetuin-a levels were measured using enzyme-linked immunosorbent assay (ELISA) method. Results: The median levels of apelin were 113.07±15.9 ng/L in FMF and 307.82±52.76 ng/L in healthy subjects (p= 0.002). The median levels of fetuin-A were 1352.2±127.61 ng/mL in the FMF group and 843.82±137.66 ng/mL in the control group (p= 0.009). In FMF patients, there was a significant correlation between apelin and fetuin-A levels (r = 0.399; p = 0.029). Furthermore, a significant inverse correlation was found between age and apelin (r= -0.499; p = 0.005), and a significant positive correlation was found between BMI and apelin (r = 0.769; p = 0.001). Additionally, a significant correlation was found between BMI and fetuin-A (r = 0.397; p = 0.030). Discussion: Lower serum apelin levels and higher fetuin-A levels were observed in FMF patients with AFP than in healthy subjects, suggesting that subclinical vascular inflammation continues during AFP in patients with FMF. Further studies with large study populations and different ethnic groups are necessary to show the role of apelin and fetuin-A in subclinical inflammation resulting from FMF.

Keywords

Apelin; Biomarkers; Familial Mediterranean Fever; Fetuin-A; Subclinical Inflammation

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Introduction

Familial Mediterranean fever (FMF) (OMIM 249100) is an auto-inflammatory disorder that shows an autosomal recessive inheritance pattern. The disease is characterized by recurrent fever attacks accompanied by abdominal pain, chest pain or joint pain, myalgia, and erysipelas-like skin lesions [1]. FMF predominantly affects Middle Eastern populations surrounding the eastern Mediterranean region, including Armenians, Arabs, Turks, and non-Ashkenazi Jews [2]. The mutations in the MEFV gene are responsible for FMF disease. The MEFV gene is located on chromosome 16p13.3; product of this gene, a 781 amino acids long protein, is termed pyrin/marenostrin [3].

The attacks of FMF are self-limited, lasting 1-3 days, and patients are usually symptom-free between the attack episodes. Positive acute-phase reactants including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and serum amyloid A (SAA) increase in the attack periods (APs) of FMF, and usually return to normal range in attack-free periods (AFPs). It has been reported that subclinical inflammation may continue even during the AFP of FMF [4,5]. Colchicine treatment commonly is utilized in the management of the attacks of FMF and in prevention of complications associated with inflammation, such as amyloidosis [6,7].

Apelin is an adipokine produced by adipocytes and a ligand of the G-protein coupled apelin receptor (APJ) [8]. In the human body, APJ is expressed by the heart, lung, liver, kidney, gastrointestinal tract, brain, adipose tissue, adrenal glands, endothelium, and plasma cells [9]. Considering the fact that apelin stimulates nitric oxide release and triggers arterial vasodilation, it is considered a potential biomarker for cardiovascular disease risk assessment. Moreover, insulin directly upregulates the expression of apelin, making this adipokine an attractive candidate protein marker for metabolic disorders such as diabetes mellitus (DM). Furthermore, low apelin levels have been found to be associated with elevated LDL levels [10] and also with VCAM-1 and E-selectin, the biomarkers of endothelial cell activation. The biomarkers have previously been found to be correlated with apelin levels [11]. Apelin level is increased by some pro-inflammatory cytokines such as TNF-α in metabolic, autoimmune, and inflammatory conditions [12]. Recently, apelin levels have also been measured in some rheumatic diseases, such as rheumatoid arthritis (RA) [13] and ankylosing spondylitis (AS) [14].

Fetuin-A is a protein secreted by the liver, kidney, bone, brain, lungs, and the cardiovascular system [15]. Fetuin-A is implicated in several diverse functions, including response to systemic inflammation, regulation of insulin and hepatocyte growth factor receptors, and bone resorption and osteogenesis [16]. Fetuin-A is known as a negative acute-phase reactant because of its decreased level in acute and chronic inflammation [17]. Fetuin-A levels were found to be decreased in certain rheumatic diseases including RA [18,19], osteoarthritis [15], and AS [20]. It has been suggested that fetuin-A can be a novel inflammatory biomarker in FMF [21].

As far as we know, there is no study investigating the role of apelin in the pathogenesis of FMF and only one study has been conducted in FMF patients for fetuin-A [21]. In light of this, we aimed to evaluate the serum apelin and fetuin-A levels in patients with FMF during AFP and to investigate their correlation with demographic and biochemical parameters.

Material and Method

Clinical Research Ethics Committee of Cumhuriyet University approved the study protocol. Before enrollment, a written informed consent was obtained from all participants. A total of thirty FMF patients during AFP who fulfilled the Tel Hashomer criteria were included in this study. For the control group, thirty age-, sex-, and body mass index (BMI)-matched healthy individuals were included in the study. Following an overnight fast, the blood samples of subjects were obtained in the morning (8:00-9:00) for the measurement of laboratory tests. The hemogram, ESR, CRP, fibrinogen, serum creatinine, uric acid, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using standard procedures in the venous blood samples. Demographic characteristics including age, BMI, and disease duration were recorded. The MEFV gene profiles of the FMF patients were obtained from hospital file records.

Measurement of serum apelin and fetuin-A levels by ELISA

A total of 7.5 mL of venous blood samples obtained from the FMF patient and control subjects were collected into a serum collection tube. These samples were centrifuged at 3000 rpm for 10 min and obtained serums were portioned. Serum samples were immediately stored at -80ºC until the measurement time. Serum samples were defrosted for the quantitative measurement of serum apelin and fetuin-A levels; commercial enzyme-linked immunosorbent assay (ELISA) kits were used.

Statistical analysis

All tests were performed using SPSS version 22.0 (SPSS IBM, Armonk, NY, USA). All demographic and quantitative data were shown as mean ± standard deviation and median (min-max). Kolmogorov-Smirnov test was used for normality assumption of continuous variables. Student's t-test or Mann-Whitney U-test was used for the comparison between groups of continuous variables. Correlations between variables were analyzed using Pearson's or Spearman's rank correlation coefficients. A p value less than 0.05 was accepted as statistically significant and all results were expressed with a 95% confidence interval.

Results

The present study consists of 30 FMF patients in AFP and 30 healthy controls. The mean ages of patients and control subjects were 29.7±10.9 and 34.3±9.6, respectively. BMI was 26.4±3.6 for patients and 27.0±3.1 for controls. There is no statistically significant difference between patients and controls in terms of age and BMI ($p > 0.05$). Of the FMF patients and controls, 20 (66.7%) were female and 10 (33.3%) were male. Mean disease duration was 9.2±7.9 years in the FMF patients. Laboratory findings of patients with FMF and control subjects are reported in Table 1.

The distribution of MEFV gene mutation frequencies in the FMF patients was as follows: no mutation in 4 (13.3%) patients, M694V heterozygous in 7 (23.3%), M694V homozygous in 3 (10%), E148Q heterozygous in 5 (16.7%), M680I (G/C) heterozygous in 2 (6.7%), M680I (G/C) homozygous in 1 (3.3%), V726A heterozygous in 2 (6.7%), and compound heterozygous mutation in 6 (20%) cases.

Figure 1 shows serum apelin and fetuin-A levels in FMF patients and controls. The median levels of apelin were 307.82±52.76 ng/L in healthy subjects and 113.07±15.9 ng/L in FMF patients (p= 0.002) (Figure 1). The median levels of fetuin-A were 843.82±137.66 mg/L in the control group and 1352.2±127.61 mg/L in the FMF group (p = 0.009) (Figure 1).

Table 2 shows the correlations between apelin, fetuin-A, and demographic and biochemical parameters. Significant correlation was found between apelin and fetuin-A levels (r = 0.399; p = 0.029). There was a significant inverse correlation between apelin and age (r= -0.499; p = 0.005) and a strong significant positive correlation was detected between apelin and BMI (r = 0.769; p = 0.001). The correlations between apelin and the other parameters were not significant. Fetuin-A was found to be correlated with BMI (r = 0.397; p = 0.030). The correlations between fetuin-A and the other demographic and biochemical characteristics were not significant.

Discussion

In the current study, we evaluated the serum apelin and fetuin-A levels in patients with FMF in AFP and compared with healthy subjects. The median levels of apelin were lower and median fetuin-A levels were higher in FMF patients compared with controls. In the FMF patients, there was a statistically significant correlation between apelin and fetuin-A levels. There was a significant inverse correlation between apelin and age, and a strong significant positive correlation was detected between apelin and BMI. Moreover, fetuin-A has been found to be correlated with BMI. We suggest that apelin and fetuin-A may be independent predictors of subclinical vascular inflammation continued during AFP in patients with FMF.

In clinical practice, developments in biomarker discovery provide important chances for the diagnosis and disease follow-up. Many biomarkers of inflammation are used by clinicians for predicting disease process, understanding disease mechanisms, recognizing, and monitoring a particular disease [22]. The implication of these biomarkers in the pathogenesis of inflammatory diseases is also a potential field of interest. Positive acute-phase reactants generally increase during the AP of FMF and return to normal range in AFP. In some patients, the levels of these acute-phase reactants do not decrease during AFP, suggesting that subclinical vascular inflammation continues during AFP [23]. In the context of this information, we tested whether apelin and fetuin-A can be used as inflammatory biomarkers in AFP of FMF patients.

There are a limited number of studies regarding fetuin-A and apelin in inflammatory rheumatic diseases. In the only study conducted with familial Mediterranean fever patients, Oncu et al [21]. measured serum levels of fetuin-A during AFP, 12 hours after an attack, and 7 days after an attack. They detected a decrease in the serum fetuin-A levels in AFP compared to 12 hours after AP. Additionally, they observed that fetuin-A was inversely correlated with positive acute-phase reactants such as CRP, ESR, fibrinogen, WBC, and ceruloplasmin. Similarly, lower serum levels of fetuin-A were reported by Saroha et al. [18] in RA patients. They asserted that low fetuin-A levels in RA patients might have resulted from the chronic inflammation developing in association with inflammatory activity and malnutrition. However, they found no correlation with clinical parameters. Sato et al.[19] reported low levels of serum fetuin-A in RA patients and found inverse correlation between fetuin-A and two positive acute-phase reactants: ESR and CRP. They also reported that fetuin-A was positively correlated with albumin, total cholesterol, and hemoglobin. Gökmen et al.[20] detected lower serum levels of fetuin-A in the AS patients compared to the control subjects. They found an inverse correlation

Table 1. Laboratory findings of patients with familial Mediterranean fever.

Variables	Patients (n=30)	Min-max
Erythrocyte sedimentation rate (mm/h)	22.9±21.7	(4-79)
C-reactive protein (mg/L)	34.2±51.8	(1-173)
Fibrinogen (mg/dL)	392.2±147.6	(233-841)
White blood cell count (10^9/L)	7.1±1.9	(4.11-10.7)
Neutrophil count (10^9/L)	4.8±1.8	(2.3-9.4)
Lymphocyte conut (10^9/L)	1.7±0.5	(0.4-2.8)
Erythrocyte count (10^{12}/L)	4.8±0.5	(4.0-5.93)
Hemoglobin (g/dL)	14.0±1.6	(10.8-17.6)
Platelet count (10^3/µl)	266.3±78.4	(154-565)
Creatinine (mg/dL)	0.65±0.17	(0.4-1.27)
Uric acid (mg/dL)	4.3±1.2	(1.9-6.7)
Alanine aminotransferase (U/L)	32.1±46.5	(10-265)
Aspartate aminotransferase (U/L)	28.2±26.6	(15-161)

Data were given mean±SD and min-max

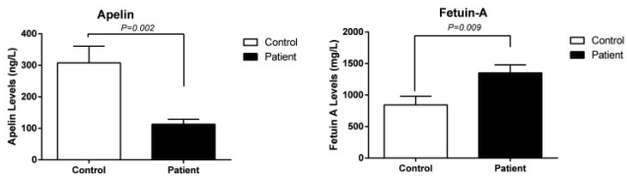


Figure 1. Serum levels of fetuin-A and apelin in FMF patients and healthy control subjects. The median levels of apelin were 307.82±52.76 ng/mL in healthy controls and 113.07±15.9 ng/mL in FMF patients (p = 0.002). The median levels of fetuin-A were 843.82±137.66 ng/mL in the control group and 1352.2±127.61 ng/mL in the FMF group (p = 0.009).

Table 2. Correlation between and serum levels of apelin, fetuin-A and laboratory findings in patients with Familial Mediterranean fever

Variables	Apelin		Fetuin-A	
	r	p	r	p
Fetuin-A	0.399	0.029	-	-
Age	-0.499	0.005	-0.144	0.448
Body mass index	0.769	0.001	0.397	0.030
Disease duration	-0.215	0.254	-0.066	0.727
Erythrocyte sedimentation rate	0.031	0.871	0.133	0.482
C-reactive protein	0.084	0.657	0.252	0.179
Fibrinogen	0.200	0.289	0.128	0.501
White blood cell count	0.143	0.452	-0.036	0.851
Hemoglobin	-0.319	0.086	-0.076	0.690
Platelet count	-0.208	0.270	0.0130	0.945
Creatinine	-0.181	0.339	-0.082	0.667
Alanine aminotransferase	-0.235	0.212	-0.135	0.476
Aspartate aminotransferase	-0.180	0.342	-0.194	0.305
Uric acid	-0.034	0.859	0.280	0.134

between CRP and fetuin-A levels. However, they found no correlation between fetuin-A and clinical parameters. In contrast, Sari et al.[24] found significantly higher fetuin-A levels in AS patients. Similarly, Tuylu et al.[25] found significantly higher fetuin-A levels in AS patients with syndesmophytes compared to those without syndesmophytes and healthy controls. Additionally, Harman et al.[26] found significantly high serum fetuin-A concentrations in the axial SpA and RA patients; however, serum levels of fetuin-A were not found to be different in the peripheral SpA patients and healthy subjects. They also observed significant correlations between fetuin-A and the clinical parameters of the axial SpA patients.

In early-stage RA (ERA) patients, Di Franco et al.[13] measured serum levels of apelin before and after disease-modifying antirheumatic drug therapy; they also measured intima-media thickness (IMT). They found decreased serum apelin levels in the ERA group, but serum apelin levels were not altered by treatment. However, IMT did not show significant changes. In non-diabetic patients with AS on treatment with infliximab, Genre et al.[14] showed that serum levels of apelin did not correlate with disease activity or metabolic syndrome. Topsakal et al.[27] investigated serum apelin and fetuin-A levels and assessed their associations with carotid intima-media thickness (CIMT) in patients with acromegaly. They found that serum levels of these proteins increased in patients with acromegaly. They found significant correlation between apelin and fetuin-A. Additionally, CIMT values were similar between acromegaly patients and controls. In the present study, we measured higher serum fetuin-A and lower apelin levels in FMF patients during AFP than in healthy controls.

Endothelial dysfunction and CIMT are used to define preclinical atherosclerosis and they are usually associated with systemic inflammatory and autoimmune diseases. Patients with inflammatory diseases such as RA and systemic lupus erythematosus are considered to have an increased risk of atherosclerotic cardiovascular complications[13,28,29]. In various studies, CIMT was measured in FMF patients, and a significant increase was observed[29-33]. In patients with Behcet's disease, Uyar et al.[28] found significantly high CIMT and coronary artery calcium scoring (CACS) and high serum fetuin-A levels compared to controls. They also observed significant correlations between serum levels of fetuin-A and CIMT and between fetuin-A levels and CACS. Turkmen et al.[34] found that serum levels of fetuin-A were inversely correlated with CACS in hemodialysis patients. They suggested that fetuin-A may play a role in increased mortality via accelerating coronary artery calcification. A significant inverse correlation was found between serum fetuin-A level and CIMT in hemodialysis patients[35]. Fetuin-A has an important role in the inhibition of insulin receptor signaling and calcification[36]. It has been suggested that high serum levels of fetuin-A may accelerate atherosclerosis, and fetuin-A and CIMT exhibit positive correlation in patients with DM[37]. Similarly, in adolescent type 1 diabetic patients, high levels of fetuin-A and increased CIMT have been found[38]. Increased CIMT is the early sign of atherosclerosis. For this reason, we think that the possible association between CIMT and fetuin-A and also apelin need to be investigated.

MEFV mutations have great importance in assessment of the severity of FMF[2,4]. In patients with FMF, homozygote M694V mutation was found to be associated with a clinically more severe course of disease, and patients carrying M694V mutation have a higher risk for amyloidosis development[4,39]. Although E148Q mutation in heterozygous state is predominantly considered to be a non-amyloidosis causing mutation, in a recent study heterozygous E148Q mutation was detected in 3 of 61 secondary (AA) amyloidosis patients[40]. In our study, ten patients had M694V, three patients had M680I (G/C), two patients had V726A, six patients had compound heterozygous mutations, and five patients had E148Q mutation; four patients had no MEFV mutations. As shown above, E148Q mutation is common in patients with FMF. For this reason, the development risk of amyloidosis in patients bearing E148Q mutation should not be ignored. The frequency of carriers of MEFV mutation is approximately 20-30% in populations who live in regions surrounding the eastern Mediterranean[1]. Subclinical inflammation was not only found in FMF patients but also was shown in patients carrying MEFV mutations [4]. When detecting amyloidosis in FMF patients, the role of CIMT and impaired endothelial function should be investigated deeply.

In conclusion, the low serum apelin and high fetuin-A levels in FMF patients in AFP compared to healthy subjects suggest that subclinical vascular inflammation continues during AFP in patients with FMF. The relatively small sample size was a major limitation of the current study. The second limitation was that we did not measure serum apelin and fetuin-A concentrations during the APs of FMF. Additionally, CIMT measurements of FMF patients were not performed in the current study. Further studies with large study populations and different ethnic groups, measuring the serum apelin and fetuin-A levels both in AP and in AFP of FMF patients, and measuring CIMT value of FMF patients. are necessary to show the role of apelin and fetuin-A in subclinical inflammation resulting from FMF.

Competing interests

The authors declare that they have no competing interests.

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Relationship between admission glucose level and st-segment resolution in stemi patients

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Abstract

Aim: Admission hyperglycemia is a common clinical condition after acute myocardial infarction (MI). The aim of this study was to study the relationship between admission glucose level and ST-segment resolution in ST-segment elevation MI (STEMI) patients treated with thrombolytics within 12 hours of the onset of chest pain. Material and Method: Data from 232 patients with a diagnosis of first STEMI were analyzed in this prospective study. All of the patients received thrombolytic therapy within 12 hours of the onset of chest pain. The patients were divided into two groups based on the presence of ≥50% ST-segment resolution. Results: Patients with <50% ST-segment resolution had higher admission glucose levels than patients with ≥50% ST-segment resolution (182.57±76.33 mg/dl vs. 150.44±53.95 mg/dl, respectively; p<0.001). Discussion: In the present study, we found that higher admission glucose levels were associated with impaired ST-segment resolution in STEMI patients treated with thrombolytics. Discussion: Our findings suggest that higher glucose values may be related to thrombolytic failure; further studies are needed.

Keywords

Admission Hyperglycemia; Glucose; Acute Myocardial Infarction; ST-Segment Elevation

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Introduction

Admission hyperglycemia is a common clinical condition after acute myocardial infarction (MI) [1, 2]. Several studies have demonstrated that admission hyperglycemia is independently associated with increased mortality after acute MI, regardless of treatment modality [3-6]. It has also been reported that non-diabetic patients with acute MI and admission hyperglycemia have higher rates of congestive heart failure, ventricular tachycardia, and atrioventricular block [4-7]. However, the mechanisms of the adverse effects of hyperglycemia are not well known.

Early reperfusion by either thrombolytics or percutaneous coronary intervention (PCI) is the main goal in the treatment of acute MI. However, impaired reperfusion occurs in one-third of ST-segment elevation MI (STEMI) patients treated with fibrinolytic therapy [8-10]. For this reason, predicting patients at risk of failed fibrinolysis is important in determining treatment strategies [8-13].

The aim of this study was to examine the relationship between admission glucose level and ST-segment resolution in STEMI patients treated with thrombolytics within 12 hours of the onset of chest pain.

Material and Method

This prospective case–control study was conducted at Ataturk Education and Research Hospital, Ankara, Turkey, between January and December 2011. The local institutional board of ethics approved the study and signed informed consent was obtained from participants. The universal principles of the Helsinki Declaration were applied.

Data from 232 patients with a diagnosis of first STEMI were analyzed in this prospective study. All of the patients received thrombolytic therapy within 12 hours of the onset of chest pain. STEMI was diagnosed based on a history of a typical chest pain lasting 30 minutes or more and ST-segment elevation of 1 mm or more in at least two contiguous leads or 2 mm or more in leads V1–V3 on electrocardiography (ECG) [7]. All of the patients underwent standard 12-lead ECGs immediately before starting thrombolytic therapy and 90 minutes after the initiation of thrombolytics. Patients with complete left bundle branch block on their admission ECG were excluded. ST-segment measurements were taken 60 ms after the J point in the single lead with maximal ST-segment elevation. At 90 minutes, this lead was examined for the achievement of ≥50% ST-segment resolution. All data were analyzed with an electronic caliper by a single investigator blinded to the study. Traditional variables that have been used to assess response to thrombolytic therapy were relief of chest pain, ST-segment resolution, and reperfusion arrhythmias. Patients with lack of resolution of ST elevation by at least 50% in the worst lead at 90 minutes were considered to proceed with rescue PCI. At the discretion of the treating operator, 118 patients received streptokinase (1.5 million U over 60 min) and 114 patients received t-PA (15mg bolus followed by an infusion of 0.75 mg/kg over 30 min [maximum 50 mg] and an infusion of 0.5 mg/kg over 60 min [maximum 35 mg]). As an adjunctive therapy, 300 mg aspirin was given to all patients on admission and daily thereafter. A loading dose of 300 mg clopidogrel followed by 75 mg once daily was given to patients younger than 75 years of age; the loading dose was not administered to patients older than 75 years [7]. All of the patients received enoxaparin according to body weight, age, and renal function. Patients with a history of significant coronary artery disease, PCI, bypass surgery, oral anticoagulation medicine, bleeding diathesis, malignancy, inflammatory disease, or hepatic or renal insufficiency were excluded from the study.

Statistical Analysis

Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Means and standard deviations for quantitative data and numbers and percentages for qualitative data were computed. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normal distribution of univariate variables. Non-parametric methods were used to analyze variables that did not have a normal distribution. Chi-square tests were used for categorical variables, where applicable. An independent samples t test was used to compare unadjusted means between groups. Non-parametric variables between groups were compared with a Mann–Whitney U test. Univariate and multivariate logistic regression analyses were used to predict the independent variables of ST-segment resolution. A receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of admission glucose level and the optimal cutoff value for predicting ST-segment resolution. The results were considered statistically significant when p values were <0.05.

Results

Baseline clinical, hematological, and biochemical characteristics of the study population are shown in Table 1. The patients were divided into two groups based on the presence of ≥50%

Table 1. The demographics, baseline characteristics, echocardiographic and hematologic parameters of the patients

	ST resolution <0.5 (n=154)	ST resolution ≥0.5 (n=78)	p value
Age, years	58.71 ± 12.33	64.95 ± 11.56	<0.001
Male, n (%)	123 (80.4%)	49 (65.3%)	0.013
Hypertension, n (%)	99 (65.1%)	35 (46.7%)	0.008
Diabetes Mellitus, n (%)	39 (25.3%)	21 (26.9%)	0.398
Smoking, n (%)	52 (34.0%)	38 (50.7%)	0.015
BMI, kg/m^2	24.31 ± 3.06	24.55 ± 3.04	0.588
Systolic BP, mmHg	108.4 ± 17.9	111.8 ± 21.6	0.217
Diastolic BP, mmHg	65.2 ± 10.8	68.9 ± 12.8	0.027
STEMI, anterior localization, n (%)	60 (39.2%)	45 (60.0%)	0.003
Mean LV ejection fraction, %	41.3 ± 10.1	37.7 ± 10.4	0.011
Thrombolytic agent-tPA, n (%)	79 (51.6%)	32 (42.7)	0.203
Hematocrit, %	42.42 ± 4.89	40.63 ± 5.15	0.012
WBC (x10^3/mL)	12.41 ± 11.08	14.63 ± 15.14	0.212
Platelet (x 10^3) - /µL	251.05 ± 71.96	257.57 ± 78.50	0.533
Time to treatment	3.26 ± 2.14	4.35 ± 3.09	0.002
Admission glucose, mg/dL	150.44 ± 53.95	182.57 ± 76.33	<0.001
Peak CK-MB, U/L	117.1 ± 105.4	144.3 ± 97.2	0.078

Data expressed as number (%), mean ± SD. The mean difference is significant at the 0.05 level.
BP: Blood Pressure, BMI: Body Mass Index, CK-MB: creatine kinase-MB, LV: Left ventricular, STEMI: ST elevation myocardial infarction

ST-segment resolution. Of the 232 patients, ≥50% ST-segment resolution was present in 154 patients (66%) and absent in 78 patients (34%). There were statistically significant differences between the two groups in terms of gender, age, hypertension, smoking, localization of MI (anterior vs. non-anterior), ejection fraction, hematocrit, diastolic blood pressure, and time of treatment. There were no statistically significant differences in diabetes mellitus, body mass index, type of thrombolytic agents (e.g., alteplase), and systolic blood pressure, or white blood cell and platelet counts, between the groups. Patients with <50% ST-segment resolution had higher admission glucose levels than patients with ≥50% ST-segment resolution (182.57±76.33 mg/dl vs. 150.44±53.95 mg/dl, respectively; p<0.001) (Table 1). The cutoff value of glucose level on admission for predicting resolution of ST-segment in the entire study population based on ROC analysis was determined to be 148.5 mg/dl, with a sensitivity of 62.7% and a specificity of 60.1% (area under the curve: 0.650; 95% confidence interval (CI): 0.577–0.732; p<0.001) (Figure 1).

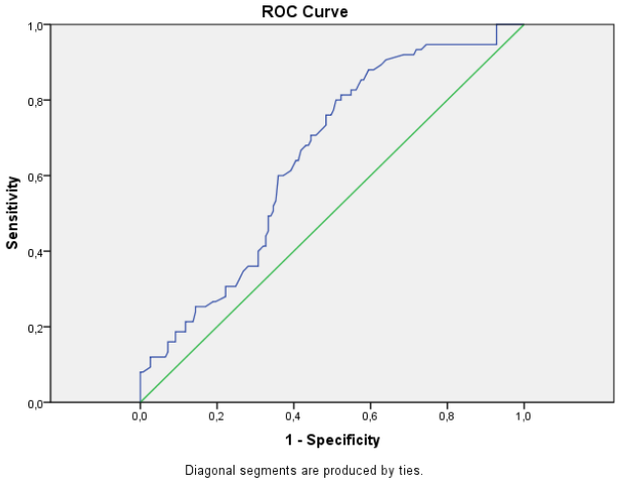


Figure 1. Area under the receiver operating characteristic curve for admission glucose measurements for predicting resolution of ST-segment in the entire study population; optimal cutoff value of admission glucose = 148.5 mg/dl. AUC=: 0.650; 95% confidence interval: 0.577–0.732; p<0.001).

Table 2. Univariate and multivariate logistic regression analysis of the predictors that can affect on ST segment resolution

	Univariable		Multivariable	
Variables	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value
Model 1: Admission glucose level as a continuous variable				
Age	0.958 (0.935-0.982	<0.001	0.975 (0.943-1.008)	0.142
Male Gender	2.176 (1.169-4.047)	0.014	1.018 (0.389-2.667)	0.971
Hypertension	2.135 (1.216-3.749)	0.008	1.419 (0.651-3.096)	0.379
Smoking	0.501 (0.286-0.880)	0.016	0.705 (0.289-1.717)	0.441
Anterior MI	0.430 (0.245-0.756)	0.003	0.463 (0.205-1.047)	0.065
LV ejection fraction	1.035 (1.007-1.064)	0.013	1.000 (0.956-1.046)	0.999
Glucose	0.992 (0.988-0.997)	<0.001	0.994 (0.988-0.999)	0.019
Hematocrit	1.074 (1.015-1.136)	0.013	1.064 (0.988-1.146)	0.103
Peak CK-MB	0.998 (0.995-1.000)	0.080	1.000 (0.996-1.004)	0.907
Diastolic BP	0.973 (0.949-0.997)	0.029	0.964 (0.935-0.994	0.019
Time to treatment	0.849 (0.762-0.946)	0.003	0.813 (0.702-0.943)	0.006
Model 2: Admission glucose level as a categorical variable				
Age	0.958 (0.935-0.982	<0.001	0.975 (0.943-1.009)	0.144
Male Gender	2.176 (1.169-4.047)	0.014	0.949 (0.362-2.489)	0.915
Hypertension	2.135 (1.216-3.749)	0.008	1.481 (0.685-3.202)	0.318
Smoking	0.501 (0.286-0.880)	0.016	0.721 (0.298-1.742)	0.467
Anterior MI	0.430 (0.245-0.756)	0.003	0.449 (0.197-1.024)	0.057
LV ejection fraction	1.035 (1.007-1.064)	0.013	1.003 (0.983-1.142)	0.908
Glucose (>148.5)	0.395 (0.224-0.698)	<0.001	0.444 (0.219-0.900)	0.024
Hematocrit	1.074 (1.015-1.136)	0.013	1.59 (0.983-1.142)	0.133
Peak CK-MB	0.998 (0.995-1.000)	0.080	1.000 (0.996-1.004)	0.921
Diastolic BP	0.973 (0.949-0.997)	0.029	0.961 (0.932-0.992)	0.013
Time to treatment	0.849 (0.762-0.946)	0.003	0.811 (0.699-0.941)	0.006

BP: Blood Pressure, CI; confidence interval, MI: myocardial infarction, CK-MB: creatine kinase-MB, LV: Left Ventricular

Univariate and multivariate linear regression analyses were performed to determine the predictors of ST-segment resolution (Table 2). Glucose level >148.5 mg/dl, diastolic blood pressure, and time of administration of thrombolytic agent were shown to be independently associated with ST-segment resolution (odds ratio [OR]: 0.444, 95% CI: 0.219–0.900, p=0.024; OR: 0.961, 95% CI: 0.932–0.992, p=0.013; OR: 0.811, 95% CI: 0.699–0.941, p=0.006, respectively).

Discussion

In the present study, we found that higher admission glucose levels were associated with impaired ST-segment resolution in STEMI patients treated with thrombolytics. Our findings suggest that higher glucose values may be related to thrombolytic failure.

ST-segment resolution, a simple and powerful tool to detect failed thrombolysis, is considered to be a marker of microvascular perfusion [14-19]. Several studies have demonstrated that greater ST-segment resolution was associated with higher rates of infarct-related artery (IRA) patency, less residual stenosis on angiography, smaller infarct size, and better left ventricular systolic function [16, 17, 20]. It has also been shown that ST-segment resolution is associated with lower mortality rate after MI [19, 21]. When complete ST-segment resolution is seen, successful reperfusion appears to have occurred at the tissue level [18, 19]. Patients with persistent ST-segment elevation experience increased morbidity and mortality despite a patent IRA, likely due to microvascular occlusion [19].

Hyperglycemia may be an important contributor to and independent predictor of increased cardiovascular mortality. Stress hyperglycemia in acute MI has been associated with high risk of in-hospital mortality, heart failure, cardiogenic shock, arrhythmias, and no-reflow phenomenon [13]. It has also been shown that long-term prognosis is worse in acute MI patients with admission hyperglycemia [15, 17].

However, the threshold of admission glucose as a predictor of

adverse events in acute MI is unclear, and the exact mechanism of stress hyperglycemia on admission for increased mortality and morbidity in acute MI is not known.

It has been demonstrated that in vitro endothelium-dependent vasodilation and in vivo coronary microvascular responses are impaired by hyperglycemia [15]. It has also been shown that hyperglycemia attenuates nitric oxide-induced effects on collateral blood flow in animals [17]. In another study, it was suggested that elevated plasma glucose might be related to increased production of vasoconstrictor prostanoids by the endothelium [18]. Glucose might play a role in myocardial injury by inducing reactive oxygen species and amplifying inflammatory immune reactions [19, 21]. When catecholamine-induced tissue lipolysis occurs with a release of free fatty acids, the optimum balance of energy of the myocardium deteriorates. Hyperglycemia is associated with increased free fatty acid concentrations, insulin resistance and impaired myocardial glucose use, and worsening ischemia [15]. It has been demonstrated that hyperglycemia is associated with increased platelet aggregation and higher levels of prothrombin fragments and tissue factor [20]. All of these changes occurring in the hyperglycemic milieu can cause a prothrombotic state and altered blood flow, resulting in microvascular dysfunction, myocardial injury, and no-reflow phenomenon, as well as impairment of ST-segment resolution [21].

Conclusion

Admission hyperglycemia in patients who present with STEMI is an independent predictor of impaired ST-segment resolution. Admission blood glucose levels may be used for better risk stratification and prediction of patients at risk of failed fibrinolysis.

Study limitations

Our study has some limitations. First, it is a retrospective study and has a small sample size. Further large-scale studies will be required to validate our results. Because this is a descriptive study, the associations can be interpreted as either cause or consequence; the relationships should be confirmed with longitudinal studies. The unavailability of data regarding glycosylated hemoglobin, insulin levels, and glucose intolerance is another limitation of our study.

Competing interests

The authors declare that they have no competing interests.

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Vitamin D status of adults in Kayseri, Turkey: Summer time population based cross-sectional study

Türkiye Kayseri ili yaz aylarında yetişkinlerin vitamin D durumu: toplum tabanlı kesitsel çalışma

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Öz

Amaç: Yapılan araştırmalar tüm dünyada eksikliği ve yetersizliğinin yüksek oranda olduğunu göstermektedir. Türkiye genelinde yapılmış bir çalışma olmamakla birlikte, yapılan çalışmalarda vitamin D eksikliğinin Türkiye'de de yüksek olduğu gösterilmiştir. Bu çalışmanın amacı toplum tabanlı olarak vitamin D eksikliği ve yetersizliği prevalansını saptamak, yaş, cinsiyet, eğitim gibi değişkenlere göre dağılımını incelemektir. Gereç ve Yöntem: 18-65 yaş arasında yetişkin bireyler üzerinde yaz aylarında gerçekleştirilmiştir. Örneklem büyüklüğü 323 olarak hesapalanmış ve araştırma 381 kişi ile tamamlanmıştır. Sosyodemografik özellikleri, fiziksel aktivite durumunu ile vitamin D düzeyini etkileyebilecek değişkenlerin sorgulanmıştır. Kan örnekleri LC-MS/MS yöntemiyle analiz edilmiştir. Bulgular: Katılımcıların yaş ortalaması 36.21±12.10'dir. Katılımcıların serum vitamin D düzey ortalaması 15.11±9.07 ng/ml olup vitamin D eksikliği %72.2 (<20 ng/ml), vitamin D yetersizliği (20 – 30 ng/ml) % 20.5 ve serum vitamin D düzeyi normal (>30 ng/ml) olanların oranı %7.3'dür. Erkeklerde vitamin D eksikliği %68.8, kadınlarda %75.7 olarak bulunmuştur. Yaz aylarında açık alanlarda bir saatten az süre geçirenlerde 1.7 kat, 35 yaş üzeri bireylerde 1.8 kat, bekârlarda 1.8 kat, Güneş kremi kullananlarda 2.4 kat ve ekonomik durumu iyi olmayanlarda 2.6 kat D vitamini eksikliği daha fazla görülmektedir. Tartışma: Kayseri ilinde vitamin D eksikliği ve yetersizliği görülme oranı yüksektir. Bu çalışmada vitamin D düzeyine en çok etki eden faktörler, cinsiyet, medeni durum, ekonomik durum, güneş kremi kullanımı ve yaz aylarında güneşten faydalanma olarak belirlenmiştir.

Anahtar Kelimeler

D Vitamini; D Vitamini Eksikliği; D Vitamini Yetersizliği

Abstract

Aim: Research shows that deficiency and insufficiency of vitamin D is high in the world. There are limited studies in Turkey but it has been shown that deficiency and insufficiency are high in Turkey. The aim of this study is to determine the prevalence of vitamin D deficiency and insufficiency and related factors in an adult population. Material and Method: This study was conducted in urban area of Kayseri in Central Anatolian region of Turkey, in adults aged 18-65 years in the summer period. The minimum sample size was calculated as 323 and the survey was completed with 381 people. A questionnaire about sociodemographic characteristics, and variables that may affect vitamin D level was administered. Blood samples were analyzed by LC-MS/MS. Results: The mean age of the participants was 36.21±12.10. The mean serum vitamin D level was 15.11±9.07 ng/ml. Vitamin D deficiency (<20 ng/ml) was found in 72.2%, vitamin D insufficiency (20-30 ng/ml) was found in 20.5% and only 7.3% of participants had a sufficient vitamin D level (>30 ng/ml). Vitamin D deficiency was found in 68.8% of males and in 75.7% of females. People who have exposure to the sun for less than 1 hour in the summer have 1,7 fold higher vitamin D deficiency. Vitamin D deficiency was 1.8 fold higher in those >35 years old, 1.8 times higher in the unmarried, 2.4 fold higher in those using sunscreen and 2.6 fold higher in those who did not have a good economic condition. Discussion: Kayseri has a high prevalence of vitamin D deficiency and insufficiency. Factors that have the most effect on vitamin D levels were determined as gender, marital status, economic status, use of sun cream and exposure to sunlight in summer.

Keywords

Vitamin D; Vitamin D Deficiency; Vitamin D Sufficiency

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Introduction

Vitamins are generally defined as water-soluble and oil-soluble vitamins, and function in different systems of the human organism [1]. Vitamin D is mainly effective on the musculoskeletal system, but it is considered to be a hormone rather than a vitamin because: as a steroid hormone it is synthesized in the human body under sunlight and affects many systems [1]. Following the discovery of Vitamin D receptors in different organs and tissues has been shown to have effects on other systems in addition to its effect on bone mineralization and calcium metabolism [2]. In addition to the effect of vitamin D on calcium absorption, it is known that it plays a role in intracellular calcium and phosphorus metabolism, which increases calcium uptake in muscle cells [3]. Vitamin D has an effect on the cardiovascular system and has been shown to strengthen cardiac output. It also affects cognitive functions positively on the neurological system, reduces the risk of cancer, has an effect on immune system regulation and low vitamin D level is associated with increased risk of death [4]. In the presence of the right angle and sufficient sunlights; Vitamin D is synthesized from 10:00 to 15:00 hours, with the effect of 280-315nm UVB rays. Vitamin D is first of all synthesized as previtamin D3; It then undergoes hydroxylation in the liver and kidneys cells and is converted to its active form (cholecalciferol, 1, 25-diOHD3) [1]. It is known that 80-90% of the vitamin D required for the human organism is synthesized by sun exposure. Vitamin D synthesized in this way is influenced by many different conditions, including age, geographical position, skin colour, use of sun cream and style of dressing [5]. On the other hand, the amount of vitamin D that can be obtained from food by the body is quite low, and sufficient vitamin D synthesis for the body is not provided in this way. Oily fish products and egg-yolk can be considered as rich food sources in terms of vitamin D [6].

The sun's zenith angle is a critical factor in allowing the human body to synthesize enough vitamin D. Sufficient vitamin D synthesis in Turkey can be achieved from May-November [7]. In studies conducted in different regions of the world, the level of vitamin D deficiency is high and vitamin D deficiency is considered as a pandemic and it is thought to affect more than one billion people in the world [8]. Although vitamin D deficiency differs from country to country and according to measurement technique, deficiency varies between 20% and 80% worldwide [9]. The incidence of vitamin D deficiency in Turkey is high, and studies report a range from 50% to 90% [10]. Investigation of Vitamin D deficiency in terms of preventive medicine and knowledge of the vitamin D deficiency rate in the population are necessary to enable professionals to carry out projects that require Vitamin D supplementation in the future.

The aim of this study is to determine the prevalence of vitamin D deficiency and insufficiency in adults inn a community-based and its distribution according to variables such as age, gender and education.

Material and Method

Setting and sample size

The study was conducted as a cross-sectional study between June and August 2016 in the urban area of Kayseri in the Central Anatolian region of Turkey. According to studies conducted in Turkey, vitamin D deficiency rate was accepted as 70% [10]. The minimum sample size was calculated as 323 people by taking a tolerance value=0.05, α=0.05 and β=0.20. To reach the minimum sample size, 400 people were taken as a sample group and research was completed with 381 (95.3%) people because of problems in blood-letting and laboratory work.

This study was approved by the Erciyes University Clinical Studies Ethical Committee and informed consent was obtained from participants.

Data Collection

Exclusion criteria in the study were as follows; vitamin D users in the last 3 months, those with chronic liver and kidney disease, any skin disease, type 1 diabetes, any malignancy, any endocrinological disease, metabolic bone disease, those on medication for bone metabolism, alcoholics and pregnant women. In order to select suitable individuals within the scope of the research a screening form was applied to 1,200 people who applied to the family health centers of urban area of Kayseri and appropriate individuals were given an invitation form. Volunteers were invited to Erciyes University Public Health Department. The questionnaire was prepared by the researchers based on the literature. A questionnaire consisting of 28 questions with socio-economic characteristics and other variables that could affect vitamin D level was applied by the face to face interview technique. After the questionnaire form was filled in, 3 cc blood samples were taken. Blood samples from donors were then transferred to the laboratory without of delay.

Laboratory Analysis

The Erciyes University Hospital Metabolism Laboratory uses liquid chromatography tandem mass spectroscopy (LC-MS / MS), which is accepted as the gold standard for 25 (OH) D analysis. Assessment of Vitamin D levels: as suggested by the Turkish Endocrinology and Metabolism Association was as follows; <20 ng / ml (50 nmol / L) deficiency, 20-30 ng / ml (50-75 nmol / L) insufficient, >30 ng / ml (75 nmol / L) sufficient [7].

Statistical Analyses

The student-t test was used for the analysis of binary variables, ANOVA was used for analysis of multiple variables, and for post hoc test the LSD test was used. Variables that may affect vitamin D deficiency were assessed by multiple analyses. Logistic regression was used for the analysis and the backwald algorithm was used as the enter model. The variables included in multiple regression analysis were as follows: age (≤35,> 35), gender, marital status (married, unmarried), economic status (good, not good), presence of chronic illness, smoking status, nutrition with fruit and vegetables (daily, less), nutrition with milk and dairy products (daily, less), physical activity status (inactive, active), use of sunscreen, sun exposure in summer and winter (more than one hour, less than one hour), clothing style, skin type and the history of bone fracture.

Results

The mean age of the participants was 36.21±12.10 years. 50.4% were male, 49.6% were female, 45.9% had a good economic status and 44.9% had a college and higher educational

Table 1. Vitamin D deficiency status according to socio-demographic characteristics

	Vitamin D Deficiency				
	n	Number	%	χ^2	p
Gender					
Male	192	132	68.8	2.27	0.132
Female	189	143	75.7		
Age					
≤35	206	143	69.4	1.70	0.192
>35	175	132	75.4		
Economic Condition					
Good	175	113	64.6	9.33	0.002
Not good	206	162	78.6		
Marital Status					
Married	196	136	69.4	1.56	0.211
Unmarried/Divorced	185	139	75.1		
Education					
Lower than high school	75	59	78.7	1.99	0.370
High school	135	96	71.1		
Higher than high school	171	120	70.2		
Sunscreen use					
Never	212	141	66.5	7.65	0.006
Continually or occasionally	169	134	79.3		
Sun Exposure in Summer					
More than 1 hour daily	219	149	68.0	4.40	0.036
Less than 1 hour daily	162	126	77.8		

level. The Vitamin D level in participants (<20 ng/ml) was found to be 72.2%. The rate of vitamin D deficiency (20-30 ng / ml) is 20.5% and that of Vitamin D sufficiency (> 30 ng / ml) was 7.3%. The prevalence of vitamin D deficiency in males was 68.8% and in females it was 75.7%. Although vitamin D deficiency was higher in females, sufficient vitamin D level was found to be higher in females than in males 8.5% and 6.3% respectively (Figure 1). The mean serum 25 (OH) D level of the participants was 15.11 ± 9.07. (Male: 16.21 ± 7.96 ng / ml, female: 13.99 ± 9.97 ng / ml, p <0.05). There was no significant difference between serum vitamin D levels according to age groups, marital status and educational status. However, the serum 25 (OH) D mean of individuals with good economic condition (16.43±9.82) was significantly higher than those who did not have a good economic condition (13.99±8.24) (p <0.05). Vitamin D deficiency was found to be higher in women, over in those over 35 years of age, in single people those with a low educational level, but there were no significant difference between groups. Vitamin D deficiency was found to be significantly higher in those who used sunscreen, who did not have a good economic condition and who were exposed to sunlight in the summer for less than one hour.

The serum 25 (OH) D mean of participants who preferred to wear clothing that does not block sunlight (16.00±9.32) was found to be significantly higher than that of those who wear clothing that blocks sunlight (13.93±7.81 (p <0.05).

According to the logistic regression analysis: vitamin D deficiency in those who had exposure to sunlight for less than one hour in summer was 1.7 fold than compared to those who had exposure to sunlight more than one hour (p <0.05). In those over 35 years of age was 1.8 fold more than that in those under 35 years individuals. Vitamin D deficiency in single individuals was about double that of married people. in those who use sunscreen it was 2.4 fold higher compared to those who never use sunscreen (p <0.05). Those who did not have a good economic condition were 2.6 times more likely to have vitamin D deficiency than those with have a good economic condition (p <0.05).

Discussion

Vitamin D deficiency is widespread in the world and high levels of vitamin D deficiency have been reported in many parts of the world [9]. Research on vitamin D deficiency in Turkey has been conducted mostly in pediatric age groups, special patient groups and women, and these studies indicate that vitamin D deficiency is a health problem in our country. This study had a population-based design. Blood samples were taken from selected individuals between June and July 2016 after excluding diseases or conditions that could cause vitamin D deficiency. Vitamin D deficiency in Kayseri province was found as 72.2%. The reason we choose the summer months for our study is because the solar rays in June and July in Turkey provide sufficient vitamin D synthesis [7]. There is only one population-based study in Turkey this was conducted in February in the Aegean region of Turkey. According to the results of that's study, vitamin D deficiency was found in 74.6% of participants[10]. Although our study showed a similar result with the study in the Aegean region, ours study was conducted in the period when the sun's rays were sufficient for vitamin D synthesis. Vitamin D deficiency was found to be higher in women, the vitamin D deficiency (<20 ng / ml) rate in men was 71.9% and it was 81.5% in women. In our study, the mean vitamin D score for women was 13.99 ± 9.97 and for men it was 16.21 ± 7.96. In a retrospective study of patients with osteoporosis, the prevalence of vitamin D deficiency in women was found as 45.3% and in males it was 38.4% [11]. In a 3-year study, patients who were referred to the physical therapy and rehabilitation polyclinic of a hospital in Istanbul reported a 2.15 fold (95% CI: 1.83 - 2.53) higher rate of vitamin D deficiency in females than in males [12]. In a study on 5531 people aged 5-101 in China, Vitamin D deficiency in women was reported as 89.0%, and in males it was reported as 84.9% [13]. In healthy volunteers in the Punjab region of India, the proportion of women with vitamin D deficiency <10 ng / mL was 52%, compared with 28% for men [14]. In Amsterdam in subjects over 65 years of age, vitamin D deficiency (<20 ng / ml) was found to be 44.7% in males and 56.1% in females [15]. According to the vitamin D results of 60,979 people in United Arab Emirates, Vitamin D deficiency was reported in 61.4% of women and in 58.3% of males [16].

Vitamin D deficiency increases with age. In the United States, 86% of women over 69 years of age have vitamin D levels below 30 ng / mL [17]. In Australia; In a population-based study with 11247 people aged 25 and over years, the prevalence of vitamin D deficiency increases with age and is most commonly seen in the ≥75 age group [18]. In our study, vitamin D deficiency was approximately double as high in individuals aged> 35 years (Table 3). The Vitamin D deficiency rate is almost double as severe in single participants (Table 3). In studies investigating marital status in the literature, similarly, it was shown that the vitamin D levels of married individuals are higher [19,20].

However, the relation of vitamin D level to marriage is not fully explained in the literature. In our study, the participants were not evaluated in this way and the effects of marriage were not investigated either the prevalence of vitamin D deficiency in rural areas in the Aegean region was as follows; 88.4% in urban areas, 76.8% in urban areas and 70.5% in semi-urban areas. Individuals living in rural areas have a 4.13 fold higher vitamin D deficiency and insufficiency rate than those living in semi-urban areas [10]. Vitamin D deficiency is 2.6 times higher in individuals who do not have good economic conditions (Table 3). Although there is no study showing daily vitamin D intake in Turkey, studies in the literature show that daily vitamin D intake increases as income level increases [21]. The use of sunscreen reduces the synthesis of vitamin D, while it protects the skin against the harmful effects of UVA and UVB. The use of SBF 8 sunscreen inhibits vitamin D syntheses >95%, while SBF 15 sunscreen inhibits over >98% of vitamin D synthesis [5]. Vitamin D deficiency is 2.6 fold higher in individuals using sunscreen and is about 2 times higher in individuals who have daily exposure to sunlight of less than one hour in summer (Table 3). Hekimsoy et al. [10] found that individuals with sun exposure had the highest score compared with individuals with vitamin D deficiency (82.4 %) who had a score of less than 8. In Egypt; in a comparison between those who were exposed to the sun for less than 5 minutes per day and those who were exposed to the sun more than 30 minutes per day; Those exposed to the sun former for less than 5 minutes were reported to be 5 times more at risk for vitamin D deficiency [22].

When serum vitamin D levels were analyzed according to the participants clothing style, the mean serum vitamin D level of subjects who were clothing which obstructed sunlight was found to be 13.93 ± 7.81 ng / ml and was significantly lower than those who were clothing which did not block sunlight (Table 2). Hekimsoy et al. [10] showed that vitamin D deficiency and insufficiency are higher in individuals who dressed in a style which blocks sunlight and reported that vitamin D deficiency is three times higher in individuals who dressed in a style which blocks sunlight. In Istanbul, the serum vitamin D levels of women who prefer traditional clothing and Islamic clothing were shown to be at a lower level than in those whose clothing styles allowed exposure to sunlight [23]. A study conducted in Jordan showed that men had significantly higher serum vitamin D levels than females. According to the preference of clothing among the women, 3 groups were formed completely covered, uncovered and western type, and the mean serum vitamin D levels were respectively, 24.3 ± 5.8 ng / ml, 28.3 ± 4.5 ng / ml and 36.7 ± 6.1 ng / ml [24].

Table 2. Serum vitamin D levels of participants according to clothing, skin type, use of sunscreen, sun exposure in summer and winter

	n	25(OH)D (ng/ml) ($\bar{X}$ ± SD)	t, F	p
Clothing				
Block sunlight	218	16.00 ± 9.32	2.215	p* = 0.027
Does not block sunlight	163	13.93 ± 7.81		
Skin Type				
White-skinned	107	15.30 ± 9.17		
Wheat colored skinned	198	14.76 ± 8.98	1,330	p* = 0,184
Dark-skinned	76	15.75 ± 9.23		
Sunscreen use				
Never	212	16.24 ± 9.82 (a)[1]		
Occasionally	125	14.01 ± 7.82 (b)[1]	4.025	p** = 0.019
Continually	44	12.82 ± 7.87 (b)[1]		
Sun exposure in summer				
Less than one hour	162	13.89 ± 8.63	2.273	p* = 0.023
More than one hour	219	16.01 ± 9.30		
Sun exposure in winter				
Less than one hour	244	14.78 ± 9.00	0.940	p* = 0.347
More than one hour	137	15.69 ± 9.20		
Total	381	15.11 ± 9.07		

* : Student-t test
** : ANOVA test, Post Hoc LSD test

Table 3. Logistic regression analysis of factors affecting vitamin D deficiency

	Odds Ratio	%95 CI	p
Age			
≤35	1		0,043311
>35	1.79	1.02 – 3.16	
Marital Status			
Married	1		0,035434
Unmarried / Divorced	1.83	1.04 – 3.23	
Economic Condition			
Good	1		0,000201
Not good	2.55	1.56 – 4.18	
Sunscreen Use			
Never	1		0,000816
Continually or occasionally	2.37	1.43 – 3.93	
Sun Exposure in Summer			
More than 1 hour daily	1		0,028838
Less than 1 hour daily	1.72	1.06 – 2.82	

Conclusion

As a result of this community-based study, it can be said that vitamin D deficiency is high in Central Anatolia. Although this study was conducted in the period when the sun's rays are sufficient for vitamin D synthesis, vitamin D deficiency and insufficiency are high. The lack of vitamin D in Turkey should be considered as a serious public health problem that concerns the population. New research should be done to ensure that healthcare providers' give their attention to this problem, take steps to prevent it or conduct intervention studies.

Limitations

It is not possible to generalize our findings to the whole of Turkey because the study was performed in a certain region, but it can be said that the life style of people in this region is very similar to the Middle Anatolian region. The participants invited may have caused bias in the sample. Individuals in distant and rural areas may have refrained from coming to Erciyes University to give blood. Questioning the variables that might affect the vitamin D level was evaluated according to the participants' statements, but their knowledge on vitamin D was not questioned.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Competing interests

The authors declare that they have no competing interests.

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Autologous serum effect on corneal endothelial damage in the phacoemulsification rabbit model

Tavsan fakoemulsıfıkasyon modelinde kornea endotel hasarına otolog serumun etkisi

Autologous serum effect to corneal endothelial damage

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Öz

Amaç: Tavşanlarda fakoemülsifikasyon ile oluşturulan kornea endotel hasarına ön kamaraya verilen otolog serumun muhtemel etkilerinin speküler mikroskopi ile değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Çalışmada dokuz adet 5 aylık (yaklaşık 3 kg ağırlığında) Yeni Zellanda cinsi albino erkek tavşanın etik kurul onayı ile her iki gözü kullanıldı. Sadece 0,2 ml otolog serum uygulanan 1. grup (6 göz), sadece 20 saniye ultrasonik titreşim uygulanan 2. grup (6 göz) ve 20 saniye ultrasonik titreşimi takiben 0,2 ml otolog serum uygulanan 3. grup (6 göz) oluşturuldu. Girişim öncesinde, işlem sonrası 1. gün ve 7. gün speküler mikroskopi, göziçi basıncı ve pakimetri ölçümleri yapılarak veriler istatistiksel olarak karşılaştırıldı. Bulgular: Postop 1. hafta sadece FAKO yapılan grupta (Grup 2) kornea kalınlığının 385µ'dan 445µ'a yükseldiği görülürken, FAKO + otolog serum verilen grupta (Grup 3) 398µ'dan 402µ'a yükseldiği ancak bu farkın istatistiksel olarak anlamlı olmadığı görüldü. Postop 1. gün 2. (FAKO) ve 3. (FAKO+otolog serum) grupların speküler mikroskopi parametrelerinden standart sapma ($p<0.05$) ve varyasyon katsayısı değerlerinin ($p<0.05$) 1.gruptan yüksek olduğu gözlendi. Postop 1. hafta ise bu parametrelerin her üç grupta da benzer olduğu ve preop değerlere döndüğü izlendi. Endotel hücre sayısı, hücre yoğunluğu, ortalama hücre alanı, en büyük ve en küçük hücre alanı ve hekzagonal hücre yüzdesi değerleri arasında ise üç zaman noktasında da gruplar arasında istatistiksel olarak anlamlı düzeyde fark saptanmadı. Tartışma: Bu çalışma, fakoemülsifikasyon işleminin ardından ön kamaraya verilen otolog serumun speküler mikroskopi ile teyit edilebilecek morfolojik değişikliklere sebep olmamakla birlikte endotel pompa fonksiyonları üzerinde muhtemel olumlu etkileri ile kornea ödemini azaltabileceğini göstermiştir.

Anahtar Kelimeler

Fakoemülsifikasyon; Kornea Endoteli; Otolog Serum; Speküler Mikroskopi

Abstract

Aim: This study used specular microscopy to evaluate the possible effects of applying autologous serum to the anterior chamber on the corneal endothelial damage created by the ultrasonic vibrations of phacoemulsification (PHACO) in rabbits. Material and Method: The study, which was approved by the Ethics Committee, involved both eyes of nine 5 month-old (about 3 kg) New Zealand genus albino male rabbits. Group 1(6 eyes) received only an application of 0.2 ml autologous serum; Group 2 (6 eyes) received only the ultrasonic vibrations for 20 seconds; and Group 3 (6 eyes) received 0.2 ml autologous serum followed by ultrasonic vibrations for 20 seconds. Measurements were made before the intervention and at the 1st and 7th days postoperatively using specular microscopy, intraocular pressure, and pachymetry metrics, and the data were compared statistically. Results: Postoperative 1st week, the cornea thickness increased from 385 µ to 445 µ in Group 2 (PHACO only) and from 398 µ to 402 µ in Group 2 (PHACO plus autologous serum). However, this difference was not statistically significant. Postoperative 1st day standard deviation ($p < 0.05$) and variation coefficient ($p < 0.05$) values of the specular microscopy parameters for Groups 2 and 3 were higher than for Group 1. Postoperative 1st week it was observed that the parameters of the three groups were similar and had returned to the preoperational values. Between the endothelial cell numbers, the cell density, the cell space average, the largest and the smallest percentage of the cell and the hexagonal cell area values, there were no statistically significant differences at the three measurement time points. Discussion: This study showed that, after the phacoemulsification process, autologous serum applied to the anterior chamber can, by positive possible effects on endothelial pump functions, reduce corneal edema without morphological changes, which can be confirmed with specular microscopy.

Keywords

Phacoemulsification; Corneal Endothelium; Autologous Serum; Specular Microscopy

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Introduction

Today, the duration and the power of the ultrasonic energy used in PHACO surgery, which is the preferred treatment method for more than 90% of cataract surgeries, is associated with various corneal damages such as endothelial cell loss and burning (1). The corneal endothelial cell loss after PHACO has been reported to vary between 1.2%-16.2% [2-4]. Risk factors for this damage include advanced age, small pupil, hard or large nucleus, large infusion volume, and the total height of the ultrasound energy (5-6). To date, approaches to reducing this damage have been viscoelastics, continuous circular capsulorhexis, and bicarbonate in the irrigation liquid. Also, there have been experiments with different breaking techniques of the nucleus and various methods such as the cold PHACO. But still the endothelial cell damage and the visual problems that result depending on the phacoemulsification continue to be a major problem. To this end, the effectiveness of different biological agent is also being researched [7-9].

Exogenous-derived growth factors can be used on the corneal epithelium to increase the epithelialization [10]. The production of growth factors with the recombinant technology is not a cost-effective approach, but the autologous serum (AS) contains a large quantity of growth factor, and is a liquid which can be easily obtained. Thus, it has epitheliotrophic potential for the ocular surface [11,12]. However, the demonstrated effect upon AS on the corneal endothelium is not known.

The endothelial cells are normally exposed to the growth factors found in the aqueous humor. However, in cases where the concentrations of growth factors are inadequate, while they are in the inactive form, or when aiming to induce and/or to extend the positive mitogenic signals with the damaged endothelial on the endothelial cell receptor, it is thought that they cannot connect effectively [13].

Specular microscopy permits measurement of the quality and the quantity of corneal endothelial cells, and is the standard method of in-vivo evaluation of the intensity and morphology of endothelial cells [14].

This study used specular microscopy to evaluate the effect on endothelial function of the application of AS in the anterior chamber in conjunction with PHACO surgery in rabbits.

Material and Method

The study followed the principles of the Local Ethics Committee of Kirikkale University, Faculty of Veterinary medicine, and confirmed by the number: 2012/46, by Kirikkale University, Faculty of Medicine Department of Ophthalmology, and with the contributions of the Faculty of Veterinary Medicine.

Nine male albino rabbits which were five months old, weighed 2500-3000 grams, and were of New Zealand genus were used. During the study period, they were kept in the appropriate cages and special nutritional conditions in the Experimental Research Center of Kirikkale University. Both eyes of all rabbits were used with the permission of the Local Ethics Committee of Kirikkale University, Faculty of Veterinary Medicine.

In accordance with the study protocol, preoperative, postoperative first and seventh day, anterior segment examination, cornea endothelial cell analysis on the central cornea with the specular microscope (SM), central corneal thickness measurement (CCT), and measurements of intraocular pressure with tonopen were performed for all the rabbits. As Mencucci and colleagues have described, the endothelium cornea damage was generated in the continuous irrigation mode and using 100% ultrasonic power [15]. The phacoemulsification application time is based on an average of the two different works respectively, as 20 sec [15, 16].

In the first phase of the study, in order to prepare the AS, after the 9 rabbits' ear surfaces were cleaned with alcohol, we entered in the marginal vein with an insulin syringe of 30 gauge. 2-3 cc's of blood were drawn and put into sterile Eppendorfs which were numbered according to the rabbit. After sitting at room temperature without the sun for two hours, and their shaped elements collapsed. Then after 10 minutes at 3000 rpm centrifuge, the serums are what remain. The serum of each rabbit was immediately placed into the sterile insulin injectors for use in surgical process.

After putting the rabbits on the operating table, the ocular surface and fornix to operate are washed with 5% povidone iodine. After securing the sterile field with a disposable drape, we put the speculum into the eyelid.

All operations were performed on the same day by the same surgeon. The eyes were divided into three group such that no rabbit had both eyes in the same group.

Group 1 (autologous serum, n= 6 eyes): We entered into the anterior chamber via upper temporal cornea-limbal junction and 0.2 cc autologous serum was given using the 30 gauge insulin injector.

Group 2 (PHACO, n= 6 eyes): Using a 3.2 mm knife we made a transparent corneal tunnel incision via upper temporal cornea-limbal junction. The continuous irrigation mode was opened. We entered into the anterior chamber by tunnel with the standard sleeve phaco probe. The phaco probe was maintained at the central (without a contact with any ocular structure, including lens and cornea), the U/S modulation worked 20 seconds with 100% power and continuously on irrigation (25 ml/min.). The wound was closed by a stromal hydration and after checking the sealing, we put on the cornea a 10/0 nylon suture.

3rd group (PHACO + autologous serum, n= 6 eyes): We followed the PHACO procedure described above. The autologous serum prepared before the procedure was given 0.2 ml into the anterior chamber taken from the insulin injector and on the same incision.

All eyes in the postoperative period were administered 1% dexamethasone (Maxidex®, Alcon®, United Kingdom) and 0.3 % ofloxacin (Siprogut®, Biofarma®, Turkey), topically applied one drop 5 times a day.

None of the cases were given anesthetic, miotic, and mydriatic agents that may produce angiogenesis toxic effects in the eye. For irrigation, balanced salt solution (BSS ®, USA) was used.

Preoperative, first postoperative and seventh day, SM (NIDEK ® CEM-530 Specular Microscope, Japan) measurements were made by the same practitioner. While analyzing the specular images obtained, we selected the most net one from eight images, and ensured that within the framework of analysis at least 50 cells were counted.

In our study we measured the quantity of the endothelial cells (NUM), the cell density (ECD), the average cell field (ACF), the

standard deviation (SD), the coefficient of variation (CV), the largest cell field (MAX), the smallest cell field (MİN), the hexagonal cell percentage (HEX), the corneal thickness (CCT), and the intraocular pressure (IOP) at three points in time. In order to evaluate each parameter as a whole, we made a curve six area calculation (CAC).

At the IOP measurements made by the tonopen (Reichert Tono-Pen AVIA, USA), we took the average of 10 measurements made automatically and consecutively.

Statistical analysis

All data were analyzed using the software Statistical Package for Social Science (SPSS) Windows version 11.5 (Chicago, IL, USA). After the descriptive statistical analyses (average ± standard deviation; median [minimum-maximum]), the evaluation of the normal distribution conformity was done with Shapiro Wilks Test. For the continuous variables, for the comparison of three groups the Kruskal Wallis test was used and for the comparison of two groups the Mann Whitney U test was used. For continuous variables, for the comparison of the one group values on three times point we used the Friedman test; and for the comparison of two times point analysis the Wilcoxon Signed-rank test was used. P < 0.05 value was considered statistically significant.

Results

After PHACO and the injection, there was no infection, the monitoring deletion and the corneal edema in the anterior chamber and all rabbits had sectoral limbal hyperemia on the incision [Figure 1].

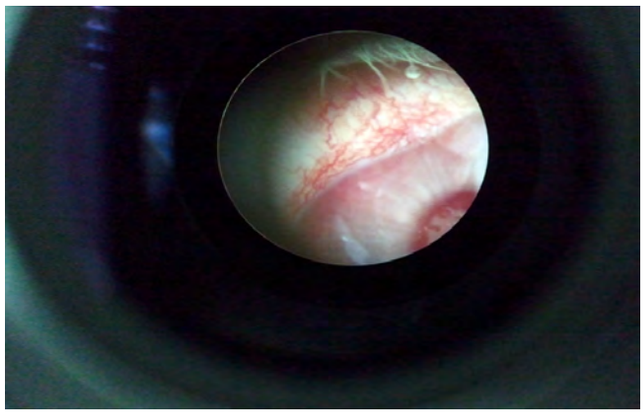


Figure 1. The sectoral limbal hyperemia on the incision

The standard deviation (SD) is the standard deviation of the values of the cell field. Among the three groups values for SD-T_0 (p=0.664), SD-T_2 (p=0.339), and SD_{CAC} (p=0.203), there was no statistically significant difference, but regarding the SD-T1 values of groups we found a statistically significant difference (p = 0.024). This was due to the fact the Group 1 SD-T1 values (p =. 041) were higher than those of Group 2 and Group 3 (respectively p=0. 041, p=0.009). There was no statistically significant difference between Group 2 and Group 3 SD-T1 values (p > 0.05) [Table 1 and Figure 2].

Table 1. The comparison of SD measurements at three time points for the three groups

Standard deviation(μm²)	GROUPS Group 1 (Average ±SD)	Group 2 (Average ±SD)	Group 3 (Average ±SD)	P
SD -T_0	57.33±22.17	60.67±12.96	61.17±22.34	0664
SD -T_1	50.50±9.27	70.00±16.04	74.50±17.71	0.024
SD -T_2	70.00±15.82	62.83±16.17	55.17±13.95	0.339
SD_{CAC} b²	294.92±46.57	331.00±41.55	327.17±44.49	0.203

Kruskal Wallis Test, SD=Standard deviation

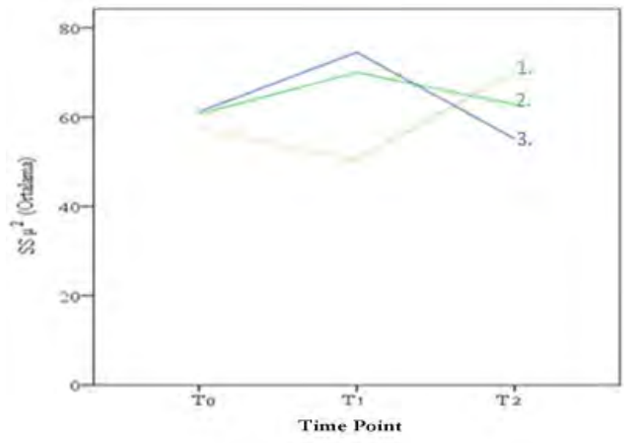


Figure 2. The measuring line chart of three groups SD measurements at three time points

There was no statistically significant difference between the SS values of Group 1 (p=0.135), Group 2 (p=0.607), and Group 3 (p=0.311) at the three time points (Freidman test).

The variation (variability) coefficient (CV) is an objective criterion of the polymegathism that shows the variability between the cell areas (CV: SD/AVG). Among the CV-T_0 (p=0.680), CV-T_2 (p=0.318), and CV_{CAC} (p=0.245) values for the three groups, there was no statistically significant difference, but we found a statistically significant difference for CV-T_1 (p = 0.013). This was because the values of Group 1 were higher than those of Groups 2 and 3 (respectively p =0.026, p = 0.004). There was no statistically significant difference between the Group 2 and Group 3 CV-T1 values (p > 0.05) [Table 2 and Figure 3].

There was no statistically significant difference between the CV values of Group 1 (p=0.084), Group 2 (p=0.738) and Group 3 (p=0.311) at the three time points (Freidman test).

There was no statistically significance difference in the three groups regarding the corneal thickness (CCT)-T_0 (p=0.605), CCT-T_1 (p=0.313), and CCT_{CAC} (p=0.291) values measured by optical pachymetry. However, there was statistically significant

Table 2. The comparison of CV measurements at three time points for the three groups

Variation coefficient (%)	GROUPS Group 1 (Average ±SD)	Group 2 (Average ±SD)	Group 3 (Average ±SD)	P
CV -T_0	15.67±5.85	16.67±3.72	16.50±5.09	0.680
CV -T_1	13.17±2.40	18.67±4.55	20.67±3.33	0.013
CV -T_2	19.67±4.63	16.67±3.67	15.67±4.23	0.318
CV_{CAC} b²	80.08±13.80	88.33±11.59	91.25±11.67	0.245

Kruskal Wallis Test, CV: variation coefficient

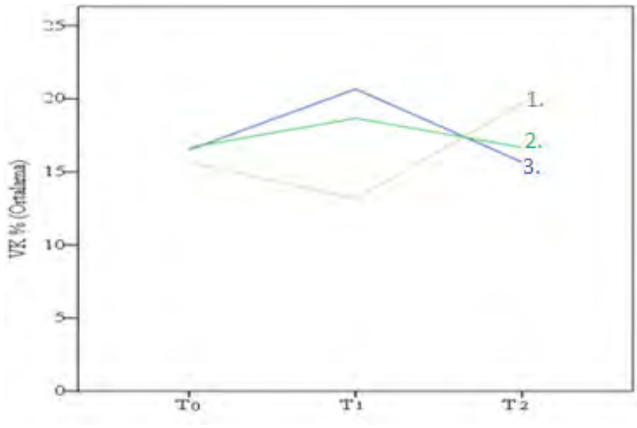


Figure 3. The measuring line chart of the three groups CV measurements at three points in time

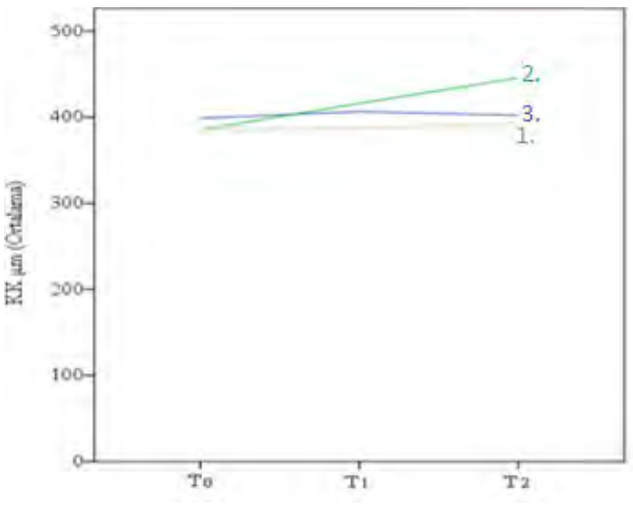


Figure 4. The measuring line chart of three groups CCT measurements at three points in time

difference for CCT-T_2 values (p = 0.048). This difference was due to the fact that the Group 2 CCT-T2 values were statistically significantly higher than the Group 1 values. There was no statistically significant difference in other binary comparisons (p > 0.05) [Table 3 and Figure 4].

Table 3. The comparison of KK measurements at three time points for the three groups

Corneal thickness (µm)	GROUPS			P
	Group 1 (Average ±SD)	Group 2 (Average ±SD)	Group 3 (Average ±SD)	
CCT-T_0 µm	384.67±30.89	385.33±12.56	398.83±28.72	0.605
CCT-T_1 µm	386.83±19.14	416.00±44.24	406.50±34.22	0.313
CCT-T_2 µm	393.67±49.19	445.50±53.11	402.17±45.85	0.048
CCT_{CAC} b^2	1946.75±151.83	2123.67±190.54	2020.00±158.51	0.291

Kruskal Wallis Test, CCT: Corneal thickness

There was no statistically significant difference between the CCT values of Group 1 (p=0.846), Group 2 (p=0.054), and Group 3 (p=1.000) at the three points in time (Freidman test).

There was no statistically significant difference in the three groups between the IOP-T_0 (p=0.419), IOP-T_1 (p=0.119), and IOP_{CAC} (p=0.058) values, but the IOP-T_2 values of groups we found a statistically significant between the level of difference (p = 0.031). This difference was due to the fact that Group 2 (p= 0.026) IOP-T2 values were statistically significantly less than the Group 1 values. There was no statistically significant difference in other binary comparisons (p > 0.05) [Table 4 and Figure 5].

Table 4. The comparison of IOP measurements at three time points for the three groups

Intraocular pressure (mmHg)	GROUPS			P
	Group 1 (Average ±SD)	Group 2 (Average ±SD)	Group 3 (Average ±SD)	
IOP-T_0 mmHg	13.00±4.69	11.33±2.07	12.83±3.06	0.419
IOP -T_1 mmHg	9.17±1.47	7.33±2.25	9.67±1.75	0.119
IOP -T_2 mmHg	8.17±1.33	6.50±0.84	7.33±0.52	0.031
IOP_{CAC} b^2	5.75±5.95	32.83±13.69	46.75±5.93	0.058

Kruskal Wallis Test, IOP: Intraocular pressure

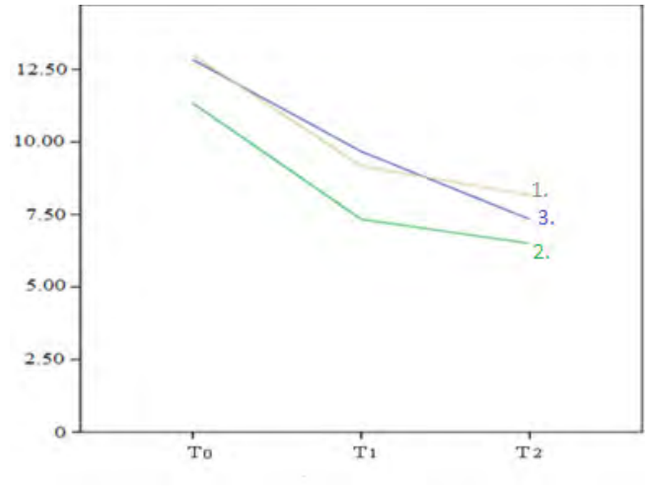


Figure 5. The measuring line chart of three groups IOP measurements at three points in time

There was no statistically significant difference in Group 1 (p=0.006) and Group 3 (p=0.008) between the IOP values at the three points in time (Freidman test). The IOP-T_0 (p=0.027) values were higher than the IOP-T_1 (p=0.027) and IOP-T_2 (p=0.046) in Group 1. The IOP-T0 values were higher than the IOP-T_1 values (p=0.027), and the IOP-T_0 (p=0.027) and IOP-T_1 (p=0.027) values were higher than the IOP-T2 values in Group 2. The IOP-T_0 (p=0.027) and IOP-T_1 (p=0.042) values were higher than the IOP-T2 values in Group 3 [Table 5].

Table 5. The comparison of the IOP values at three points in time in the three groups

GIB	GIB-T_0- GIB-T_1	GIB-T_0- GIB-T_2	GIB-T_1- GIB-T_2
Group 1	0.026	0.046	⊠0.05
Group 2	0.027	0.027	0.027
Group 3	0.074	0.027	0.042

IOP: Intraocular pressure

Discussion

We analyzed many parameters related the corneal endothelial cells and compared the values of three groups at three points in time (preoperative, post operative1st day and post operative 1st week). Within the groups and between the groups, we did not find statistically significant differences between the endothelial cells numbers, the cell density, the average cell area, the percentage of the largest and smallest cells, and the percentage of the hexagonal cell values. However, across groups we determined the following:

At T1 time point (post operative 1st day):

• The standard deviation and the variation coefficient values of Group 2 (PHACO) and Group 3 (PHACO + AS) groups higher than Group 1 (AS).

At T2 time point (post operative 1st week):

• In Group 2 (PHACO) the corneal thickness increased from 385μ to 445μ, while in Group 3 (PHACO + AS) it increased from 398μ to 402μ. However, this difference was not statistically significant.

• Group 2 CT (corneal thickness) values were higher than those of Group 1 (much higher to be statistically significant from Group 3), and the IOP values were less than those of Group 1 (much less to be statistically significant from the Group 3).

The increase of the variation coefficient which shows the high polymegathism (the difference between the cell areas) due to the increase of the standard deviation, is an expected finding (CV=SD/AVG×100). In Groups 2 and 3, for which we applied PHACO, it shows that the phacoemulsification operation caused the high polymegathism as expected. But because this difference was not maintained through the T2 time point, it means a reduction in variability between the cell areas; on the 1st week after a surgery that not applied high PHACO, have been due to completing the normal healing process of the endothelial cells.

At the T2 time point, the Group 2 CT values were higher than those of Group 1. This might have occurred because the endothelium pump functions were more affected without the application of AS into the eyes. Non application of phacoemulsification operation in Group 1, and then the phacoemulsification process in Group 3, to give the AS to anterior segment not occur the morphologic differences that we can confirm by SM, may not result in statistically significant increase (corneal edema) of the corneal thickness because of the possible positive effects on the endothelial pump functions.

The reason that Group 2 IOP values were lower than in Group 1 is due to the smaller incision in Group 1. (The entry is by a 3,2 knife into the anterior segment in Groups 2 and 3 and by an insulin injector 30 gauge in Group 3.) There was also a difference (that did not reach statistical significance) in IOP between Group 1 and Group 3 which may be due to possible positive effects of AS on the incision or to random effect. But when EGF is added to the cell culture environment of the cornea endothelium cells, the cells present the fibroblast view and take a spindle shape [17]. Still the transformation of the polygonal endothelium cells to the elongated multilayered fibroblast-like cells by the basic fibroblast growth factor (FGF), and the increase of the endothelium cell quantity [8], we can say almost the positive effects of AS.

In our analysis there was no statistically significant difference between groups regarding the endothelial cell count, the cell density, the average cell area, the percentage of largest and smallest cells, the hexagonal cell area, and the corneal thickness values, but in Group 3 the IOP measurement of the 1st day was higher than on the 7th day. In Group 2 the IOP measurement of the 0 day was higher than the 1st and 7th days, and the measurement of 1st day was higher than the 7th day. In Group 2 the IOP measurement of the 0 day was higher than the 1st and 7th days (Table 6). In this case 1st next week, we see that the leak increases, and we think that the IOP can be low due to the saturation could not be stressful enough or because of the topical drops or finally the mechanical trauma that the rabbit's own implements.

The results of this study have shown that generally among the three groups the parameters measured with SM did not change along the trace. There are several reasons why this may be.

Table 6. The comparison of the IOP values intergroup at the different time points

	Group 1	Group 2	Group 3
IOP	$T_0>T_1$ $T_0>T_2$	$T_0>T_1$ $T_0>T_2$ $T_1>T_2$	$T_0>T_2$ $T_1>T_2$

IOP: Intraocular pressure, T0: Preoperative IOP, T1: Postoperative 1st day IOP, T2: Postoperative 7th day IOP

The first reason is that the rabbit corneal endothelial damage done by phacoemulsification may not be sufficient to demonstrate an effect. In a study made by Rothschild and his colleagues the average duration of phacoemulsification was determined as 13.9 ± 5.0 mm (up to a maximum of 6-7 min of ultrasonic energy is the amount of time that is running) [18]. In our study, the processing time was limited to 20 seconds, whereas in the literature it ranges from 10-30 seconds [15, 19]. Also, we didn't do the lens emulsification and lens implantation in rabbits. During the emulsification it's possible the insufficient endothelial damage in the challenge applied because of the tracked nucleus parts shock, and the endothelium wasn't exposed to stress factors such as the liquid turbulence and surge.

The second possible reason is that the properties obtained in our measurements are the specifications of paracentral and pericentral cornea regions depending on the difficulty of evaluating the central cornea on the rabbits during SM assessment (because of the fixation impossibility). Hence each measurement was taken from a different point in the image is likely to be, also if in the short term in the rabbits made the GAA measuring cornea must remain open, and therefore the quality of the measurement can be reduced.

The third reason is that, given the small sample size (due to guidelines of the Ethics Committee to use the minimum experimental animal quantity), the results may not reach statistical significance.

The fourth reason is that the growth factors may have different effects in different experimental animals. For example, there is some evidences that the transformable growth factor (TGF)-β1 increases the DNA synthesis in human [20] and bovine corneal endothelial cell cultures [21], but it is ineffective in rabbit corneal endothelial cells [22]. Also, there are some studies indicating that the effect of inhibitory [23] onto the cells.

Freitas Valbon et al. evaluated the central corneal thickness for PHACO patients in the preoperative period, and the postoperative first and seventh day. They found that the central corneal thickness shows a decline in the postoperative period compared to the preoperative period [24]. Another study found that the central corneal thickness for PHACO patients increases in the postoperative first hour and stays high on the first day measurements, but by the end of the postoperative week has rebounded to the preoperative levels [25]. In our study, we found that the Group 2 corneal thickness values were higher than the Group 1 values only at the T2 time point. In the intergroup evaluation, we did not find a significant difference in corneal thickness between the three time points between the groups receiving PHACO (Groups 2 and 3) and the group that did not (Group 1).

Conclusion

The observed loss of endothelial cells after cataract surgery is an inevitable result of the procedure. The important steps during cataract surgery and the perioperative care attention can reduce the endothelial cell loss, but further reduction of the endothelial cell loss will positively affect the results of this commonly-performed procedure.

We can expect that body fluids which contain growth factors will have positive effects in healing the corneal endothelium. This study was done in order to evaluate the OS's effects on the corneal endothelium which applied on the OK after the phacoemulsification operation. It showed that although the damage created on the rabbit's corneal endothelium by the phacoemulsification did not reach a statistically significant level, the corneal edema can be reduced with the possible positive effects on the endothelial pump functions.

In this case, our work can be attached within the methodological problems in the interventional and evolutional framework, but also can be connected to the type II fault (in reality, there is a situation that cannot be in working order) which can occurred depending on the sample size.

In future studies to evaluate the OS effects on corneal endothelial damage resulting from phacoemulsification, increasing the sample size and doing the preliminary tests in terms of the methodological issues will provide clearer results.

Competing interests

The authors declare that they have no competing interests.

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Comparison of three different midurethral sling operations using urodynamic evaluation

Üç farklı midüretral sling operasyonunun ürodinamik inceleme kullanılarak karşılaştırılması

Comparison of midurethral slings

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Present study was carried in Eskisehir Osmangazi University, Department of Obstetrics and Gynecology and the manuscript has not been published elsewhere.

Öz

Amaç: Stress üriner inkontinansı olan hastalarda modifiye midüretral sling, tension-free vajinal tape ve transobturator tape operasyonlarının ürodinamik inceleme ile etkinliklerininin karşılaştırılması amaçlanmıştır. Gereç ve Yöntem: Stres üriner inkontinansı olan ve 2003 ile 2012 yılları arasında midüretral sling operasyonu olan 65 hasta çalışmaya dahil edildi. Preoperatif ve postoperatif ürodinamik değerlendirmeler analiz edildi. Sistometri operasyonları kür oranlarını saptamak için kullanıldı. Valsalva kaçak noktası basıncı, objektif kür oranlarını değerlendirmek ve karşılaştırmak için belirlendi. Bulgular: Operasyon tipleri arasında belirgin farklılık saptanamamıştır. Objektif kür oranları; modifiye midüretral sling, tension-free vajinal tape ve transobturator tape için sırasıyla %83.3, %88.9 ve %91.3 olarak saptanmıştır. Tension-free vajinal tape, intrinsik sfinkterik yetmezlikte diğer operasyon tiplerine göre daha etkin bulunmuştur. Valsalva kaçak noktası basıncı operasyonların başarısını göstermek için kullanılmıştır. Basınç değerlerine göre, stres üriner inkontinans hastalarında objektif olarak tam kür veya iyileşme sağlandı. Sadece 8 hastada postoperatif valsalva sonrası kaçak tespit edildi, bu hastalarda da preoperatif düzeylere göre valsalva kaçak noktası basınçları daha yüksek değerlerde saptandı. Tartışma: Midüretral sling operasyonlarının etkinlikleri gruplar arasında farklı bulunmadı. Valsalva kaçak noktası basıncı objektif kür oranlarını belirlemek için önemli bir parametredir. Modifiye midüretral sling tekniği karşılaştırılabilir başarı oranı ile daha ekonomik bir yöntem olarak gözükmektedir.

Anahtar Kelimeler

Modifiye Midüretral Sling; Stres Üriner İnkontinans; Tension-Free Vajinal Tape; Transobturator Tape; Valsalva Kaçak Noktası Basıncı

Abstract

Aim: To use urodynamic evaluation to compare the effectiveness of modified midurethral sling, tension-free vaginal tape, and transobturator tape in the treatment of stress urinary incontinence. Material and Method: A total of 65 patients with stress urinary incontinence underwent midurethral sling operations between 2003 and 2012. Preoperative and postoperative urodynamic evaluation data were analysed. Cystometry was used to determine the cure rates of operations. Valsalva leak point pressure was obtained to assess and compare the objective cure rates. Results: No significant differences were noted between different operation types. Objective cure rates of procedures were established as 83.3%, 88.9%, and 91.3% for modified midurethral sling, tension-free vaginal tape, and transobturator tape, respectively. Tension-free vaginal tape was more effective in intrinsic sphincteric deficiency than other operation types. Valsalva leak point pressure showed the effectiveness of the operations. According to pressure values, stress urinary incontinence were cured or improved in patients objectively. Only 8 patients had positive Valsalva leak point pressure postoperatively and the mean of postoperative Valsalva leak point pressure values was higher than that of preoperative levels. Discussion: Effectiveness of midurethral sling operations did not differ between groups. Valsalva leak point pressure is an important marker to determine objective cure rates. Modified midurethral sling techniques are more economical with comparable success rates.

Keywords

Modified Midurethral Sling; Stress Urinary Incontinence; Tension-Free Vaginal Tape; Transobturator Tape; Valsalva Leak Point Pressure

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Introduction

Urinary incontinence (UI) is defined as the complaint of any involuntary leakage of urine [1]. Stress urinary incontinence (SUI), which mainly occurs during physical activity due to the urethral sphincteric insufficiency, may affect up to 60% of women with UI in a pure or mixed form accompanied by detrusor overactivity (DO) [2-4]. The mainstay of the treatment of SUI has been improving urethral sufficiency using a variety of types of operations. Minimally invasive midurethral sling operations developed in recent decades, including tension-free vaginal tape (TVT) and transobturator tape (TOT), have had high success and low complication rates and have been accepted as gold standard procedures for SUI [5-9]. However, the high cost of the sling devices and meshes is a significant burden for effective treatment of SUI in developing countries with limited healthcare sources. In response, many modified techniques have been developed to reduce the cost without decreasing the success [10]. In the literature there are only a few studies that compare TVT to pubovaginal sling and TOT to pubovaginal sling [11]. Additionally, there are no more studies about synthetic pubovaginal sling procedures.

The aim of our study is to compare cure rates, efficacy rates, and complication rates among patients who underwent TVT, TOT, and modified midurethral sling operations for anti-incontinence surgery.

Material and Method

The study population consisted of patients who underwent midurethral sling operations for stress urinary incontinence (SUI) and mixed urinary incontinence (MUI) between April 2003 and April 2012. The study was approved by the Ethics Review Board and conducted in Eskisehir Osmangazi University, Department of Obstetrics and Gynecology.

Eigthy-six patients were evaluated retrospectively. Urogynecological evaluation and urodynamic studies were performed preoperatively for all patients. Twenty-one patients who did not come to their follow-ups and whose medical information couldn't be gained or had missing data were excluded from the study population. We assessed age, number of parity, and type of delivery (spontaneous vaginal or caesarean section) as demographic parameters.

Urodynamic studies (cystometry), which were routine procedure for SUI operations in our clinic, were performed on all patients preoperatively. Urine testing and culture were obtained before the urodynamic test. Postvoiding residual volume (PVR) was assessed before starting the urodynamic testing by sterile catheterization. Maximum bladder capacity, maximum vesical pressure, VLPP (valsalva leak point pressure), and maximum detrusor pressure were evaluated by the urodynamic test and were recorded with a computer program. VLPP was obtained with the subject seated when the total infused volume reached 200 mL by asking the patient to perform a Valsalva maneuver until urine loss was directly observed. We retrospectively analysed the data obtained from these recordings.

According to patients' complaints and urodynamic test results we categorized them into two groups: SUI and MUI. We diagnosed the SUI by confirmation of positive stress test during the urodynamic test. For patients who had MUI and who had no response to any medications, we recommended and performed surgery for SUI.

We performed three different operation types during the study period. 'Modified midurethral sling (MMUS)' operations were performed using the abdominovaginal route with synthetic mersilene mesh. In this technique, first an pfannenstiel incision was performed and a trocar was directed top-to-bottom to the vaginal incision. Then synthetic mersilene mesh was fixed to the trocar and pulled out by the trocar from the abdominal incision. After that, sutures of the mesh were adjusted and then tied. The second operation type was TVT. In this technique we used the bottom-to-top technique (from the vaginal incision to pubic bone). The third operation type was TOT. We performed an inside-to-outside technique named TVT-O and developed by de Leval, hereafter referred to as TOT. All of the operations were performed by a single experienced surgeon. Intraoperative complications were identified. Patients who had mesh erosion were recorded.

Patients were invited to the hospital with a telephone call asking them to come for evaluation. They were informed about this study and informed consent was obtained. Present complaints, particularly those related to stress urinary incontinence, were questioned as 'present or absent.' Urodynamic tests were performed to detect objective cure rates. Before the urodynamic tests, PVR was established by sterile catheterization. As with the preoperative procedure, test data was recorded with a computer program.

After these evaluations 'subjective cure rates' and 'objective cure rates' were determined. The absence of involuntary urine leakage was designated 'subjective cure' and negative stress test and no VLPP in the urodynamic test was designated 'objective cure.'

Statistical analysis was performed to compare operation types and to detect differences between preoperative and postoperative data. Statistical analysis was conducted using SPSS version 20.0. One-way ANOVA, Independent Samples Kruskal-Wallis Test, Pearson Chi-Square Test, Paired-sample t-Test, and Related-samples Wilcoxon Test were used. A p value <0.05 was considered statistically significant.

Results

We evaluated 65 patients; modified midurethral sling (MMUS), TVT, and TOT operations were performed for 24, 18, and 23 patients, respectively. Demographic characteristics of patients and preoperative urodynamic results were assessed (Table 1). In the preoperative diagnoses of patients, 28 patients (43.1%) had pure stress urinary incontinence and 37 patients (56.9%) had mixed urinary incontinence. One bladder perforation was seen as an intraoperative complication; it occurred during the MMUS procedure. Among all patients, the rate of bladder perforation was evaluated as 1.5% but for the MMUS procedure this rate was evaluated as 4.1%. Bladder perforation was determined intraoperatively by cystoscopy. The patient was followed with 168 hours of bladder catheterization. After catheterization there was no problem and the patient was discharged from hospital. We did not see any major complications, such as major vessel and nerve injury, other than the bladder perforation. Follow-up duration of our patients was in a wide range, from 11

Table 1. Demographic characteristics and preoperative Urodynamic results of patients

	MMUS (n=24)	TVT (n=18)	TOT (n=23)	p
Age (years)	52.04±10.25	51.72±8.29	57.43±12.12	>0.05
Parity (numbers)	3.75±2.11	3.05±1.43	3.69±1.60	>0.05
Number of SVD	3.82±2.12	2.88±1.53	3.65±1.64	>0.05
Capacity of bladder (ml)	411.33±66.74	391.27±80.24	395.00±80.38	0.646†
Maximal Vesical Pressure (cm H_2O)	19.20±9.35	26.27±14.73	18.30±9.20	0.186‡
Maximal Detrusor ressure (cm H_2O)	13.75±7.21	22.50±14.07	16.04±8.14	0.083‡
PVR (ml)	16.45±15.70	9.44±11.99	15.21±24.83	0.031‡
VLPP (cm H_2O)	72.61±97.38	78.28±103.15	79.87±114.21	0.449†

†, Oneway ANOVA Test ‡ Independent Samples Kruskal-Wallis Test Values are given as mean ±SD, MMUS, modified midurethral sling PVR, Postvoiding residual volume SD, Standard deviation SVD, spontaneous vaginal delivery TVT, tension-free vaginal tape TOT, transobturator tape VLPP, valsalva leak point pressure

months to 114 months. Mean evaluation durations in postoperative period were 76.04, 46.11, and 25.78 months for MMUS, TVT, and TOT respectively (p>0.05).

We did not determine any statistical significance for VLPP values postoperatively. There were only 8 cases that had positive VLPP postoperatively so the statistical analysis was not applicable for VLPP.

Preoperative and postoperative urodynamic test results were evaluated. When we compared maximum vesical pressure and maximum detrusor pressure between preoperative and postoperative urodynamic tests, we determined that the values of both parameters decreased after the operations and these decreases were statistically significant (p<0.05). In the analysis of VLPP values, the mean of postoperative values was higher than that of preoperative values and this was statistically significant (p<0.05).

Eight patients had VLPP postoperatively. We determined that significant improvement and satisfaction were obtained postoperatively for most of these 8 patients.

VLPP, a parameter for objective diagnosis of stress urinary incontinence, was used to detect response of the treatment postoperatively. Preoperative and postoperative mean values of VLPP were compared between operation types (Table 2). Among postoperative urodynamic evaluation of 13 patients who had <60 cm H2O pressure of VLPP preoperatively, 11 of them (84.6%) had no VLPP and only 2 had positive VLPP (15.4%) postoperatively. These two patients had higher VLPP levels than their preoperative levels; the increase in VLPP may demonstrate the effectiveness of operations so we determined these results as improvement. We established improvement in patients who had 60-100 cm H2O pressure of VLPP and >100 cm H2O pressure of VLPP with a rate of 84.6% and 92.3%, respectively. We compared the classification of postoperative VLPP values and we did not find any significant differences between operation types (p>0.05) (Table 3). Evaluation of postoperative VLPP values are significant and important in terms of 'objective cure' assessment. Comparative analysis of operation types showed that 'objective cure' rates were 83.3%, 88.9%, and 91.3% for MMUS, TVT, and TOT respectively (Table 3).

In the follow-up process 3 patients experienced mesh erosion. The rate of erosion was 4.6% among all patients; 8.3% (n=2) in the MMUS group; 0% (n=0) in the TVT group; and 4.3% (n=1) in the TOT group. When we compared rate of mesh erosion between operation types, there was no statistical significance (p>0.05).

Discussion

We compared sling operations for patients with SUI or MUI and evaluated subjective and objective cure rates. We found that subjective cure rates for MMUS, TVT, and TOT were 79.1%, 94.4%, and 91.4% respectively. Objective cure rates for MMUS, TVT, and TOT were 83.3%, 88.9%, and 91.3% respectively. We did not determine any significant differences between operation types in terms of objective and subjective cure rates.

There are several studies that compare the effectiveness of sling operations. In the Cochrane meta-analysis that evaluated cure rates of TVT and TOT, cure rates were reported as 73% for both operations [12]. In a randomized study, Richter et al. showed no significant differences for objective cure rates between TVT and TOT operations (TOT-77.7% vs TVT-80.8%) [13]. Hung et al. compared TVT and pubovaginal sling with synthetic mesh, finding 91.3% and 93% improvement in TVT and pubovaginal sling with synthethic mesh, respectively [14].

We determined objective cure rates using urodynamic evaluation (cystometry). Urodynamic evaluation provides some data to detect the stress component of urinary incontinence. In particular, VLPP values give more information to clinicians in understanding of ISD (intrinsic sphincteric deficiency). Although there are some differences among patients, most clinicians

Table 2. Comparison of preoperative and postoperative urodynamic outcomes according to operation types

		MMUS (n=24)	p	TVT (n=18)	p	TOT (n=23)	p
Bladder Capacity (ml)	Preoperative	411.33±66.74	0.201†	391.27±80.24	0.429†	395.00±80.38	0.136†
	Postoperative	390.29±72.67		404.22±56.14		414.43±79.25	
Maximal Vesical Pressure (cm H_2O)	Preoperative	19.20±9.35	0.278†	26.27±14.73	0.003†	18.30±9.20	0.113‡
	Postoperative	17.20±7.30		17.94±12.68		13.69±6.81	
VLPP (cm H_2O)	Preoperative	71.00±18.52	0.068‡	108.50±33.23	§	74.00±41.01	§
	Postoperative	121.75±15.10		105.00±14.14		128.00±2.82	
Maximal Detrusor Pressure (cm H_2O)	Preoperative	13.75±7.21	0.445‡	22.50±14.07	0.008‡	16.04±8.14	0.092‡
	Postoperative	14.54±6.23		16.16±12.19		12.21±7.10	
PVR (ml)	Preoperative	16.45±15.70	0.104‡	9.44±11.99	0.500‡	15.21±24.83	0.350‡
	Postoperative	11.95±13.55		6.66±8.40		10.43±18.02	

†Paired Samples t-Test, ‡Related-Samples Wilcoxon Test §, statistical significant was not evaluated Values are given as mean ±SD, MMUS, modified midurethral sling PVR, Postvoiding residual volume SD, Standard deviation TVT, tension-free vaginal tape TOT, transobturator tape VLPP, valsalva leak point pressure

Table 3. Postoperative VLPP and Objective Cure rates between operation types

		MMUS n (%)	TVT n (%)	TOT n (%)	p
Postoperative VLPP (cm H2O)	Absent	20 (83.3)	16 (88.9)	21 (91.3)	0.834
	<60	0 (0)	0 (0)	0 (0)	
	60-100	1 (4.2)	1 (5.6)	0 (0)	
	>100	3 (12.5)	1 (5.6)	2 (8.7)	
Objective Cure Rate		20(83.3)	16 (88.9)	21 (91.3)	>0.05

Pearson Chi-Square Test MMUS, modified midurethral sling TVT, tension-free vaginal tape TOT, transobturator tape VLPP, valsalva leak point pressure

think that a VLPP value below 60 cmH2O confirms the diagnosis of ISD [15]. We classified VLPP values according to the pressure levels and compared postoperative findings between operation types. When we evaluated the patients who had VLPP values below 60 cm H2O, a complete cure was obtained in 84.6% of patients. Higher pressure values of VLPP (>100 cm H2O) raised the success rate to 92.3% in the present study. Similarly, Young et al. found significant differences between patients according to whether they had ISD and they showed significantly higher cure rates in the no-ISD group (p<0.001) [16]. Another study indicated that low VLPP values (<60 cm H2O) may be an independent marker for treatment failure [17]. Rechberger et al. showed that low VLPP levels lead to poor treatment response in TOT operations but not in TVT operations [18]. The success rates of our study for ISD patients was 100% in the TVT group and 75% in the TOT group. Similar to our study, Kim et al. established that the success rate of TVT was significantly higher than for TOT in patients who had ISD (TVT, 95.2% vs TOT, 82.7%) [19]. They showed risk factors of treatment failure and found that TOT is the only risk factor associated with treatment failure after 12 months follow-up. Therefore TVT is considered the preferred method in patients with ISD because it is a more obstructive technique than TOT [20]. Contrary to these studies, some authors have concluded that TOT is comparable to TVT in ISD [13,21]. Another study which compared pubovaginal sling, TVT, and TOT observed similar complication rates among operations for ISD; however, cure rates for TOT were lower (34.9%) than for TVT (87%) and pubovaginal sling (87.3%) [22]. When we evaluated the objective cure rates of patients according to VLPP values, we did not find any significant differences between operation types (MMUS, TVT, and TOT; 83.3%, 88.9%, and 91.3% respectively) (p=0.834).

In several studies, similar cure rates were reported but in the present study we determined higher objective cure rates than in other studies. Some studies that approved VLPP values as objective criteria showed lower cure rates compared to our study [13,23].

The most important complication of midurethral sling operations is bladder perforation. It is also the most common complication of TVT at a rate of 3.5-6.6% [24-27]. In a study that compared TVT and pubovaginal sling with synthetic mesh, the rate of bladder perforation was 4.3% in TVT patients and 0% in pubovaginal sling patients (p=0.287) [14]. Castillo-Pino et al. found that bladder injuries occurred in the TVT group at a rate of 5.5% and no bladder perforation was shown in the TOT group (p=0.14) [23]. In our study, one bladder injury occurred, and it was in the MMUS group. The rate of bladder injury was 4.1% in the MMUS group and there was no bladder complication in the TVT and TOT groups.

Another important complication is mesh erosion, which develops in the late postoperative period. A meta-analysis by Novara et al. did not find any significant differences between TOT and TVT with regard to mesh erosion [28]. Abouassaly et al. found that mesh erosion occurred at a rate of 0.4% and 1.4% in TVT and TOT operations, respectively [26]. Some researchers think that the hammock-shaped structure of TOT creates more contact area than the U-shaped structure of TVT, leading to increased inflammation and erosion rates in TOT operations [29]. In the present study, we established mesh erosions in 3 patients, 2 of them in the MMUS group (8.3%) and the other one in the TOT group. There was no mesh erosion in the TVT group. These rates are high compared to the literature, but may be explained by the small sample size.

According to the cost-effectiveness analysis of our study, TOT and TVT operations have higher costs because they use special materials. Only prolene or mersilene mesh is required for modified sling operations and this decreases the operation cost. Average costs of TOT and TVT currently are $300-400 (USD), whereas the cost of mesh for modified sling operations is approximately $10-15. As we have seen, modified sling operations have significantly lower materials costs than TVT and TOT operations. In one study, the cure rate was determined as 81.3% for pubovaginal sling operations with polypropylene mesh, and their low cost was also established [30]. ElSheemy et al. compared surgeon-tailored modified technique (STM) with original TVT-O [31]. There was no significant difference in cure rates between operation types (p=0.654), but surgical cost decreased significantly from $500 to $10. They also found MUI and urgency improvement similar to our study. Polypropylene self-tailored mesh has been used by many surgeons and costs of surgery have decreased significantly [32-34]. When TVT-O (with STM) was compared to TVT in one study, it was reported that cure rates did not show any significant difference, while surgical costs were significantly reduced by the STM method [35]. The surgeon-tailored mesh method has an advantage in developing countries with few financial resources and it may be considered as a low-cost alternative for treating SUI patients. We performed MMUS operations as a cost-effective method with similar cure rates compared to TVT and TOT.

Our study has several limitations. Firstly, this study is not a randomized controlled study. Non-random patient selection method is the main limitation. Heterogenous study groups with SUI and MUI is another limitation of our study. Follow-up duration is in a wide range and it is variable in our study. Objective questionnaires were not used to determine subjective cure rates in the present study. However, the strengths of our study include that it is single experienced surgeon data and VLPP is used to detect the objective cure rate of operations. There are few studies using single surgeon data and VLPP is not commonly used to demonstrate the objective cure rates of operations.

In conclusion, the subjective and objective cure rates of patients treated with MMUS, TVT, and TOT were similar and there was no statistically significant differences. VLPP provides a quantitative component of urodynamic evaluation that is useful in SUI

patients and especially for ISD. Modified sling operations may be preferred in some situations instead of TVT or TOT because of low costs. Further prospective randomized controlled trials are required to confirm our results.

Competing interests

The authors declare that they have no competing interests.

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Internal splinting method for isolated zygomatic arch fracture using endotracheal tube: A new method

İzole zigomatik ark kırıklarında endotrakeal tüpün internal splint olarak kullanılması: Yeni bir yöntem

Use of the endotracheal tube for zygomatic arch fractures

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Öz

Amaç: Bu çalışmanın amacı şişirilmiş endotrakeal tüpün yeni, basit bir internal siplint yöntemi olarak izole zigomatik ark fraktürlerinde kullanımının sonuçlarını değerlendirmek. Gereç ve Yöntem: Bu yöntem ile izole zigomatik ark fraktürüne sahip 16 erkek ve 4 kadın toplam 20 hasta opere edilmiştir. Zigomatik ark fraktürleri Gillies yöntemi ile redükte edildikten sonra endotrakeal tüp zigomatik ark arkasına yerleştirilerek internal siplint olarak kullanılmıştır. Üç tanesi insilün bağımlı diabet olan hastaların yaş ortalaması 29 bulunmuştur. Hastalar postop ortalama 6,8 ay takip edilmiştir. Hastalar preop ve postop 1.gün ve 3. aylarda hem klinik hem de bilgisayarlı tomografi (BT) ile değerlendirilmiştir. Bulgular: Postoperatif dönemdeki klinik ve BT değerlendirmelerinde yetersiz redüksüyon, yetersiz stabilizasyon, fasiyal sinir yaralanması ve enfeksiyon gibi herhangi bir komplikasyon ile karşılaşılmamıştır. Tüm hastalar bu yöntemi iyi tolare etmiş ve bir şikayetleri olmamıştır. Tüm hastalarda normal zigomatik ark kontürü ve yüz simetrisi görülmüştür. Tartışma: Bu yeni yöntem basit ve komplikasyonsuzdur. Ayrıca küçük bir kesi ile girilip endo trakeal tüp tamamen temporal fasya altına yerleştirildiği için enfeksiyon riskini en aza indirmektedir (özellikle diyabet hastalarında). Endotrakeal tüp kafının şekli nedeniyle redükte edilmiş kırık hattına daha geniş yüzeyli basınç uygulamakta ve yer değiştirmemektedir. Bu nedenle bu yeni yöntem izole zigomatik ark kırıklarının tedavisinde kullanılabilir.

Anahtar Kelimeler

Endtrakeal Tüp; İnternal Splint; İzole; Zigomatik Ark; Fraktür

Abstract

Aim: The aim of this study was to evaluate the results of the inflated endotracheal tube for simple internal splinting in the treatment of isolated zygomatic arch fractures as a new method. Material and Method: A total of sixteen male and four female patients with isolated zygomatic arch fractures were reconstructed using this method. Reconstruction was performed with temporal approach and internal splinting method and inflated endotracheal tube was used for internal splinting. The median age of the patients was 29 years. Three patients had insulindependent diabetes mellitus. Mean follow-up after surgery was 6.8 months. Patients were evaluated both clinicall and with computerized tomography scan (CTS) preoperatively, postoperative 1 day, and postoperative 3 months. Results: We did not encounter any complications such as poor reduction, insufficient stabilization, facial nerve injury, or infection. All patient tolerated the method well and did not complain about comfort. All patients demonstrated normal zygomatic contour and facial symmetry. Discussion: This new method is simple, easy and complication free. In addition, a small incision is used and the internal splint is totally embedded under the temporalis fascia to minimize the risk of infection, especially for patients with diabetes mellitus. The endotracheal tube applies pressure over a longer segment of reducted fracture and there is no displacement because of the elliptical shape of the cuff. Therefore, this new method can be used for the treatment of isolated zygomatic arch fractures.

Keywords

Endotracheal Tube; Internal Splint; Treatment; Isolated; Zygomatic Arch; Fractures

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Introduction

The zygomatic arch is formed by temporal and zygomatic processes. It is palpable and visible on the cheek and the temporal area. Its sharp upper border is obscured by the attachment of temporal fascia, and the lower border is attached to the masseter muscle [1]. Between the zygomatic arch and the skull, the coronoid process of the mandible moves freely when the mouth is opened and closed. A fracture, which generally depresses this arch, implicates a partial or total obstruction of the movement of the condyle and of the coronoid process of the mandible, affecting the opening and closing of the mouth [2].

Isolated zygomatic arch fractures (IZAF) account for approximately 4.5% [3] to 10% [4] of all fractures of the midface. They usually result from a direct force of low velocity during sports, falls, traffic accidents, or assaults. Various methods have been used in the treatment of IZAF. The aim of the present study was the investigate whether the endotracheal tube (Figure 1) could serve as a versatile method in IZAF and its advantages over similar methods.

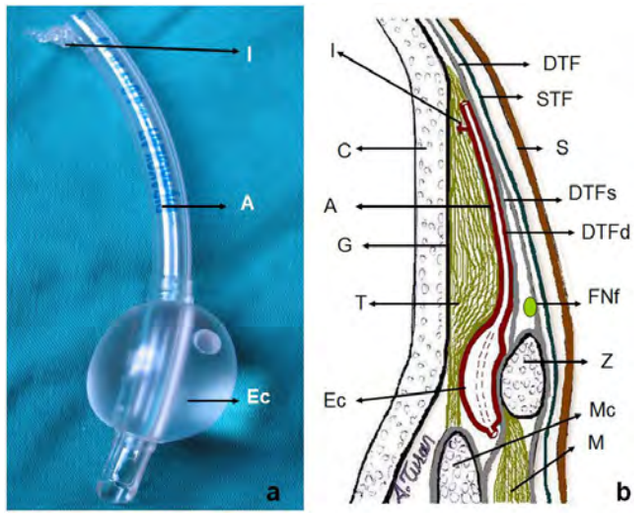


Figure 1. Appearance of prepared pediatric endotracheal tube and schematic diagram after introduction under the zygomatic arch. a: Inflated pediatric endotracheal tube after being prepared for the new method. b: Schematic diagram of the inflated pediatric endotracheal tube after introduction under the reducted zygomatic arch fracture. I, inflating lumen; A, air connector; Ec, cuff of the endotracheal tube; G, galea; C, calvarium; T, temporalis muscle; DTF, deep temporal fascia; DTFs, superficial layer of DTF; DTFd, deep layer of DTF; STF, superficial temporal fascia; FNf, frontal branch of the facial nerve; S, skin; Z, zygomatic arch; Mc, coronoid process of mandible; M, masseter muscle.

Material and Method

A four-year (2013–2017) retrospective study involving 20 patients admitted and treated for isolated zygomatic arch fractures at the department of plastic, reconstructive and aesthetic surgery was done.

Sixteen male and four female patients with isolated zygomatic arch fractures were treated using this method. Patients were evaluated both clinically and using computerized tomography scan (CTS) preoperatively (Figure 2), postoperative 1 day, and postoperative 3 months. Postoperative assessment was performed by means of clinical and radiographic (CTS) examination to check the position of the inflated tube under the zygomatic arch (Figure 3).



Figure 2. Preoperative radiologic and intraoperative clinical views of Case 1. a: Axial computerized tomography scan (CTS) image showing medial displacement of the two fragments in a "W" or "M" shaped pattern of the left isolated zygomatic arch fracture (arrow); b: The prepared pediatric endotracheal tube over the malar area and a skin incision made for the Gillies approach (arrow). ET, endotracheal tube.



Figure 3. Postoperative clinical and radiologic view of Case 1. a: The postoperative appearance of the malar area and sutured Gillies incision (arrow); b: The postoperative axial CTS image showing internal splinting of the reducted left zygomatic arch fracture (arrow). ET, endotracheal tube.

Operative Technique

The fracture site of the zygomatic arch and the incision site were outlined with a marking pen. The incision site was determined according to the length of the endotracheal tube so that the cuff of the tube would stay beneath the fracture site (Figure 2b). A pediatric endotracheal tube with a 4 mm internal diamater was used in all patients (ID 4mm, CE&ISO Goldenwell China) (Figure 1a). Depending on the case, approximately 8-10cm above the fracture site a skin incision of 2cm length was created in the hair-bearing scalp as described by Gillies (Figure 2b). Dissection was carried down to the deep temporal fascia, just superficial to the temporal muscle. A blunt dissector was passed through the incision downward on the surface of the temporal muscle until it reached the deep surface of the displaced arch, so that a cleavage plan could be prepared under the deep temporal fascia between the zygomatic arch and the incision site. An elevator was used to reduce the depressed segment of the arch. Adequate reduction was evaluated by palpating the skin directly overlying the arch fragments and comparing it with the non-fractured site. The pediatric endotracheal tube was introduced through the incision to serve as an internal splint under the reducted arch. The cuff of the tube was inflated with 5 to 7 ml saline. Inflating lumen of the cuff was cut above the bifurcation point after being fixed with several knots (Figure 1a). The cranial end of the tube was anchored to

the deep temporal fascia with a single 4-0 nylon suture. The tube was embedded in the subfascial plane and the skin was closed primarily (Figure 3a). The endotracheal tube was kept under the zygomatic arch for 3 weeks. The patients received a central myotonolytic agent (tizanidin 1x 6 mg, p.o.) during this postoperative period to minimize the displacement force of the masseter muscle. The endotracheal tube was removed after 3 weeks.

Case Reports

Case 1: A 28-year-old woman admitted to our clinic with an IZAF on the left side. On the CTS a depressed fracture of the zygomatic arch was observed (Figure 2a). Closed reduction and internal splinting with an endotracheal tube was performed through a temporal approach. Reduction was evaluated with CTS one day postoperatively (Figure 3b) and the patient was discharged. Control CTS demonstrated a normal zygomatic contour and facial symmetry.

Case 2: A 44-year-old man presented with an isolated fracture of the left zygomatic arch (Figure 4a). The medical history revealed that he had sustained a road traffic accident several days prior. Closed reduction and internal splinting with an endotracheal tube were performed with the same method as described previously (Figure 4b). Reduction was evaluated with CTS one day postoperatively (Figure 5) and the patient was discharged. Postoperative 12 month CTS demonstrated a good reduction and contour of the zygoma (Figure 6). The patient healed without any complications.

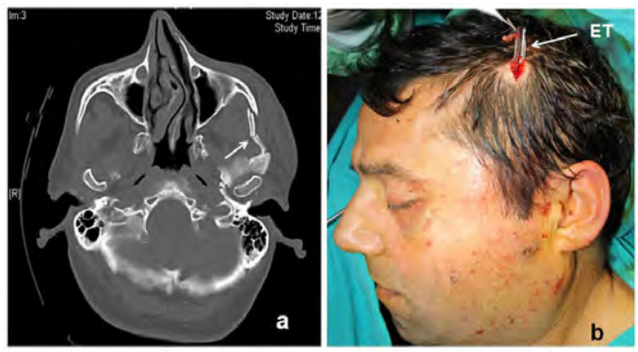


Figure 4. Preoperative radiologic and intraoperative clinical views of Case 2.
a: The axial CTS shows an isolated fracture of the zygomatic arch on the left side (arrow).
b: Preoperative views of Case 2 after introduction and inflation of the endotracheal tube. ET, endotracheal tube.

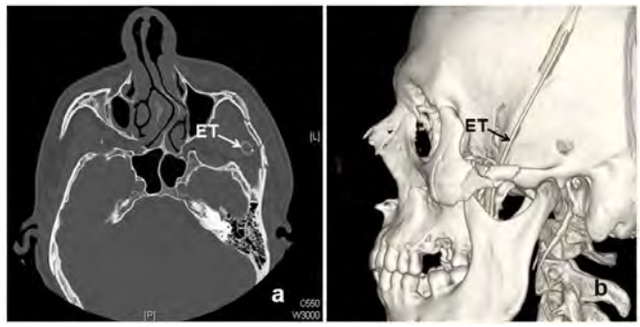


Figure 5. Radiologic views of Case 2 at postoperative 1 day.
a: The axial CTS views of the inflated endotracheal tube under the reducted zygomatic arch (arrow). ET, endotracheal tube.
b: The 3D-CTS views of the reducted zygomatic arch fracture and inflated endotracheal tube under the zygomatic arch (arrow). ET, endotracheal tube.

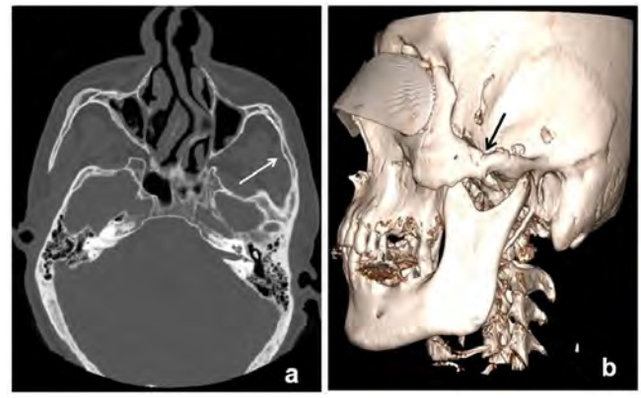


Figure 6. Radiologic views of Case 2 at postoperative 12 months .
a: The axial CTS demonstrates a good reduction and anatomical contour of the zygoma (arrow).
b: The 3-D CTS demonstrates a good union of fractured segments of the zygomatic arch (arrow). The patient healed without any complication.

Results

The median age of the patients was 29 years. The etiology of the fractures was a direct punch over the zygomatic arch in seven patients (35%) and traffic accident in the remaining thirteen (65%) patients. Three patients were suffering insulin-dependent diabetes mellitus. Eight patients were operated on under local anesthesia, whereas general anesthesia was necessary for twelve. All patients were discharged one day postoperatively. Median follow-up after surgery was 6.8 months (range: 3 to 14 months). The endotracheal tubes used as a internal splint were kept in place for 21 days in all patients. None of the 20 patients needed a secondary operation. In the present study, no complications such as poor reduction, insufficient stabilization, facial nerve injury, or infection were encountered. This method was well tolerated by all patients. In all patients, a normal zygomatic arch contour and facial symmetry was achieved.

Discussion

The reported rate of IZAF ranges between 4.5% and 10% among midface fractures [3,4].

Isolated fracture of the zygomatic arch is not unusual and is generally a result of a direct blow to the face. In the radiological examination, medial displacement of the two fragments in a “W” [5] or “M” [2] shape is observed in most of the cases. Treatment options for isolated zygomatic arch fractures range from closed reduction without fixation (stabilization) to open reduction with fixation [6], and sometimes multiple incisions to achieve a successful reduction.

There is a consensus in the literature that open reduction and rigid fixation is the treatment of choice for comminuted and displaced fractures. However, the best method of management in reduction and fixation of less-severe fractures is still controversial. In this context, open reduction procedure carries a potential risk for facial nerve injury, scalp numbness, and alopecia [7]. In routine clinical practice, closed reduction with or without stabilization generally is used for treatment of IZAF.

In some long-term follow-up studies on IZAF, good results have been reported with the closed reduction only method [8]. In a clinical study, Rodriguez and Casado [5] have found that more than 90% of the fractures were stable enough not to require any additional measures due to the splinting effect of the tem-

poralis fascia and the ventral periosteum of the arch. They suggested that reduction only is sufficient in the treatment of these cases. On the other hand, some authors recommended internal [9] or external [10] splinting for stabilization and protection after closed reduction of the IZAF. Their standpoint is that the pull force of the masseter muscle and external pressures on the fractured site can redisplace the fractured segments.

Closed reduction takes less operating time, leaves minimal incision scars, and incurs less soft tissue violation. Moreover, because the periosteum is not violated, better bony union can be expected. Inadequate mechanical fixation and poor visualization are the main disadvantages of the closed reduction techniques [11]. Closed reduction is performed through temporal [12], transoral [13], and transcutaneous [14] approaches in most cases of IZAF. Endoscopically assisted closed reduction techniques have some advantages such as magnified direct visualization, a decreased complication rate, and a better result than the conventional methods. However, this technique has the disadvantage of a relatively longer operative time and is more expensive [15]. The transoral approach has several advantages, such as absence of a skin incision, technical ease, and minimal dissection and bleeding [16]. However, it is very easy to introduce the oral flora into the infratemporal fossa and the risk of infection is increased with this method. On the other hand, the transcutaneous approach is easier as it directly approaches the fracture site with less risk of infection [17] and shorter operating time [18]. Various devices have been manufactured for the transcutaneous approach to reduction of IZAF, such as bone hooks [19], screws [20], curved mosquito [17], and towel clips [18].

Closed reduction with a curved mosquito can cause hematoma because of blunt dissection through the masseter muscle [17]. Reduction with the insertion of a bone hook can be technically difficult while dealing with a depressed arch [21] and using a towel clip can cause inadvertent facial nerve injury [18]. Transcutaneous screw reduction seems to be a less invasive method for zygomatic arch fractures; however, it is difficult to apply in older patients where the bone is friable [20]. Therefore, it seems reasonable to assume that splinting of the fractured segments after closed reduction is a safer method in the treatment of IZAF. There are two main methods described in the literature for stabilization and protection of the fractured bone segments after closed reduction. These methods are known as external splinting and internal splinting. Orthopedic finger splints [22] and custom-made devices have been used for external splinting. However it is difficult to adapt them where there is considerable soft tissue swelling [10]. Also, there can be pressure necrosis of the skin beneath the splint and a risk for facial nevre injury [23]. The present author reveals that this method is more comfortable in comparison of external splinting methods in terms of physical appearance.

Foley catheter [19] and epistaxis balloon [23] have been used for internal splinting of reducted arc fractures. The main idea is that internal splints serve as a more comfortable method than external splints. Both the Foley catheter and the epistaxis balloon are made of flexible rubber so they need a rigid guide to be introduced under the fractured arch. Also it is difficult to bury both tubes under the skin owing to their design. In comparison, burying the endotracheal tube is an advantage. Also, the semi-rigid structure of the tube does not necessitate any rigid guide for its introduction.

The Foley catheter is inclined to superior or inferior displacement under the reducted zygomatic arch because of its spherical shape. The other alternative method for the treatment of fractures is use of the endotracheal tube. The endotracheal tube method was first described by Turan et al. for internal splinting of the reducted IZAF [24]. The advantage of using the endotracheal tube is the elliptical shape of the cuff, which applies pressure over a longer segment of reducted fracture and avoids displacement. The endotracheal tube method offers the possibility of readjusting the volume of the cuff to maintain the appropriate position of the fractured segments. The modification of burying the inflation tube under the temporalis fascia was made after the publication of the first letter [24] and the patient series was increased. Usage of the Botulinum toxin has already been described for eliminating the displacing force of the masseter muscle on the fracture site [25]. In the present study, tizanidine was used instead of botulinum toxin to minimize the pull of masseter muscle. Also, in our study we did not paralyze the masseter muscle because muscle activity is known to enhance fracture union.

This method eliminates the potential problems inherent to external splinting methods and it has advantages over other internal splinting methods. For these reasons, this method can be suggested in the treatment of isolated zygomatic arch fractures.

Conclusion

Use of an endotracheal tube for splinting after closed reduction of IZAF has many advantages such as small incision, easy access to the fracture site, ease of burying the tube under the skin, less risk of infection, and better splinting of the fracture owing to the elliptical shape of the cuff of the endotracheal tube. Therefore, this new method can be used as an alternative approach in the treatment of IZAF fractures with satisfactory results in clinical practice.

I have no financial relationship with the organization that sponsored the study.

Conflict of Interest Statement:

The present author discloses that they have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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The prevalence of chronic obstructive pulmonary disease in Bolu province of Turkey

Bolu ilinde kronik obstruktif akciğer hastalığının prevalansı

Copd in Bolu province of Turkey

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Öz

Amaç: Günümüzde Kronik Obstrüktif Akciğer Hastalığı (KOAH), tüm dünya ülkelerinde önemli bir sağlık sorunu haline gelmiştir. Diğer hastalıkların mortalite oranlarının yıllar içinde düşmesine karşılık KOAH prevalansı ve mortalitesi giderek artış göstermektedir. Bu araştırma Bolu il merkezinde KOAH prevalansını belirlemek amacıyla yapıldı. Material and Method: Bolu il merkezinde oturan, ev tespit fişlerinden rastgele yöntemle seçilen 35 yaş ve üstü 500 kişiye solunum fonksiyon testleri yapıldı. Çalışmaya katılan bireylerden 285'i (%57) erkek, 215'i (%43) kadın idi. KOAH'nın tanısı için 'Obstruktif Akciğer hastalıkları için Global İnsiyatif' kriterleri ile birlikte spirometri kullanıldı. Bulgular: KOAH prevalansı % 8.6 (43 kişi) bulundu. KOAH tespit edilen hastaların hiç biri hafif evrede değildi. % 34.9'i orta, % 41.86'sı ağır ve % 23.25'i çok ağır evrede idi. KOAH tespit edilen hastaların % 97.67'sinde (43 kişiden 42'sinde) sigara içme öyküsü vardı. Çalışmaya katılan erkeklerin % 9.82'sinde (285 kişiden 28 kişide), kadınların % 6,97'sinde (215v kişiden 15 kişide) KOAH saptandı. Tartışma: KOAH'ın, Bolu il merkezinde önemli bir halk sağlığı sorunu olduğu düşünüldü.

Anahtar Kelimeler

Kronik Obstruktif Akciğer Hastalığı; Epidemiyoloji; Prevalans

Abstract

Aim: Chronic Obstructive Pulmonary Disease (COPD) is increasingly recognized as a leading cause of global morbidity and mortality throughout the world. The prevalence and mortality of COPD have increased through years. This study was conducted to explore the prevalence of COPD in the central Bolu province of Turkey. Material and Method: Pulmonary function testing (PFT) was performed on 500 subjects above the age of 35 years who were selected randomly using 'Family Identification Cards' in each governor office in central Bolu. Of the 500 subjects, 285 (57.0%) were male. The diagnostic criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) with spirometry was used to diagnose COPD. Results: The prevalence of COPD was found to be 8.6% (43 of 500 subjects). None of the diagnosed subjects had stage 1 disease in terms of GOLD stage definition. Stage 2, stage 3, and stage 4 diseases were found in 34.9%, 41.8%, and 23.3% of COPD-diagnosed subjects, respectively. Smoking history was positive in 42 of 43 subjects with COPD (97.7%). In terms of all subjects, COPD was diagnosed in 9.8% of males (28 of 285) and 6.9% of females (15 of 215). Discussion: COPD was defined as a significant public health problem in Bolu province of Turkey.

Keywords

Chronic Obstructive Pulmonary Disease; Prevalence; Smoking

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by almost irreversible airflow restriction in the lungs. Air flow restriction is generally progressive and caused by an abnormal inflammatory response in the lungs due to the harmful particles and gasses. Tobacco use is accepted as one of the most significant risk factors. Although COPD is a lung disease, it may cause serious systemic problems [1]. In Turkey, the number of people with COPD is estimated to be around 2-3 million. A high frequency of smoking, inadequate spirometry means in the primary health care units, and other shortcomings in the prevention and diagnosis of the disease cause COPD to be one of the significant public health problems in Turkey [2-5]. This study aimed to explore the prevalence of COPD in Bolu province of Turkey.

Materials and Method

This study was designed as a cross-sectional study and the study design was approved by the local ethics committee. The study included 500 subjects above the age of 35 years who were selected randomly by using the Family Identification Cards in the local governor offices in Bolu province of Turkey. There are 37 districts in central Bolu and each has a local governor. The data were collected between May 2007-July 2007. A face-to-face interview was performed with each selected subject and a questionnaire form was filled out. In addition, spirometry testing, age, height, and weight of the subjects were recorded in the outpatient clinic of the Department of Chest Diseases in Bolu Izzet Baysal University. At least 3 spirometry recordings were performed and the best results were included. The diagnosis of COPD was made by using the diagnostic criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1,6,7].

The collected data and the spirometry results were analyzed by using the SPSS 10.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA). Values were expressed as mean±standard deviation. The normality of the values was analyzed by using the Shapiro-Wilk test. Independent samples t-test or Mann-Whitney U test were used according to the Shapiro-Wilk test result. Categorical comparisons were performed by chi-square test. Differences were considered significant at $p < 0.05$.

Results

The study comprised 500 subjects (285 male, 215 female). The age, height, and weight of male and female subjects are shown in Table 1.

The frequency of the symptoms did not differ between male and female subjects (Table 2).

Table 3 shows the smoking-related history and occupational exposure to dust and biomass with respect to gender in COPD patients. The subjects who never smoked and had at least one smoking family member were classified as passive-smoker.

The most frequent stage of COPD was stage 3 (severe COPD) (Table 4).

Table 1. Age, height, and gender characteristics of male and female subjects

	Male (n=285, 57%)		Female (n=215, 43%) (%43)		Total (n=500)	
	Min-Max[max]	Mean	Min-Max[max]	Mean	Min-Max[max]	Mean
Age (years)	35-87	63.9±15.9	35-79	52.4±14.3	35-87	58.2±15.3
Height (cm)	163-192	169.4±8.9	141-174	155.1±7.3	141-192	165.3±8.2
Weight (kg)	51-105	71.4±13.9	41-104	69.7±13.6	41-105	70.9±13.7

Min-Max: Minimum-Maximum

Table 2. The diagnostic, obstructive, and symptom characteristics of patients with COPD.

	Female (n=15)	Male (n=28)	Total (n=43)
COPD prevalence	6.9% (15/285)	9.8% (28/215)	8.6% (43/500)
Previous diagnosis of COPD	0.03% (1/285)	1.0% (5/215)	1.2% (6/500)
Cough	86.6% (13/15)	100.0% (28/28)	95.3% (41/43)
Sputum	80.0% (12/15)	96.4% (27/28)	90.7% (39/43)
Wheezing attacks	73.3% (11/15)	57.1% (16/28)	62.8% (27/43)
Dyspnea	86.6% (13/15)	89.2% (25/28)	88.3% (38/43)

COPD. Chronic obstructive pulmonary disease

Table 3. The frequencies of smoking-related history and occupational exposure in male and female subjects with COPD

	Male (n=28)		Female (n=15)		Total (n=43)	
	n	Percentile	n	Percentile	n	Percentile
Smoker	23	82.1	12	80	35	81.4
Smoked in the past	5	17.9	2	13.3	7	16.3
Never smoked	0	0	1	6.7	1	2.3
Smoking history	28	100	14	93.3	42	97.7
Passive smoker	0	0	1	0.06	1	2.3
Occupational exposure to dust	12	42.9	3	20	15	34.9
Biomass exposure	4	14.3	6	40	10	23.3

COPD. Chronic obstructive pulmonary disease

Table 4. The distribution of COPD subjects, using GOLD staging

Stages of COPD	n	Percentile (%)
Stage 1 (Mild COPD)	0	0
Stage 2 (Moderate COPD)	15	34.9
Stage 3 (Severe COPD)	18	41.9
Stage 4 (Very Severe COPD)	10	23.3
Total	43	100.0

COPD. Chronic obstructive pulmonary disease

Discussion

This study found the COPD prevalence in the population over 35 years of age in Bolu province of Turkey as 8.6%. The prevalences of COPD in male and female subjects were 9.8% and 6.9%, respectively.

Two important problems arise in studies investigating the epidemiology of COPD. The first is the selection of the study population and the second problem is possible sampling errors. This causes difficulty in comparing the results of different studies and also the evaluation of the progress of the disease.

In this study, we selected the subjects in a randomized way by using the cluster and systematic sampling from the Fam-

ily Identification Cards in order to minimize the sampling errors. The spirometric evaluation criteria used in this study is the widely accepted GOLD criteria [1].

In their large study including 14223 participants, Prescott et al. found that COPD has a three times higher prevalence in people with low socioeconomic status [8]. Respiratory symptom prevalence in the population over 40 years of age was investigated in the IPERBOC study in Spain [9]. Cough, sputum, and dyspnea prevalences were found as 13.5%, 10.7%, and 10.4%, respectively. The prevalence of chronic bronchitis was higher in the male population (8.3% in males and 1.4% in females). In our study, cough, sputum, and dyspnea prevalences were found as 39.6%, 30.2%, and 27.8%, respectively. The higher prevalences in our study compared to IPERBOC study may have originated from the higher prevalence of smoking-related history and higher occupational exposure.

Ozlu et al. investigated the prevalence of COPD in the population above 30 years of age in the Trabzon province of Turkey in 2004 [10]. That study is one of the pioneer studies using the criteria suggested by GOLD and ATS. A total of 613 subjects were included and a face-to-face interview and spirometry testing were performed. COPD prevalence according to GOLD criteria in their study was found as 0.98%. The prevalences in male and females were 1.7% and 0.3%, respectively. According to ATS criteria, overall prevalence, prevalences in male and in female populations were 2.8%, 4.1%, and 1.6%, respectively. COPD prevalences found by Ozlu et al. are significantly lower than in our study.

Ekici et al. compared the biomass-exposed and -nonexposed female populations above 40 years old [11]. All the subjects were nonsmokers. The prevalence of airflow obstruction (FEV_1/FVC<%70) in biomass-exposed females was 13.6%, a ratio lower than 28.5% in nonexposed females.

Some risk factors such as tobacco use, occupational dust exposure, air pollution, and biomass exposure may cause COPD [1]. The cause of the high prevalence of COPD in Bolu province of Turkey is possibly because of the high prevalence of smoking (57.6%) and occupational biomass exposure.

The most significant risk factor for COPD is smoking [12]. Smoking is responsible for 90% of COPD in industrialized countries [6]. According to the PIAR investigation report in 1998 in Turkey, 62.8% of males and 24.3% of females are smokers [13]. The prevalence of smoking in Bolu province (57.6%) is above the average for Turkey (43.0%) [13]. In this study, the high prevalence of severe COPD and continuing use of tobacco suggests the inconvenience in Turkey for patients in obtaining treatment and follow-up. These data show inadequate public health campaigns against smoking. This necessitates taking the required precautions.

Recent studies show that the prevalence of COPD in women is approaching the prevalence in men [14]. This is caused by increasing prevalence of smoking in women in recent years [6,15-17]. Similar prevalences of smoking and occupational exposure between men and women in the Bolu province support this suggestion. In our study, 14.8% of males and 40.0% of females with COPD had biomass exposure. This shows that biomass exposure may also be a more significant risk factor than anticipated.

COPD prevalence increases throughout the world. The mortality of COPD varies significantly between countries [6,18]. The reason for this difference is possibly because of the differences in smoking behaviors, environmental and genetic factors, and infections.

As in other areas of the world, the actual prevalence of COPD in Turkey is thought to be higher than reports indicate [3-5]. In Turkey, the high prevalence of smoking, inadequate spirometry, and inadequate health care in the diagnosis and follow-up of the disease in the primary health care units result in COPD being a significant public health problem in Turkey.

The epidemiologic data is important in controlling COPD, a preventable disease that causes social and economic problems. We think that the prevalence data related to Bolu province may enlighten future studies in Turkey. In conclusion, according to GOLD criteria, the prevalence of COPD in central Bolu province is 8.6%. The prevalences in males and females are 9.8% and 6.9%, respectively. The prevalence of smoking in subjects with COPD was 97.7%. The prevalence of COPD for passive smokers and those with occupational and biomass exposures were 2.3%, 34.8%, and 23.3%, respectively. The prevalence of small airway obstruction was 43.4%. Smoking is the most significant risk factor for both males and females. Other risk factors are passive smoking, biomass exposure, and occupational exposure. Most of the subjects (41.9%) with COPD had severe disease in terms of the GOLD criteria. Preventive measures should be taken for this prevalent public health problem.

Human Rights Statement: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

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Competing interests

The authors declare that they have no competing interests.

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Evaluation of effects of resveratrol on brain nitric oxide and energy metabolism in metabolic syndrome model

Metabolik sendrom modelinde resveratrolün beyin dokusu nitrik oksit ve enerji metabolizması üzerine etkilerinin değerlendirilmesi

Resveratrol and metabolic syndrome

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Öz

Amaç: Yüksek fruktoz diyeti, beyni nörodejenerasyona ve fonksiyon bozukluğuna duyarlı hale getiren nitrozatif strese yol açmaktadır. Bu çalışmada, fruktozla beslenen sıçanlarda metabolik sendromun (MetS) beyin dokususunda nitrozatif stres ve enerji dengesi üzerindeki etkisinin incelenmesi ve resveratrol uygulamasının muhtemel koruyucu etkilerinin belirlenmesi amaçlanmıştır. Gereç ve Yöntem: Yetişkin erkek Sprague-Dawley sıçanlar kontrol, fruktoz, resveratrol ve fruktoz+resveratrol olmak üzere 4 gruba ayrılmıştır (n=8). MetS %20'lik fruktozun içme suyu içinde verilmesiyle oluşturulmuş, resveratrol uygulaması ise günlük 10 mg/kg dozda oral gavaj yoluyla yapılmıştır. Sistolik kan basınçları (SKB) ölçülmüştür. 8 hafta sonunda, serum trigliserit, glukoz, insülin düzeyleri ile beyin dokusu ATP/ADP oranı, nitrik oksit (NOx) ve 3-nitrotirozin (3-NT) seviyeleri belirlenmiştir. Ayrıca, dokulardaki endotelyal ve indüklenebilir nitrik oksit sentaz (eNOS ve iNOS) protein düzeyleri western blotlama tekniği ile belirlenmiştir. Bulgular: Fuktoz uygulaması, kontrol grubuna göre SKB, serum trigliserit, insülin seviyelerini anlamlı şekilde artırmış ve insülin direncine neden olmuştur. Kontrol grubuyla karşılaştırıldığında, fruktoz doku ATP/ADP oranı ile 3-NT ve NOx düzeylerinde belirgin değişikliğe yol açmamıştır. Resveratrol uygulaması 3-NT ve NOx seviyelerini etkilemezken; resveratrol ve fruktoz+resveratrol gruplarında ATP/ADP oranlarında anlamlı azalmaya neden olmuştur. eNOS ve iNOS proteinleri hiçbir grupta saptanamamıştır. Tartışma: Bulgularımız 8 haftalık yüksek fruktoz diyetinin beyin dokusunda NO üretimi, enerji metabolizması ve protein nitrasyonu üzerinde etkili olmadığını göstermiştir. Tek başına ya da fruktozla birlikte uygulanan resveratrol ise bu dozda pro-oksidan olarak etki etmiştir.

Anahtar Kelimeler

Fruktoz; Resveratrol; ATP; Beyin

Abstract

Aim: A high fructose diet promotes nitrosative stress that makes the brain susceptible to dysfunction and neurodegeneration. The aim of this study was to examine the possible resveratrol effects on brain nitrosative stress and energy balance in the fructose-mediated metabolic syndrome (MetS) model. Material and Method: Adult male Sprague-Dawley rats were separated into four groups (n=8 in each group): control, fructose, resveratrol and fructose plus resveratrol. MetS was induced by fructose solution 20% in tap water, and resveratrol was applied at the dose of 10mg/kg daily by oral gavage. Systolic blood pressures (SBP) were measured by the tail-cuff method. After the experimental period of eight weeks, serum triglycerides, glucose, insulin and total brain tissue ATP/ADP ratio, nitric oxide (NOx) and 3-nitrotyrosine (3-NT) levels were measured. Also tissue endothelial and inducible nitric oxide synthase (eNOS and iNOS) protein levels were determined by western blotting. Results: Fructose increased SBP, serum triglycerides, insulin levels and induced insulin resistance significantly compared to the control group. In comparison with control group, fructose did not cause significant differences in tissue ATP/ADP ratio, 3-NT and NOx levels. While resveratrol had no effect on NOx and 3-NT levels, it caused a decrease in the ATP/ADP ratio in both the resveratrol and resveratrol plus fructose groups. iNOS and eNOS proteins were not detected in any of the groups. Discussion: These results indicate that a high fructose diet for eight weeks did not influence NO production, energy metabolism or protein nitration in rat brain tissues. Nevertheless resveratrol acted as a pro-oxidant at that dose when administered with fructose and alone.

Keywords

Fructose; Resveratrol; ATP; Brain

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Introduction

Metabolic syndrome (MetS) diagnosis implies positive results for at least three metabolic alterations including insulin resistance, hypertension, endothelial dysfunction, hyperinsulinemia and dyslipidemia [1]. It has been reported that high-dietary fructose consumption leads to an increased insulin resistance index, increased insulin and triglyceride levels, and hypertension, which characterize MetS [2]. The involvement of the brain in the pathogenesis of MetS is related to neurochemical changes [3]. However, little is known about the effects of fructose on brain tissue. Some early studies have suggested that fructose can not penetrate the blood-brain barrier in significant amounts. By contrast, accumulating evidence indicates that neuronal cells are able to metabolize fructose, and fructose intake has been shown to disturb the plasma membrane of rat neurons, impairing neuronal function [4]. In addition, it was found that long-term fructose -drinking leads to insulin resistance, impaired insulin signaling, oxidative stress, neuroinflammation, and cognitive impairment [5]. An inflammatory state in the brain regulatory centers, such as the hypothalamus, disrupts its metabolic function and the neuronal and neuroendocrine regulation of a number of physiological processes, such as energy balance, glucose metabolism, and insulin resistance [3,6].

Sustaining the redox homeostasis is essential for the survival of brain cells due to their high metabolic energy requirement to maintain electrochemical gradients, neurotransmitter release, and membrane stability. Brain antioxidant levels are restricted compared to other organs and less able to compensate for reactive and nitrogen species (RONS) generation [7]. Recent studies have indicated the hypothesis that nitric oxide (NO) is a mediator of neuronal injury. It can diffuse freely out of the neurons producing it, reacting with superoxide ($O_2^{\bullet-}$) to form peroxynitrite, its important diagnostic marker, for 3-nitrotyrosine (3-NT), and trigger cell death in the surrounding neurons of the cerebral cortex, cerebellum, and hippocampus [7,8].

Resveratrol (3,4,5-trihydroxystilbene) is present in high concentration in the skin and seeds of grapes. It has several biological effects, including a potent antioxidative effect, antiplatelet, estrogenic, and anti-inflammatory activity [9,10]. Preliminary time-course and dose-response data have revealed that daily administration of various doses of resveratrol to healthy animals for up to seven days is safe and even neuroprotective [11]. Although its mechanism of action is not completely clear, this compound has a strong antioxidant/scavenger activity that protects brain tissues against ischemic damage by interfering with mitochondrial homeostasis [12]. Little is known about the precise effect of resveratrol on the fructose-induced MetS model in brain tissue depending on the nitrosative stress and ATP production. The aim of this study was to examine possible resveratrol effects on brain 3-nitrotyosine (3-NT), nitric oxide (NOx) levels as nitrosative stress markers, and ATP/ADP ratio for energy balance in fructose-fed rats.

Material and Method

Chemicals

Trans-resveratrol (≥99%) was purchased from Cayman Chemical (Spi-Bio, Montigny le Bretonneux, France). D-Fructose (≥99%) was purchased from Sigma-Aldrich (St. Louis MO, USA). Primary and secondary antibodies for western blotting were purchased from Cell Signaling Technology (Danvers, MA, USA).

Animals and Experimental Design

This study was conducted in accordance with the regulations of the Animal Experimentation Ethics Committee of Gazi University (G.Ü.ET-10.037). Thirty-two adult male Sprague-Dawley rats weighing 225±10 g were housed at 20-24°C with a 12-h light/12-h dark cycle and provided with standard rat chow and tap water that was freely available.

Rats were randomly divided into four groups (n=8 in each group) as follows:

1. Control Group: Rats fed a standard rodent diet and tap water.
2. Fructose Group: Rats fed a standard rodent diet and tap water supplemented with 20% fructose [13].
3. Resveratrol Group: Rats fed a standard rodent diet and tap water, and resveratrol administered at the dose of 10 mg/kg body weight in 0.1% ethanol solution per day by oral gavage [14]. Resveratrol solution was prepared freshly every day.
4. Fructose plus Resveratrol Group: Rats fed a standard rodent diet and tap water supplemented with 20% fructose, and resveratrol administered at the dose of 10 mg/kg body weight in 0.1% ethanol solution per day by oral gavage.

Since ethanol was used as the vehicle for resveratrol, the control and fructose groups received 0.1% ethanol solution proportionately with body weight. The experiment was carried out for 8 weeks, at which time, the animals were sacrificed under ketamine (30 mg/kg bw) and xylazine (6 mg/kg bw) anesthesia. Blood samples and brain tissues were taken.

Measurement of Systolic Blood Pressure and Serum Analysis

Systolic blood pressures (SBP) were measured by the tail-cuff method at the beginning of the study, at the end of week 4, and at the end of week 8. Serum glucose and triglyceride levels were measured by enzymatic methods using autoanalyzers. Serum insulin level was estimated by using a commercially available ELISA kit (Millipore, MA, USA). Insulin resistance was determined by the Homeostasis Model Assessment index (HOMA-IR) using the formula: [insulin (mU/L) x glucose (mmol/L)]/22.5.

Measurement of Tissue Nitric Oxide (NOx) and Protein Levels

Tissue NOx (nitrite plus nitrate), which are known to be the end products of NO, was determined by using a commercially available colorimetric kit (Cayman Chemical, Spi-Bio, Montigny le Bretonneux, France). Tissue total protein concentration was evaluated by the BCA protein assay kit (Thermo Fisher Scientific, Rockford, IL, USA).

Measurement of Tyrosine Nitration (3-NT) and ATP-ADP Levels

For 3-NT analysis, total brain tissue homogenates were prepared according to the method described by Kamisaki et al. [15]. All samples were analyzed by HPLC with electrochemical detector (ECD) using the method described by Maruyama et al. [16]. Tissue ATP and ADP levels were measured by HPLC diode array detector, using the method described by Szabo et al. [17].

Western Blotting Assay for eNOS and iNOS

Total brain tissues were homogenized with ice cold RIPA buffer. Immunochemical analyses were performed wherein 20 µg protein of brain samples were separated with SDS-PAGE. The separated proteins were then transferred from the gels onto a PVDF membrane, and then blocked. The membranes were incubated with the primary antibodies against either rat eNOS (1:1000) or rat iNOS (1:1000). Then, the membranes were incubated with the appropriate HRP-conjugated secondary antibody (anti-rabbit (1:5000)). iNOS electrophoresis standard and rat aorta tissue were used as positive controls for iNOS and eNOS respectively.

Statistical Analysis

The statistical analyses of the results were calculated using a computerized statistical package (SPSS 16.0 for Windows, Chicago, IL, USA). Each mean value was compared by one-way analysis of variance (ANOVA) and Tukey for multiple comparisons. All statistical tests were two-tailed, and $p<0.05$ was considered statistically significant.

Results

SBP and Serum Parameters

In comparison with the control group, fructose administration caused a significant increase in SBP, serum triglycerides, insulin levels and HOMA-IR (Table 1).

Tissue NOx, eNOS and iNOS Protein Levels

NOx levels did not change significantly among groups (Table 2). In the fructose plus resveratrol group, NOx was higher than in the other groups, but not at a statistically significant level. iNOS and eNOS proteins were not detected in any groups (Figure 1).

Tissue 3-Nitrotyrosine, ATP and ADP Levels

Fructose or resveratrol administration did not cause significant changes in 3-NT levels compared to the control group (Table 2). In the fructose plus resveratrol group, 3-NT levels significantly increased compared to both the fructose and resveratrol groups ($p<0.05$). A significant difference between ATP/ADP ratios of control and fructose groups was not found (Table 3). ATP/ADP ratios were diminished in both the resveratrol and fructose plus resveratrol groups compared with other groups ($p<0.05$). Moreover, the lowest ATP/ADP ratio was observed in the fructose plus resveratrol group.

Table 1. SBP and serum values related to MetS at 8 weeks

	SBP (mmHg)	Triglycerides (mg/dl)	Glucose (mmol/L)	Insulin (mU/L)	HOMA-IR
Control	125.3±1.29	36.00±8.07	12.299±2.19	4.79±1.80	2.67±1.11
Fructose	160.1±1.40[a]	93.75±15.85[a]	13.195±1.54	28.21±6.02[a]	16.71±4.89[a]
Resveratrol	124.3±1.10[b]	55.12±7.49[a,b]	14.236±1.725	8.403±1.238[a,b]	5.342±1.172[a,b]
Fr+Rsv	127.3±2.27[b]	143.62±27.68[a,b,c]	11.294±2.338[c]	34.266±7.334[a,c]	17.021±4.481[a,c]

ap<0.05, compared to control group
bp<0.05, compared to fructose group
cp<0.05, compared to resveratrol group

Table 2. Tissue NOx and 3-NT levels

	NOx (mmol/g tissue)	3-NT (nmol/mg protein)
Control	1.344±0.266	43.136±3.992
Fructose	1.264±0.228	38.905±4.391
Resveratrol	1.262±0.181	38.381±4.258
Fructose+Resveratrol	1.421±0.236	49.173±7.404[b,c]

bp<0.05, compared to fructose group
cp<0.05, compared to resveratrol group

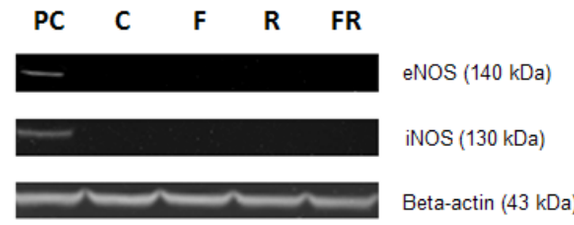


Figure 1. Tissue eNOS and iNOS protein levels
(PC: Positive control, C: Control, F: Fructose, R: Resveratrol, FR: Fructose+Resveratrol)

Table 3. Tissue ATP, ADP levels and ATP/ADP ratio

	ATP (µmol/g tissue)	ADP (µmol/g tissue)	ATP/ADP
Control	0.026±0.003	0.119±0.028	0.228±0.039
Fructose	0.027±0.005	0.120±0.010	0.226±0.037
Resveratrol	0.013±0.001[a,b]	0.094±0.018	0.146±0.025[a,b]
Fructose+Resveratrol	0.013±0.001[a,b]	0.127±0.013	0.103±0.013[a,b,c]

ap<0.05, compared to control group
bp<0.05, compared to fructose group
cp<0.05, compared to resveratrol group

Discussion

Nowadays, it is known that one of the main reasons of increasing incidence of MetS is dietary high fructose consumption. Fructose encourages insulin resistance, glucose intolerance, hypertriglyceridemia, and hypertension in animal models [3]. In our study, we used male Sprague-Dawley rats and fructose administration was accomplished by giving daily prepared 20% D-gructose in tap water for eight weeks. At the end of the study, fructose intake induced the MetS criteria of hypertension, hyperinsulinemia, insulin resistance, and hypertriglyceridemia compared with the control group. Thus, the MetS model was succesfully demonstrated (Table 1).

Data from animal studies show that diet with higher fructose content result in rapid insulin resistance, compensatory hyperinsulinemia and brain abnormalities [18]. It was found that long-term fructose -drinking causes impaired insulin signaling, oxidative stress, neuroinflammation and cognitive impairment in the brain [18-20]. Oxidative/nitrosative stress is reported as one of the earliest events in the pathogenesis of neurodegenerative diseases. Recent studies have supported the hypothesis that nitric oxide (NO) production by neuronal nitric oxide sythase (nNOS) activity is a crucial step

in the pathophysiology of cell death in the brain. NO is a free radical that has several important biological functions. It acts as a vasodilatator and neurotransmitter; in addition, it reacts with O2•- to form peroxynitrite and induce cell death in neurons of the cerebral cortex, hippocampus, and cerebellum [8,21]. Endogenous formation of NO by glutamate receptor activation in cortical neurons leads to rapid and reversible inhibition of mitochondrial ATP synthesis. It has been reported that persistent exposure of mitochondria to NO causes peroxynitrite generation which in turn damages complex-I by nitration of essential tyrosine residue, of which the diagnostic marker, 3-NT [22]. Similarly, diet-induced metabolic disturbances are associated with insufficient formation of ATP, leading to neuropathology [23].

In the present study, brain tissue eNOS and iNOS proteins were analyzed; no detectable level was measured by western blotting in any groups. Fructose drinking for 8 -weeks did not induce the formation of iNOS. Neither was eNOS formation in total brain tissue demonstrated. Our results were consistent with a previous study that NO, formed by nNOS, has a major signaling function in the central and peripheral nervous systems. And nNOs has been thought to account for 95% or more of all NOS catalytic activity in the brain [24].

In our study, as a result of fructose feeding, neither NOx nor 3-NT levels changed significantly, but the systemic symptoms of MetS were induced. Fructose did not effect our parameters, and it did not cause nitrosative stress in the brain. Our results were also consistent with the data from the evaluation of the effect of fructose on oxidative/nitrosative stress of brain carried out by Lopes et al. [4]. They observed NOx levels were not altered during 8-week fructose diet, which may not be sufficient to cause oxidative/nitrosative stress in total brain tissues. In addition, fructose administration did not cause alteration in the ATP/ADP ratio compared with the control group in our study. It is known that high fructose consumption causes cellular ATP depletion, and this situation leads to production of inflammatory proteins, endothelial dysfunction, and oxidative stress [25,26]. In the present study, after feeding fructose, free radical-mediated damage and ATP depletion were not observed. This may be related to the dose and duration of the applied fructose, and the use of total brain tissue may also have been a contributing factor. In recent studies, the hippocampus region of the brain has been shown to be particularly sensitive to high calorie diet such as fructose feeding [27].

To date, resveratrol has been used as a beneficial molecule in clinical and experimental studies. It is accepted to be effective on neurological disorders by attenuating oxidative/nitrosative stress. The beneficial effects are believed to be due to its antioxidative properties [28]. Resveratrol diminishes oxidative stress by directly scavenging free radicals and indirectly increasing endogenous cellular antioxidant defences [29,30]. Further studies suggest that oral 8-week resveratrol administration reduces oxidative DNA damage and also regulates NO levels and eNOS activity, down regulating iNOS activity in rat brains [31]. A previous study has reported that high doses of resveratrol block the insulin signaling, thereby reducing glucose uptake [32]. This compound is able to pass the blood-brain barrier. It exerts neuroprotective effects, upregulates antioxidant enzyme, and is an anti-inflammatory agent [33].

Another important aim of this study was to investigate the effect of resveratrol on NOx, 3-NT levels and ATP/ADP ratio in total brain tissue in the fructose-mediated MetS model. In the present study, resveratrol had no effect on either NOx or 3-NT levels. But when administrated with fructose, in contrast with its previously-observed protective effects, resveratrol increased 3-NT levels, leading to nitrosative stress in the brain. It is unclear how resveratrol increased nitrosative stress in the fructose plus resveratrol group and there has been no report on the cytotoxic property of resveratrol when administrated with fructose. This study may be the first report. Every antioxidant is in fact a redox (reduction–oxidation) agent and thus might become a pro-oxidant to accelerate lipid peroxidation and/or induce DNA damage under special conditions [34]. Resveratrol is known for its antioxidant properties; however, this compound has been proposed to have cytotoxic and pro-oxidant effects depending on its concentration, time of exposure, and cell type [35]. Ahmad et al. reported that resveratrol elicited pro-oxidant properties as evidenced by an increase in intracellular O2•- concentrations in leukemia cells [36]. The pro-oxidant effects of resveratrol were shown on rat liver microsomal systems, and resveratrol increased hydroxyl radical generation [37]. Similarly, Fotiou et al. observed that resveratrol lead to an up-regulation of synaptosomal NO synthase in the rabbit brain, and released NO was converted to peroxynitrite with free oxygen radicals [38]. In our study, when fructose is administered along with resveratrol, it may a effect resveratrol's oxidation/reduction status and thus lead to excess RONS formation, which in turn increases 3-NT levels.

In our study, the ATP/ADP ratio decreased significantly in both the resveratrol and fructose plus resveratrol groups. Mitochondria are a key target of resveratrol and it modulates the mitochondrial respiratory chain function. Complex-I is an important enzyme of respiratory chains and plays a crucial role maintaining mitochondrial homeostasis, not only though its role in ATP production but also in ROS formation. It has been reported that resveratrol binds to the complex-I nucleotide side, which either stimulates or inhibits its activity, according to the resveratrol concentration. At low doses, resveratrol may act as an antioxidant, stimulating the cellular proliferation and the antioxidant response, while at higher concentrations, it may become a pro-oxidant molecule, including cellular damage and decreasing ATP production in the brain [39]. In the present study, decreases in ATP/ADP ratio in both the resveratrol and fructose plus resveratrol groups may be related to resveratrol's dose and its antagonistic effect with fructose.

Our results indicate that fructose consumption at the administered dose and duration did not influence NO production, protein nitration, or ATP/ADP ratio in brain tissue. Resveratrol both alone and together with fructose caused ATP depletion and increased 3-NT levels in brain tissue, thus playing a pro-oxidant role in our experimental conditions. Further experimental studies (e.g., different resveratrol' doses, nNOS analysis and/or investigation of distinct brain areas particularly) are needed to clarify the underlying mechanism of resveratrol on disturbances of these parameters in fructose-fed rats.

Ethical Responsibilities

All institutional and national guidelines for the care and use of laboratory animals were followed.

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Competing Interests

The authors declare that they have no competing interests.

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The effect of locally administered organic silicon on calvarial bone defects

Lokal olarak uygulanan organik silikonun kalvaryal kemik defektleri üzerindeki etkisi

Effect of organic silicon on bone formation

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Öz

Amaç: Bu çalışmanın amacı lokal olarak uygulanan organik silikonun otojen kemik grefti uygulanan kritik boyuttaki kalvaryal kemik defekti üzerine etkisini incelemek. Gereç ve Yöntem: 24 adet rat Grup C (pasif kontrol), Grup Au ve Grup Si olmak üzere üç gruba ayrıldı. Hayvanlar kafatasında 5 mm çapında kritik boyutta defektler oluşturuldu. Grup C'de defekt bölgesine steril salin solüsyonu emdirilmiş absorbe olabilen kollajen tampon yerleştirildi. Grup Au'da, steril salin emdirilmiş absorbe olabilen kollajen tampon, otojen greft yerleştirilen defekt alanına uygulandı. Group Si'de, 500 mg organik silikon emdirilmiş absorbe olabilen kollajen tampon otojen greft uygulanan defekt alanına yerleştirildi. Bütün denekler işlemden 28 sonra ötenazi yoluyla sakrifiye edildi. Stereolojik analiz işlemi uygulandı ve yeni kemik oluşumu ve bağ doku hacim ölçümü yapıldı. Bulgular: Stereolojik sonuca göre, Grup Si'de ortalama yeni kemik hacmi 1.79 ± 0.48 mm3 bulundu ve diğer gruplar arasındaki farkın istatistiksel olarak anlamlı olduğu tespit edildi ($p \leq 0.05$). Grup Au ve C 'deki ortalama yeni oluşan kemilkhacmi ise sırasıyla, 1.50 ± 0.51 mm3 and 1.04 ± 0.03 mm3 bulundu. Bağ dokusu hacmi, grup Au'da daha yüksek olmasına rağmen grup Si ile aralarında anlamlı bir fark bulunamadı. Tartışma: Lokal olarak uygulanan organik silikonun otojen greft uygulanmış kritik boyuttaki kalvaryal defektlerde kemik rejenerasyonunu arttırdığı ortaya konulmuştur.

Anahtar Kelimeler

Silikon; Kemik Oluşumu; Kalvarya

Abstract

Aim: The purpose of this study was to investigate the potential of the local administration of organic silicon on autogenous grafted critical-sized cortical bone defects. Material and Method: Twenty-four rats were divided into three groups: group C (passive control), group Au, and group Si. A 5-mm diameter critical-size defect was created in the calvarium of each rat. In group C, only a sterile saline-treated absorbable collagen sponge was applied to the defect area. In group Au, autogenous graft was performed and sterile saline-treated absorbable collagen sponge was applied on the autografted defect area. In group Si, autogenous graft was performed and a 500 mg silicon-treated absorbable collagen sponge was applied to the autografted defect area. All animals were euthanized at 28 days postoperative. Stereologic analyses were performed. New bone area and connective tissue volumes were measured. Results: Stereologic analysis showed that the difference between group Si with a mean bone formation of 1.79 ± 0.48 mm3 and groups Au and C was statistically significant ($p \leq 0.05$), the latter having mean bone formations of 1.50 ± 0.51 mm3 and 1.04 ± 0.03 mm3 respectively ($p \leq 0.05$). Connective tissue volume was larger in group Au than in group Si, but the difference was not statistically significant. Discussion: Locally administered organic silicon enhances bone regeneration in critical-size calvarial rat defects filled with autogenous graft.

Keywords

Silicon; Bone Formation; Rat

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Introduction

Surgical procedures involving bone play an important role in oral and maxillofacial surgery. Various sized bone defects may occur after cysts or tumour excision or orthognathic surgery. Some bone defects can be repaired by the body, but in cases of large defects, physiological regenerative capability may be exceeded [1]. The type of bone defects that will not heal spontaneously during the lifetime are called critical-sized bone defects. Critical-sized bone defects need extra surgery such as a grafting procedure [2]. Today, autogenous graft is regarded as the gold standard. In extensive large defects, different materials can be used to hasten bone formation by stimulating surrounding tissues and making a positive contribution to the graft materials [3].

Bone is the most important structure of the human skeletal system and also plays a role as a connective tissue to support other organs of this system. It consists of cells, intracellular material, and extracellular matrix. Osteoblasts are responsible for matrix formation, ossification, and bone damage repair. Bone extracellular matrix involves minerals, collagens, water, non-collagen proteins, and other organic materials [4]. 70% of organic matrix is formed by collagens. Type I collagen is the most common type. In healthy bones, the rate of Type I collagen is 95%. Type I collagens join to form different tissues, such as bone, dentine, tendon, skin, and cartilage; they are synthesized by fibroblasts, osteoblasts, odontoblasts, and chondroblasts [5]. Basically, bone repair is a kind of connective tissue healing. The steps of the healing process for bone formation are similar to those for soft tissue, except that for soft tissue, osteoblasts and osteoclasts are responsible for the reconstruction and the remodeling of ossifying tissue [6].

Silicon (Si) is one of the most abundant minerals in nature. It can be found in drinking water and some phytonutrients. Silicon participates in the structure of different organs, such as bone, nails, hair, and skin [7]. In the literature, studies have shown the effect of silicon on different bone mechanisms, such as biocalcification [8], osteoblast activity and bone mineralization [9], and bone mineral density [10]. Reffitt et al. [11] reported that Si enhances osteoblastic differentiation and stimulates Type I collagen synthesis.

The aim of this study was to investigate the potential of the local administration of organic silicon on autogenous grafted critical-sized calvarial defects in rats.

Material and Method

The 6- to 8-week-old Wistar rats (n = 24) used in this study were housed in standard cages in rooms with a relative humidity of 40–60% and a temperature of 22 ± 1°C. The illumination system of the room was configured to automatically provide 12 h of light and 12 h of darkness. This study was approved by the Animal Experimentation Committee of Bülent Ecevit University, Zonguldak, Turkey.

Surgical procedure

All surgical procedures were performed under sterile conditions in the surgical suite of an animal laboratory. Each rat was anesthetized by intramuscular injection of 3 mg xylazine hydrochloride/kg (Rompuns; Bayer, Leverkusen, Germany) and 35 mg ketamine hydrochloride/kg (10% [w/v] Ketasol; Richter Pharma AG, Wels, Austria). After anesthesia, the right side of the mandible was shaved and sterilized using conventional methods, and articaine (in a 1:200,000 weight ratio with epinephrine; Ultracain-DS, Hoechst Marion Roussel, Istanbul, Turkey) was injected for hemostatic purposes. Under general anesthesia, the rat calvarium was shaved and the cutaneous surface was disinfected with povidone iodine solution. A semilunar incision was then made and a full-thickness flap was reflected, exposing the parietal and frontal bones. A 5-mm-diameter (critical size) calvarial defect was made with a trephine used in a low-speed hand-piece under continuous sterile saline irrigation. The defect included a portion of the sagittal suture. Care was taken during the surgery to avoid damage to the dura mater. In two groups, defects were filled by autogenous graft. The flap was closed using a reverse-cutting 4/0 needle and undyed, Polyglactin 910, braided absorbable sutures; the skin was closed using 3/0 silk sutures. As prophylaxis against postoperative infection, 10 mg/kg cefazolin sodium (Sefazol; M Nevzat, Istanbul, Turkey) was injected daily for 5 days.

Autogenous bone grafts were harvested from the left tibia of the rats. The medial surface of the left legs of the subjects were shaved and the area was disinfected with povidone iodine solution. The legs were given the flexion position and longitudinal incisions of 20-25 mm were made periosteally in order to reach the medial surfaces of the tibia. The medial surfaces of the tibia were exposed with blunt dissection and soft tissues were excluded. Autogenous bone graft, covering the cortex and medula layers of the bone, was obtained by using a round-tipped, stainless steel drill with a diameter of 3 mm under sterile saline solution.

Experimental groups

After surgery, the rats were divided into three groups of eight and treated as follows:

Group C: Only a sterile saline-treated absorbable collagen sponge (ACS) was applied to the defect area.

Group Au: A sterile saline-treated ACS was applied on the autografted defect area.

Group Si: A 500 mg silicon-treated ACS was applied to the autografted defect area.

The animals were euthanized by lethal anesthetic injection 28 days after surgery. The skin was dissected, and the calvaria of the animals were removed and immediately immersed in 10% (v/v) buffered formaldehyde.

Tissue processing and stereological methods

Our routine histological procedures featured sample fixation in 10% (v/v) formalin for 10 days and decalcification with 5% formic acid for 21 days; the samples were then gradually dehydrated in ethanol (70, 80, 96, and 100%), placed in xylene for clearing, and paraffin-embedded. The tissue blocks were sectioned at 5 µm thickness using a microtome (Leica RM2255, Germany) and stained with hematoxylin-eosin.

Between 16 and 25 slides from each rat were stereologically analyzed. The first section was randomly chosen, followed by every tenth slide (this was, thus, a systematic random sampling strategy). The sections were photographed under a light microscope fitted with a camera at x10 magnification (Zeiss Primostar, Germany), and the Cavalieri method was used to calculate

the volumes of connective tissue and newly formed bone. The dimensions of the point-counting test grid were 80 μM x 80 μM. The Cavalieri method (an unbiased stereological technique) was used to estimate the following parameters: the volume of newly formed bone (Vnb) and the volume of connective tissue (Vct).. We used a point-counting grid for area estimations. The Vnb and Vct were estimated using the following formula:

Volume (V) = t × a/p × ∑p,

where V is the mean volume of the calvaria, t is the mean section thickness, a/p is the inter-point area, and ΣP is the total number of points on entire serial sections of the calvaria. The coefficient of error (CE) and the coefficient of variation (CV) for volume estimations of connective tissue and newly formed bone were confirmed to be within appropriate ranges. We counted the number of points in each segmental compartment. These point counts were used to estimate the volume of each compartment using the following formula:

Volume= t × a/p × P, where t is the section thickness, a/p is the area of each point on the point-counting grid, and P the total number of points touching the surface areas of the sections [12].

Statistical analysis

The Shapiro–Wilk test was used to confirm the normal distribution of the data. The μCT and stereological parameters were analyzed using the Kruskal–Wallis nonparametric test, followed by post-hoc group comparisons with the Bonferroni-adjusted Mann–Whitney U test, after a failed normality test of the data. For the Bonferroni correction, α = 0.05 / 3 = 0.016 was considered to indicate statistical significance. All tests were performed using statistical software (SPSS version 19.0; SPSS Inc., Chicago, IL, USA). P < 0.05 was considered to indicate statistical significance.

Results

All animals tolerated the surgery well and survived the post-surgical period. No wound dehiscence, wound infection, or abscess formation was observed at any surgical site.

Histological evaluation

New bone formation were observed in all groups. In group C, new bone formation was only at defect margins and a thin layer of connective tissue was lying between defect borders. In groups Au and Si, new bone formation was around graft particles and also near the defect margins. In both groups, connective tissue also was between graft particles (Fig-1).

Stereological analyses

In group Si, mean connective tissue volume was 1.56 ± 0.07 mm3, whereas mean values in the Au and C groups were 1.61 ± 0.07 mm3 and 0.89 ± 0.05 mm3, respectively (Fig 2). The differences between group C and the other two groups were statistically significant (p ≤ 0.05). Connective tissue volume was larger in group Au than in group Si, but the difference was not statistically significant.

Mean new bone volume in group Si was 1.79 ± 0.48 mm3, whereas mean volumes in the Au and C groups were 1.50 ± 0.51 mm3 and 1.04 ± 0.03 mm3, were statistically significant (p ≤ 0.05). Also new bone formation in group Si was superior to that in group Au and the difference was statistically significant (p ≤ 0.05) (Fig 3).

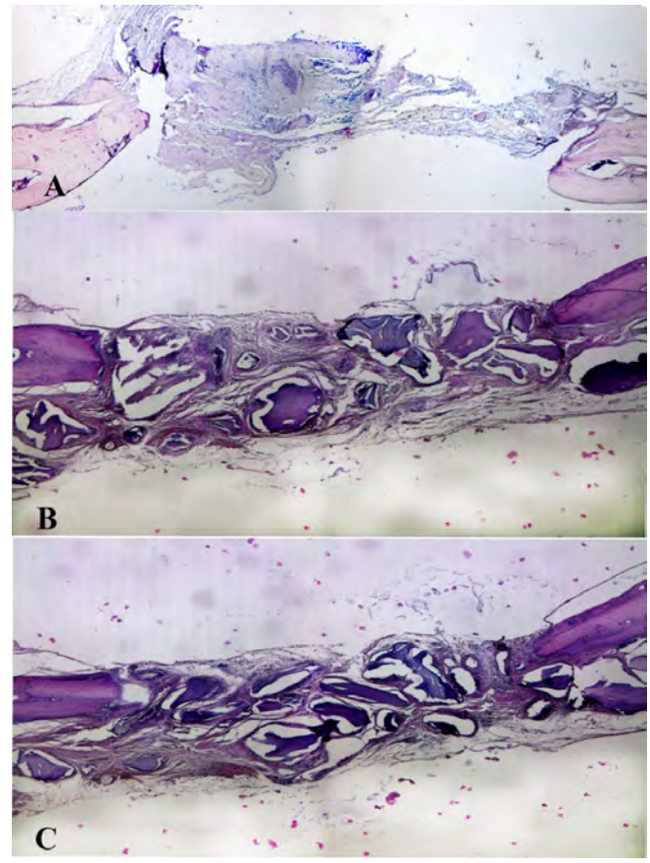


Figure 1. Panoramic views of the defects. (A) Group C; (B) Group Au; (C) Group Si.

Discussion

Silicon is one of the most common elements in nature, also taking part in the structure of many organs. We hypothesized that silicon may increase new bone formation with autogenous graft in rats. To test the hypothesis, 5 mm diameter critical-sized calvarial defects were created in rats; defects were filled by autogenous graft in the non-control groups, and local organic silicon was administered in the organic silicon group. New bone formation and connective tissue volumes were analyzed by stereologic methods.

In our study, rats were used as an experimental animal model. Rats have similar physiological properties as humans and are one of the most common animals used as models for bone formation. Rats are easy to care for and are not expensive [13]. In the literature, there are different calvarial critical defect sizes in rats; diameters can range between 4 and 8 mm. We used 5 mm calvarial defects as a critical-sized defect in our study. There was no defect healing between defect margines in the control group, consistent with the literature [14].

Silicon is one of the most essential elements for the human body. It plays an important role in the skeletal system. Different studies have investigated effects of silicon on bone metabolism and different components of bone. Kim et al. [9] examined the effect of Si on bone mineralization and osteoblast activity at the cellular level. Mature osteoblasts were treated by different doses of Si. They reported that Si affected bone metabolism positively by increasing osteoblast mineralization. Bu et al. [15] investigated the effect of two different doses of silicon on bone

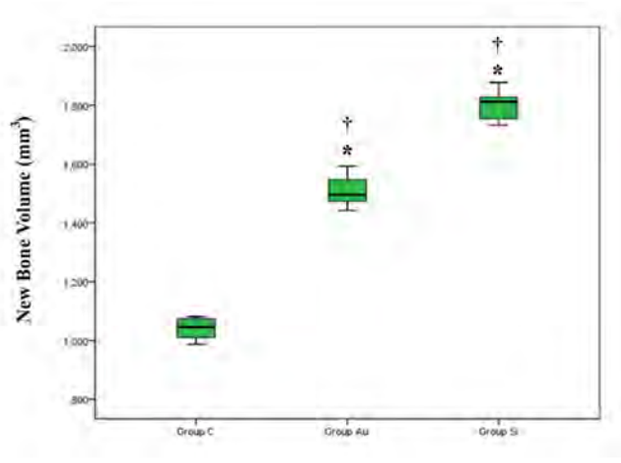


Figure 2. The connective tissue volume (mm^3) from stereological analysis in defects

* Statistically significant difference among groups (Bonferroni-adjusted Mann–Whitney U test)

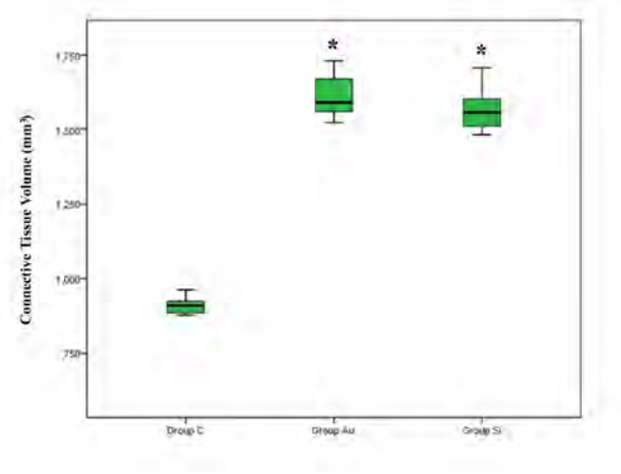


Figure 3. The new bone volume (mm^3) from stereological analysis in defects

* Statistically significant difference among groups (Bonferroni-adjusted Mann–Whitney U test)

metabolism and inflammatory mediators in ovariectomized rats. They stated that silicon did not increase bone mineral density but decreased bone resorption by inhibiting expression of bone resorptive mediators. In another study, the effect of silicon was examined on Type I collagen synthesis in human osteosarcoma cells and primary osteoblast-like cells. According to the study, silicon stimulated Type I collagen synthesis and osteoblastic differentiation [11]. Gereli et al. [16] investigated the effect of locally injected silicon on Achilles tendon healing. Biomechanics, histological, and immunohistochemical analyses were made. They found that silicon injection increased fibroblastic growth factor level and enhanced tendon healing. Although there have been studies about the effect of silicon on various bone mechanism and metabolism, to our knowledge there is no study about the effects of organic silicon on defect treatment. We investigated the effect of local administered organic silicon on bone formation in critical-sized defects. Consistent with the literature, we found that silicon had a positive effect on defect treatment and increased new bone formation.

In our study, new bone formation and connective tissue volume measures were made by stereological analyses. In stereological methods, sections are analyzed in 3D space so it shows more results that are more reliable than in conventional histological analyses [17]. Based on stereological analyses, silicon had a positive effect on bone formation compare to the other groups. Group Au had higher connective tissue volume than group Si, but the difference was not significant.

In conclusion, according to our histological and stereological findings, this experimental study showed that organic silicon could have positive effects on autogenous graft compared with control and autogenous groups. Further studies are needed for establishing the optimal dose to maximize the anabolic actions and to minimize the side effects of organic silicon on bone.

Ethical Responsibilities

All institutional and national guidelines for the care and use of laboratory animals were followed.

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Competing interests

The authors declare that they have no competing interests.

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Decreased density of interstitial cajal-like cells correlate with cholelithiasis in children

Çocuklardaki kolelitiazisin interstisyel cajal-benzeri hücre yoğunluğunun azalması ile ilişkisi

Interstitial cajal-like cells

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Öz

Amaç: Çocuklardaki kolelitiazis örneklerindeki (interstisyel Cajal-benzeri hücre) ICLC yoğunluğun analiz edilmesi ve kontrol örneklerle karşılaştırılması amaçlanmıştır. Gereç ve Yöntem: Kolelitiazisli 20 ve kolesistitli 15 hastadan laparoskopik olarak safra keseleri rezekte edilmiştir. Doku örnekleri rutin histolojik inceleme için işlenmiş, ek olarak tüm kesitler immünohistokimyasal olarak CD117 ve Mast hücre triptaz antikorları ile boyanmıştır. Bulgular: Örnekler ICLC yoğunlukları açısından karşılaştırılmış ve kolelitiazisli grupta ortalama 23.30, kontrol grubunda ise 39.07 olarak saptanmıştır. ICLC ortalama sayılarındaki bu fark istatistiksel olarak anlamlı bulunmuştur (p=0.044). Tartışma: Safra taşı olan çocukların muskularis propriadaki (interstisyel Cajal hücresi) ICC veya ICLC yoğunlukları, safra taşı olmayan kontrol grubu çocukların örneklerine göre önemli ölçüde düşük bulunmuştur. Düz kas kontraksiyonu ile ilişkili olan ICC ve ICLC sayıları safra kesesi motilitesini etkileyebileceği düşünülmektedir. Bu çalışmada gözlenen histopatolojik farklılıkların çocuklardaki kolelitizasinin patofizyolojisinin açıklanmasında yardımcı olabileceği sonucuna varılmıştır.

Anahtar Kelimeler

Safra Taşı; İnterstisyel Cajal-Benzeri Hücre; Mast Hücresi; CD117/c-Kit; Safra Kesesi Motilitesi

Abstract

Aim: The present study aimed to analyze numbers of (Interstitial Cajal-like cells) ICLCs found in cholelithiasis specimens and compare them with controls specimens of children. Material and Method: Gallbladders were resected laparoscopically from 20 patients with cholelithiasis and 15 patients with cholecystitis. Tissue samples were processed for routine histological examination. Additionally, all sections were immunohistochemically stained with CD117 and Mast Cell Tryptase antibodies. Results: When specimens were compared for the density of ICLCs, mean number for the control group was 39.07, whereas for the cholelithiasis group it was found to be 23.30. The difference of means of ICLCs in these groups was found to be statistically significant (p=0.044). Discussion: We found that the density of (Interstitial cells of Cajal) ICC or ICLCs in the muscularis propria was significantly lower in specimens from children with gallstone disease than in specimens derived from the gallstone-free, which served as controls. Gallbladder motility may be affected by the number of ICC or ICLCs which are in interaction with smooth muscle contraction. The histopathological differences observed in this study may help to elucidate the pathophysiology of cholelithiasis in children.

Keywords

Gallstones; Interstitial Cajal Like Cells; Mast Cells; CD117/c-Kit; Gallbladder Motility

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Introduction

Cholelithiasis is the most common gallbladder disorder. Among the causes of cholelithiasis gallbladder hypomotility, mucus hypersecretion, and bacterial infections might be considered.

Interstitial cells of Cajal (ICC) are found along the entire gastrointestinal tract and contribute to regulation of gut motility [2,3]. Interstitial Cajal-like cells (ICLCs) are believed to be involved in innervation and motility, and a decrease in their number and/or density has been linked to a variety of intestinal motility disorders of the gallbladder [4,5,6]. We investigated the distribution of the ICLCs in the gallbladder because of their potential role in contributing to gastroenteric motility which on the other hand is also assumed to be essential in gallstone formation. Since ICLCs are involved in inducing smooth muscle contraction, a decrease in the density of these cells in the muscular layer of the gallbladder could induce gallbladder hypomotility and possibly lead to gallstone formation [4]. In recent years, several studies have been published regarding the ICLCs, performed experimentally or in specimens obtained from adults. However, to our knowledge, there has been no study published yet investigating the relationship between density of ICLCs and gallstone disease in children. The present study aimed to analyze numbers of ICLCs found in cholelithiasis specimens and compare them with cholecystitis-only (gallstone-free controls) specimens of children.

Material and Method

Gallbladders were resected laparoscopically from 20 patients with cholelithiasis and 15 patients with cholecystitis. The diagnosis of cholecystitis and symptomatic gallstone disease was made when cases presented clinically with crampy right upper quadrant abdominal pain radiating to the upper back or right shoulder (biliary colic) and confirmed by ultrasonographical investigation. Seven patients underwent cystectomy due to gallstones related to a hemolytic disease. Three patients were thalassemia major. Four patients were hereditary spherocytosis. All 35 patients underwent laparoscopic cholecystectomy with no conversion to open procedure. Cholecystitis-only specimens served as controls.

Tissue samples were processed for routine histologic examination with standard formalin fixation and paraffin embedding, and 5 µm thin sections were stained with hematoxylin-eosin. In addition, all sections (fundus, body, and neck of the three gallbladders) were immunohistochemically stained for CD117 (c-kit Oncoprotein) and Mast Cell Tryptase (AA1, 1:100, Thermo Scientific, USA) as follows: 3µm thin sections were cut, dried, and deparaffinized before placing them on the Ventana Benchmark GX immunostainer (Ventana, Tucson, AZ). Diaminobenzidine was used as a chromogen.

The antibody panel included CD117 (T595, ready-to-use, Leica, Newcastle, United Kingdom). We used skin sample as positive controls for CD117 and reactive lymph node for Mast Cell Tryptase. For negative controls, the primary antibodies were omitted. ICLCs were counted per 10 consecutive high-power fields (original magnification ×400; objective ×40, and eyepiece ×10) and means were calculated.

Mast cells which are mostly found in the mucosa and submucosa, and which also stained positive for CD117 were distinguished from ICLCs according to their morphological features (round or oval shaped and a centrally located nucleus) and by Mast Cell Tryptase staining, which is negative for ICLCs. Interstitial Cajal-like cells were predominantly spindle in shape (Fig).

Data are expressed as mean ± standard deviation. Chi-square test was used for statistical analysis, using SPSS v10.0 software (SPSS; Chicago, IL, USA). ***P*** values less than 0.05 were considered as statistically significant. Local ethics committee approval this study.

Results

The mean age for the control group (n=15) was 11, and 12.7 years for the study group (n=20). When specimens were compared for the density of ICLCs, mean number for the control group was 39.07±8.02, whereas for the cholelithiasis group it was found to be 23.30±3.50. The difference of means of ICLCs in these groups was found to be statistically significant (p=0.044). Cases with cholelithiasis had usually mean ICLCs numbers <30, whereas cases without a gallstone had >30. The distributions of ICLCs are given in detail in Table 1. Detail the distributions of CD117 positive ICLCs are shown figure.

Table 1. Distribution of ranked ICLCs numbers.

Number of ICLCs	Cholelithiasis (n)	Cholecystitis (n)	Total n of specimen
<20	3	-	3
21-30	16	1	17
31-40	1	9	10
41-50	-	3	3
>50	-	2	2
	20	15	35

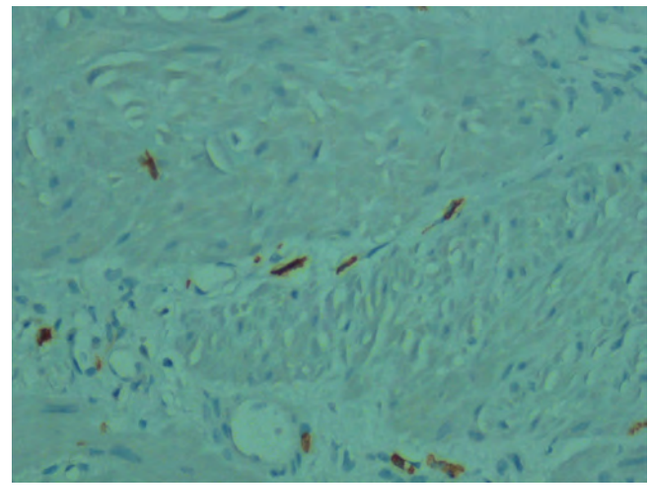


Figure. Distribution of CD117 positive ICLCs (CD117, X 400)

Discussion

Interstitial cells of Cajal (ICC) were first described by Ramón Santiago y Cajal in 1889 [3]. ICC or ICC-like cells that generate pacemaker activity are now being described in many muscular organs including the genitourinary tract, blood vessels, appendix, gallbladder and the uterus. Further studies successfully identified ICC or ICC-like cells by advanced techniques like electron microscopy and immunohistochemistry [7]. The ICC were detected predominantly within the muscularis propria, and they are regarded as important players for intestinal motility

which in case of their decrease also may point to their role in dysmotility conditions [2,8]. In pathologic conditions like motility disorders as observed in diabetic gastroenteropathy, slow-transit constipation, chronic idiopathic intestinal pseudo-obstruction, Hirschsprung's disease, Chagas disease, achalasia and hypertrophic pyloric stenosis the role of ICC has been recently investigated [8, 9, 10]. Ortiz-Hildago first suggested that ICLCs were present in the human gallbladder [3]. Previous studies and research were performed in guinea pig and murine models [5, 11]. Lavoie et al. have suggested the potential a role for ICLCs in the generation and propagation of spontaneous rhythmicity of the gallbladder [5].

Our study was performed in gallbladder specimens laparoscopically removed from children. In our study, we detected that the density of ICLCs in the muscularis propria was significantly lower in the patients with cholelithiasis than in cholecystitis (gallstone- free, controls). As to our knowledge, only one study has evaluated the ICLCs in the pathology of cholelithiasis but in adult specimens.

Arthur et al. examined the distribution of the ICLCs specimens from controls and patients with cholelithiasis with immunohistochemistry. They found a significant decrease in the density of ICLCs in cholelithiasis, even unrelated to the different stages of inflammation. They also evaluated cholesterol saturation index values in cholelithiasis and gallstone-free controls and found an increased cholesterol saturation index in the patients with gallstones, correlating with a lesser ICLCs density. Another important mechanism for the decrease of ICLCs in cholelithiasis was associated with chronic inflammation [8, 12].

Conclusion

In conclusion, we found that the density of ICC or ICLCs in the muscularis propria was significantly lower in specimens from children with gallstone disease than in specimens derived from the gallstone-free, which served as controls. Gallbladder motility may be affected by the number of ICC or ICLCs which are in interaction with smooth muscle contraction. Disrupting this interaction or a decrease in numbers of stimulating ICC or ICLCs would cause the smooth muscle surrounding the gallbladder function less effectively. The histopathological differences observed in this study may help to elucidate the pathophysiology of cholelithiasis in children.

Competing interests

The authors declare that they have no competing interests.

Funding

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Animal and human rights statements

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Does the use of magnifying loupes an effective factor in preventing urethrocutaneous fistula and meatal stenosis in hypospadias repair with tipu in children?

Çocuklarda tıpu ile hipospadias onarımında başarıyı etkileyen faktörler: büyütücü luplar üretrokütanöz fistül ve meatal stenozu önleyici bir faktör mü?

Magnifying loupes in hypospadias repair

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The study was presented at 34th Annual Congress of Pediatric Surgery between 26 - 30 October 2016, in Girne, Turkish Republic of Northern Cyprus.

Öz

Amaç: Bu çalışmanın amacı, Tubularize insize plak üretroplastiyle hipospadias onarımı yapılmış çocuklarda üretrokütanöz fistül ve meatal stenozun oluşumunu etkileyen belirleyicilerin ayrıştırılmasıdır ve büyütücü lupların üretrokütanöz fistül ve meatal stenozun oluşumuna etkisinin araştırılmasıdır. Gereç ve Yöntem: 2008'den 2016'ya kadar 130 hasta tek bir cerrah tarafından hipospadias nedeniyle Tubularize insize plak üretroplastiyle opere edildi. 130 hastanın dosyaları geriyedönük olarak incelendi. Tüm hastaların ameliyat yaşları, hipospadias tipi, ek anomaliler, kordi, komplikasyon oranı, büyütücü lup kullanımı, üretral kateter uygulama süresi ve hastanede kalış süresi değerlendirildi. Bulgular: Yaş ortalamaları (IQR) 3(4.5)yıl (5ay-15yıl) olan 130 çocuğun 103'ü distal hipospadiasa sahipti ve bunlar 7 glanüler, 60 koronal, 13 megameatus, 23 subkoronal hipospadias içermekteydi. Yirmiyedi çocuk proksimal hipospadiasa sahipti 20'si midşaft ve 7'si penoskrotal hipospadiastı. Yirmibeş hasta 1 yaşından küçüktü. Ellibeş hastada büyütücü lup (2.5X) kullanıldı. Dört üretrokütanöz fistül, 7 meatal stenoz, 2 üretrokütanöz fistül ve meatal stenoz, 1 meatal stenoz ve üretral çekilme olan 14 hastaya (10.8%) tekrar müdahale gerekmiştir. Üretrokütanöz fistül ve meatal stenoza göre; yaş (≤ 1y karşın >1y), hipospadias tipi (distal karşın midşaft ve penoskrotal), ek anomaliler ve kordinin sonucu etkilemediği tespit edildi, buna karşılık büyütücü lup kullanımının univariate and multivariate logistic regression analizlerinde önemli derecede sonucu etkilediği tespit edildi ($p < 0.05$). Fakat büyütücü lup kullanılan 55 hasta kullanılmayan 75 hasta ile karşılaştırıldığında guruplar arasında yaş dağılımı, hipospadias tipi, ek anomaliler, kordi, üretral kateter uygulama süresi ve hastanede kalış süresi yönünden anlamlı bir fark tespit edilmedi ($p>0.05$). Tartışma: Büyütücü lup kullanımı çocuklarda hipospadiasın Tubularize insize plak üretroplastiyle onarımından sonra üretrokütanöz fistül ve meatal stenozu önleyici etkin bir faktördür.

Anahtar Kelimeler

Çocuklar; Hipospadias; Büyütücü Lup; Tubularize İnsize Plak Üretroplasti; Üretrokütanöz Fistül

Abstract

Aim: To investigate factors affecting urethrocutaneous fistula and meatal stenosis in repairing hypospadias through tubularized incised plate urethroplasty in children and the effects of magnifying loupes in preventing urethrocutaneous fistula and meatal stenosis. Material and Method: Operated with tubularized incised plate urethroplasty due to hypospadias between 2008-2016; 130 patients were retrospectively evaluated for age, type of hypospadias, associated anormalies, chordee, complication rate, magnifying loupes, and urethral catheterization and hospitalization times. Results: At mean intraoperative age (IQR) of 3 (4.5) years (5months-15years), 130 patients were enrolled. Of 130 cases, 103 children had distal hypospadias, including seven as glanular, 60 as coronal, 13 as megameatus, and 23 as subcoronal, and 27 had proximal hypospadias, including 20 as midshaft and seven penoscrotal hypospadias. Twenty-five patients were younger than one year. Magnifying loupes (2.5X) were used in 55 cases. In 14 patients, four with urethrocutaneous fistula, seven with meatal stenosis, two with urethrocutaneous fistula and meatal stenosis, and one diagnosed with meatal stenosis and glans dehiscence, reintervention was required. For urethrocutaneous fistula and meatal stenosis: age (≤1y versus >1y), type of hypospadias (distal versus proximal), associated anomalies, and chordee had no effects on outcome, whereas magnifying loupes affected the outcome significantly in univariate and multivariate logistic regression analyses. We found no other statistical difference in factors likely to cause such a difference in outcome, including age, type of hypospadias, associated anormalies, and chordee, when comparing the 55 and 75 cases performed with and without loupe. Discussion: Using magnifying loupes is effective in preventing urethrocutaneous fistula and meatal stenosis after tubularized incised plate urethroplasty in children with hypospadias.

Keywords

Children; Hypospadias; Magnifying Loupes; Tubularized Incised Plate Urethroplasty; Urethrocutaneous Fistula

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Introduction

Hypospadias are known as the most common urogenital anomalies with the prevalence rate ranging between approximately 0.4 and 8.2 per 1000 live births, and a probable increase in the incidence of hypospadias has been suggested in recent reports [1,2]. For the treatment of these anomalies, numerous and various techniques have been developed and are still being performed [3]. One of these techniques is tubularized incised plate urethroplasty (TIPU). This technique was described and developed for the first time by Snodgrass in order to correct distal hypospadias [4], and the indication of TIPU was later extended to include midshaft and proximal penile hypospadias with no or mild curvature [5]. In the primary cases, the most common problem has been urethrocutaneous (UC) fistula; meatal stenosis is known as the second most common complication of hypospadias [6,7].

A magnifying loupe is an instrument used to increase the efficiency and quality of medical practices, and the use of magnifying loupes by clinicians in surgical settings increases visual acuity [8]. As in other surgical areas, magnifying loupes are essential and beneficial devices in thepractice of pediatric surgery and urology, as they enable surgeons to identify and define critical anatomic structures accurately in younger patients. Loupes with 2.5X–4.5X magnification are the most frequently used types, although an operating microscope may be needed in some circumstances, such as for hypospadias repair [9,10]. In the present study, we aimed at investigating the factors affecting the formation of UC fistula and meatal stenosis in the repair of hypospadias through TIPU in children, and the effects of magnifying loupes in preventing UC fistula and meatal stenosis.

Material and Method

From 2008 to 2016, 130 patients were operated due to primary hypospadias with TIPU by the single surgeon (C.K.). The hospital records of 130 patients were reviewed retrospectively, and all patients were evaluated as to intraoperative age, type of hypospadias, associated anomalies, chordee, type of suture material used, complication rate, use of magnifying loupes, and the lengths of time of urethral catheterization and hospitalization.

In 55 of the 130 cases, the operations were conducted with the use of 2.5X magnifying loupes (HEINE HR ® binocular loupes, Heine Optotechnik, Herrsching, Germany) and 75 cases were performed without their use. The reason for this was that magnifying loupes were obtained in the department only after the first 75 cases had been operated. Informed consent was obtained from the parents of all children. The procedure was performed in one stage under general anesthesia, and routine local penile block was conducted at the beginning of surgery. The penis was degloved, and an artificial erection test was performed to find out whether chordee was present. Ventral chordee was corrected with a dorsal plication, if needed. Also, a tourniquet to the root of the penis was used for hemostasis in all patients. Two parallel vertical incisions were performed at the junction of the urethral plate and glans wings, isolating the urethral plate. Then, the urethral plate was widened by a longitudinal midline dorsal incision from the meatus to its distal extent and tubularized by using 6-0 polyglyconate absorbable sutures with a 2-layer subepithelial closure. A single suture running distally was tied and then returned proximally over a 6 Fr or 8 Fr urethral catheter. Double dartos flaps, most often obtained from ventral dartos, were used to cover the neourethra. In occasional cases where a ventral dartos was lacking a dorsal dartos was formed as a button-holed flap and transposed ventrally. Glansplasty also began distally at the point where a normal meatus could be located. Glans wings were approximated in a single layer of interrupted subepithelial 6-0 polyglyconate absorbable sutures.

While no suprapubic diversion was performed in any of the 130 patients, circumcision was performed as a routine part of the surgical procedure. The operation was finished with the application of gauze dressing to the penis, and the gauze dressing was opened on the second postoperative day. Urethral catheters were placed in the patients with distal hypospadias for approximately seven postoperative days and in those with midshaft and penoscrotal hypospadias for 14 postoperative days. All patients were prescribed trimethoprim/sulfamethoxazole (6 mg/kg/day of trimethoprim) twice per day and analgesics, including paracetamol of 15 mg/kg/dose three times per day. Patients over the age of 2 years also received oxybutynin as 0.2 mg/kg per dose (highest dose, 5 mg) twice per day during catheterization, when needed. Patients with distal hypospadias were hospitalized for seven days, while those with midshaft and penoscrotal hypospadias were hospitalized for 14 days. However, the cases under the age of 3 years were discharged with an open drainage system into doubled diapers on the second postoperative day. The patients underwent follow-up examinations at the 10th day and at the first and sixth month after the discharge, with more frequent examinations if required. The complications were classified as UC fistula, meatal stenosis, glans dehiscence, urinary tract infections, urinary retention, and postoperative bleeding. Meatal stenosis was suspected for patients having difficulty in voiding and/or a narrow meatal orifice or inability to pass an 8 Fr catheter at the postoperative sixth month. No patients were given any preoperative testosterone. The mean follow-up period was 29 months, ranging between 4 months and three years.

Statistical analyses were performed using SPSS for Windows 15.0 (SPSS, Chicago, IL). The appropriateness of variables to normal distribution rates was evaluated with visual histogram and probability graphics using analytic methods, such as the Kolmogorov-Smirnov and Shapir-Wilk tests. Descriptive analyses were shown using median and interquartile range (IQR) for abnormal variables and frequency tables for ordinal variables. The univariate analyses to identify variables associated with patient outcomes were investigated using the chi-square, Fisher's exact, and student's t-tests where they were appropriate. In multivariate analyses, the possible factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictors of patient outcomes. $p< 0.05$ was considered statistically significant. The study was approved by the local researchethics committee.

Results

The mean intraoperative age (IQR) of 130 patients was 3 (4.5) years (ranging between 5 months-15 years). Of 130 children, 103 had distal hypospadias, including seven as glanular, 60

as coronal, 23 as subcoronal, and 13 as megameatus intact prepuce; the other 27 patients had proximal hypospadias, including 20 as midshaft and seven as penoscrotal hypospadias. Twenty-five of the patients were younger than one year. Magnifying loupes (2.5X) were able to be used in only 55 of 130 cases. As well as hypospadias, associated anomalies, such as two undescended testes, two inguinal hernias, two hydroceles, one urethral duplication, one penile torsion, one urolithiasis, and two vesicoureteral refluxes were present in 11 cases. There was also minimal ventral chordee (< 30°) in another 11 cases.

In 14 patients (10.8%), UC fistula (in four), meatal stenosis (in seven), urethrocutaneous fistula and meatal stenosis (in two), and meatal stenosis and glans dehiscence (in one) were diagnosed and reintervention was required (Table 1). In addition, postoperative bleeding (in five), urinary tract infection (in one), and urinary retention (in one) were also observed. During the repair period in children treated with TIPU due to distal hypospadias, while the rate of UC fistula was 5.8%, the rate of meatal stenosis was found as 3.8%.

Operated patients with hypospadias were divided into two groups as those with and without magnifying loupes. While the mean age (IQR) of the cases with magnifiying loupes was 3.5 (4.1) years (range 5 months-15 years), the mean age (IQR) was found as 3 (4.8) years (range 6 months-11 years) in the cases without the loupes. Mean urethral catheter and hospital stay times were found as 6.29±2.75 and 4.85±2.75 for the cases with loupes and 5.57±2.08 and 4.75±2.05 for those without loupes, respectively (Table 2).

Based on the univariate analysis, although the use of magnifying loupes was found to be significant and to affect the outcome, such factors as age (≤1 year versus >1year), type of hypospadias (distal versus midshaft and penoscrotal), associated anomalies, and chordee were found not to affect the outcome. The findings are presented in Table 3. On the other hand, the multivariate analysis based on the logistic regression method showed that only the use of magnifying loupes influenced the occurences of UC fistula and/or meatal stenosis due to hypospadias repair, independent of age, type of hypospadias, associated anomalies, and chordee [Odds Ratio: 0.198 (95% CI: 0.04-0.9)] (p<0.05).

We found no difference in the distribution of parameters likely to cause such difference, including age (≤ 1 year vs >1 year, p=0.246), mean intraoperative age (group with loupe vs group without loupe, p=0.412), type of hypospadias (distal vs midshaft and penoscrotal, p=0.259), associated anomalies (yes vs no, p=0.135) and chordee (yes vs no, p=0.391). In addition, no statistical difference was found in the mean urethral catheterization and hospitalization times between the two groups (p>0.05). However, in terms of UC fistula and/or meatal stenosis development, a statistically significant difference was found between the groups (p<0.05).

Discussion

Among other techniques, TIPU has been the most frequently used method in the repair of hypospadias. In the primary cases, fistulas and meatal stenosis are the most frequently encountered complications ranging between 0-9% and 0-21% respectively [4,6,11-13]. In our study, while fistulas were found

Table 1. Outcome of TIPU regarding type of hypospadias

Type of hypospadias			UC fistula	MS	UCF and MS	MS and GD	%
Distal 103 (%79,2)	Glanular n (%)	7 (5.4%)	1	1			9.7
	Coronal n (%)	60 (46.1%)	1	3			
	Subcoron n (%)	23 (17.7%)	1		2		
	Megamea intact prepuce n (%)	13 (10%)	1				
Proximal 27 (20.8%)	Midshaft n (%)	20 (15.4%)		3			14.8
	Penoscrotal n (%)	7 (5.4%)				1	
Total (n)		130	4	7	2	1	10.8

TIPU, tubularized incised plate urethroplasty; UCF, urethrocutaneous fistula; MS, Meatal stenosis; GD, glans dehiscence

Table 2. Demographic data and distribution of patients' characteristics

		Loupe	No loupe	p
Patients n		55	75	
Mean age (year) (IQR)		3.5 (4.1)	3 (4.8)	.412[b]
	≤1year n	8	17	.246[a]
	>1year n	47	58	
Type of hypospadias	Distal n	41	62	.259[a]
	Midshaft and penoscrotal n	14	17	
Ventral chordee	Yes n	6	5	.391[a]
	No n	49	70	
Associated anomaly	Yes n	7	4	.135[a]
	No n	48	71	
Hospitalization Mean ±SD		4.85±2.75	4.75±2.05	.798[b]
Catheterization Mean±SD		6.29±2.75	5,57±2,08	.092[b]
UCF and/or MS		2	12	.025[a]

IQR, interquartile range; UCF, urethrocutaneous fistula; MS, Meatal stenosis; a, chi-square test; b, Manne-Whitney U test.

Table 3. Comparition of success rate of TIPU regarding postoperative UC fistula and /or meatal stenosisfactors (chi-square test)

		Success n	UCF and/or MS n	p
Age	≤1year	23	2	.619
	>1year	93	12	
Type of hypospadias	Distal	93	10	.446
	Midshaft and penoscrotal	23	4	
Chordee	Yes	9	2	
	No	107	12	.407
Associated anomaly	Yes	10	1	.851
	No	106	13	
Loupe	Yes	53	2	.025
	No	63	12	

TIPU, tubularized incised plate urethroplasty; UCF, urethrocutaneous fistula; MS, Meatal stenosis

as 5.8% with TIPU in distal hypospadias, the rate of meatal stenosis was determined as 3.8%. We evaluated the factors affecting the development of UC fistula and/or meatal stenosis in our study.

In a study performed by Leung et al., the complications of UC fistula and/or meatal stenosis are reported to be minimized by selecting the appropriate procedure, careful handling of tissues, optical magnification, use of stents, and use of fine, absorbable material [14]. The use of optical magnifying loupes in the repair of hypospadiac abnormalities in children is wellknown. To be successful in hypospadias surgery, the best approach is the selection of the proper dissection method and meticulous approximation of tissues. So the magnification process becomes an important tool in hypospadias surgery in small children. Among various magnification tools, high-powered simple glasses, loupes, and operating microscope are commonly used devices. The decision on which tool is used depends upon their availability and the familiarity of the surgeon with the use of the magnification tool [15]. To the best of our knowledge, however, there have been no studies investigating the use of loupes in TIPU in the literature. In a study where 14 patients with hypospadias were operated on with the help of a video telescopic operating microscope, Frykman et al. reported that no complications were determined [16]. Also, in another study performed with a new head-mounted miniaturized microscope (Varioscope®M5, Life Optics Co., Chicago, Ill., USA) in the surgical correction of hypospadias by Chiummariello et al., the complication rate of the surgical procedure was reported to have decreased from 8.9% to 2.3% [17]. Likewise, while we determined a 3.6% complication rate of UC fistula and/or meatal stenosis in our cases operated on by using loupes, the rate was 16% in those without the use of loupes. The statistical difference between the groups demonstrated that the complication rate significantly decreased; however, we found no other statistical difference likely to cause such a difference in the complication rate, including age, type of hypospadias, associated anormalies, or chordee, when comparing the 55 cases with the 75 cases without the use of a loupe.

The widely acknowledged optimal age for repair of hypospadias is between approximately 6 and 12 months after birth, according to the recommendations of the American Academy of Pediatrics [2,18]. For this reason, the hypospadias operations we performed were grouped as ≤ 1 year and >1 year of age. In the study performed by Huang et al., patient age during the repair of hypospadias was reported as a significant risk factor for the development of UC fistulas after primary hypospadias repair [19]. Despite the widespread concern that older age at time of repair increases complications, in a study where a multivariate analysis of 669 consecutive prepubertal boys undergoing hypospadias repair via TIPU was performed by Bush et al., it was found that increasing age showed no risk for urethral complications. It was also suggested that surgery could be performed in full-term, healthy boys at any time after 3 months of age with no urethral complications [20]. Similarly, while an 8% rate of UC fistula and/or meatal stenosis was observed in the cases (≤ 1 year) with hypospadias operated through TIPU in our study, the rate was detected as 11.4% in those over 1 year of age, with no other significant differences between the groups.

In another study where the types of hypospadias were evaluated by Chung et al., it was emphasized that the formation of UC fistulas after hypospadias repair was significantly associated with the location of the hypospadia [21]. A univariate analysis conducted by Nicol et al. also demonstrated that fistulas, glans dehiscence, diverticulum, stricture and/or meatal stenosis were more common in patients with midshaft and proximal hypospadias (27% in midshaft/proximal repairs vs 9% in primary and reoperative distal TIPU) ($p<0.0001$) [22]. In contrast to the studies by Chung et al. and Nicol et al.,in our study when the cases with distal hypopadias were compared with those with midshaft and penoscrotol hypospadias, we observed no significant difference. We consider that the absence of this difference may arise from the fact that the cases with midshaft and penoscrotol hypospadias had no severe chordee or that many had midshaft hypospadias.

In a study investigating chordee as another risk factor, Ozturk et al. reported that such possible risk factors as severe chordee, middle and posterior localized hypospadias, and use of a pedicle island flap could lead to an increase in the rate of postoperative complications [23]. Counter to the findings of Ozturk et al., no significant difference was found in our study; the absence of such a difference may be associated with the existence of minimal chordee in our cases with hypospadias.

In the study performed by Khuri et al,. among other congenital anomalies associated with severe hypospadias were ureteropelvic junction obstruction, vesico-ureteric reflux, renal agenesis, persistent Mullerian structures, intersex disorders, undescended testis, and inguinal hernia with or without hydrocele [24]. Similarly, we detected associated anomalies in 11 of our cases.

Limitations: Although glans width <14 mm is reported as a risk factor for complications of hypospadias repair, the fact that we did not measure glans size is the only limitation of our study.

Conclusion

We were able to prove that success of hypospadias repair is directly related to the use of a magnifying loupe. Use of a magnifying loupe is an effective factor in preventing UC fistula and meatal stenosis after TIPU in children with hypospadias. The human eye's ability to discriminate potentially fine anatomical structures is limited, possibly leading to complications in hypospadias repair.

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Conflict of interest

The authors have declared there are no conflicts of interest.

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Late-diagnosed penetrating stab Wounds in diaphragm and herniation

Delici-kesici alete bağlı geç tanı almış diyafragma yaralanmaları ve herniasyon

Penetrating stab wounds in diaphragm and herniation

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Öz

Amaç: Travmatik diyafragma rüptürü, künt veya kesici-delici yaralanmaların iyi bilinen, ancak kolaylıkla gözden kaçabilen önemli bir komplikasyonudur. Bu çalışmanın amacı, delici-kesici alete bağlı geç tanı almış diyafragma yaralanmaları konusunda merkezimizin deneyimlerini aktarmaktır. Gereç ve Yöntem: Ocak 2016- Mayıs 2017 tarihleri arasında kliniğinimizde tedavi edilen, travmatik diyafragma rüptürü sonrası diafragmatik herniasyon saptanan yedi hastanın kayıtları retrospektif olarak incelendi. Bulgular: Hastaların 6'sı erkek, 1'i kadın ve yaş ortalamaları 28.2 (20-45) idi. Geç tanı alan hastaların travmatik yaralanma sonrası hastaneye başvuru ortalama süreleri 3.8 (2-6) aydı. Hastaların tümünde diyafragmanın sol tarafında yaralanma vardı. Diafragmatik yaralanmalarda ortalama defekt genişliği 6.9 (3-10) cm idi. Dört hastaya laparatomi, 3 hastaya ise laparoskopi ile fıtık kesesi eksizyonu ve diafragma onarımı uygulandı. Ameliyat esnasında ve sonrasında morbidite ve mortalite gözlenmedi. Tartışma: Delici kesici alete bağlı diyafragma yaralanmalarında ameliyat öncesi tanı koymak zordur. Özellikle abdomino-torakal bölgenin künt ya da penetran yaralanmalarından sonra diyafragma rüptürünün olabileceğinin akla getirilmesi erken tanı ve tedavi için önemlidir.

Anahtar Kelimeler

Penetre Travma; Diafragma; Geç Tanı

Abstract

Aim: Traumatic diaphragm rupture is a well known, but easily overlooked, complication of blunt or sharp injuries. The aim of this study was to convey our experience of traumatic diaphragm injuries with delayed diagnosis. Material and Method: Between January 2016 and May 2017, the records of a total of seven patients with diaphragmatic herniation after traumatic diaphragmatic rupture treated in our clinic were retrospectively reviewed. Results: Six of the patients were male, one patient was female and the mean age was 28.2 (20-45). The mean follow-up period of patients with delayed diagnosis after traumatic injury was 3.8 (2-6) months. All of the patients had an injury on the left side of the diaphragm. The mean defect width in diaphragmatic injuries was 6.9 (3-10) cm. Four patients underwent laparotomy and 3 patients underwent laparoscopy with hernia excision and diaphragm repair. No morbidity and mortality were observed during or after the operation. Discussion: It is difficult to diagnose penetrating diaphragm injuries before surgery. It is especially important for early diagnosis and treatment to remember that diaphragm rupture may occur after blunt or penetrating injury of the abdominal- thoracic region.

Keywords

Penetrating Trauma; Diaphragm; Late Diagnosis

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Introduction

Three out of four cases of traumatic diaphragm ruptures (TDR) that arise from thoraco-abdominal injuries are related to non-penetrating injuries, while one out of four is related to penetrating injuries [1]. In the immediate post-trauma period TDR is very hard to diagnose if there are no specific symptoms or radiologic findings. Some cases may not be diagnosed until many years later. Increasing morbidity and mortality due to rupture is related to late diagnosis of such cases. The cases that are not initially diagnosed may lead to complications of gastrointestinal herniation, strangulation, or sepsis [2]. In this study we provide the experiences of our center with regard to late-diagnosed penetrated diaphragm injuries.

Material and Method

In this study, the records of seven cases of herniation that arose from late-diagnosed TDRs were examined retrospectively. This study differs from other studies because it examines the records of late-diagnosed cases between 2016 January – 2017 May at the General Surgery Clinic of Health Sciences University Mehmet Akif İnan Training and Research Hospital. The demographic features of patients such as age and gender, chest x-ray, tomography results, diagnosis duration, surgery duration, amount of bleeding in the surgery operation, post-operative monitoring. and rate of morbidity and mortality were noted. Informed consents were obtained from the patients who participated in this study.

Results

Six male patients and 1 female patient were examined; the mean age was 28.2 (20-45). These patients had been followed up conservatively in various centers because no sharp object wounds were found on the diaphragm. Subsequently, they applied to the emergency service or general surgery polyclinic of our hospital with the complaints of respiratory distress, hematemesis, stomach ache, and chest pain. All the patients were monitored for diagnosis by chest x-ray and thoracic abdominal tomography, which are routinely performed when there is a suspicion of TDR. The mean duration between trauma and application to our hospital was 3.8 (2-6) months. All of the patients had injuries on the left side of the diaphragm. Three patients had thoracic herniation at the stomach and omentum, while four patients had thoracic herniation only at the omentum (Fig. 1a,b,c,d). The average width of the defect at the diaphragm wounds was 6.9 cm (Fig. 1e). Four patients received laparotomy and three patients received laparoscopic hernia sac excision and diaphragm repair (Fig. 1f). Five patients received primary diaphragm repair, and dual mesh was used for two patients after diaphragm repair. The average surgery period was 95 (60-140) minutes. During the surgery the amount of bleeding averaged 120 (25-400) ml. The average hospitalization duration was 3.4 (2-5) days. No morbidity or mortality were recorded during or after the surgery.

Discussion

The serious complications of diaphragm rupture in the late period are associated with herniation of the abdominal visceral organs [3]. TDRs are usually accompanied by injuries. In some cases the diagnosis is made immediately after the trauma, while in some it may only be diagnosed after many years [4]. In a meta-analysis of 980 cases, Shah et al. found that the rate of the late diagnosis was 14.6%. Early diagnosis can be done only if there is a suspicion of diaphragm rupture [5]. Therefore, when there are sharp object injuries at the lower chest and sides of the upper abdomen, diaphragm wounds should be suspected [6]. As a result of elective thoracoscopy performed 6 months after the trauma, Uribe RA et al. found that 9 (32%) of 28 patients with left thoraco-abdominal injuries had diaphragm

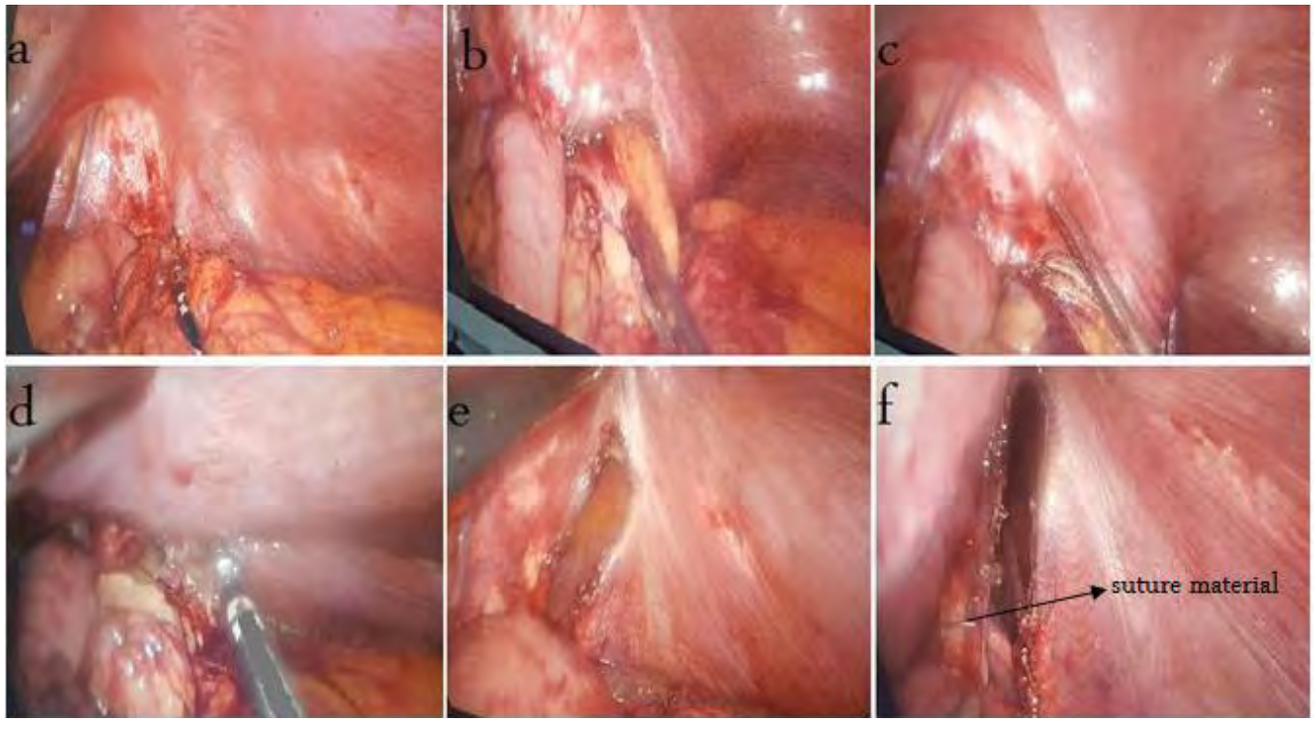


Figure 1. View of the left diaphragm with laparoscopic approach. (a,b,c,d) Omentum and stomach fundus in the diaphragmatic hernia sac (e) defect area after the hernia sac excision (f) repair of the diaphragm

wounds that weren't found during the pre-operative examinations [7]. The diagnosis was not made within the first injury trauma period for any of our seven patients.

Traumatic diaphragm rupture diagnosis can be made through complaints of the patient, findings of physical examinations, serial chest x-rays, baric gastrointestinal system x-ray, thoracoabdominal x-ray, magnetic resonance, thoracoscopy, or laparoscopy [8]. If a nasogastric tube is bent at the thorax, this finding helps the diagnosis. Direct radiology can reveal the following: the integrity of the diaphragm is lost, plural haustra of intestine and gas areas are observed in the thorax, the diaphragm is observed above its normal anatomic position, pleural effusion, atelectasis, bulk observation in the lungs, mediastinal shift, pneumothorax, and hydro pneumothorax [9].

According to its clinical presentation, the herniation of traumatic diaphragm has three phases: acute phase, latent phase, and obstructive phase. The acute phase starts just after the injury and continues until the stab wound recovers. In this period the injuries of the diaphragm may not be noticed due to hemodynamic instability related to injuries of the visceral organs and vascular tissues. Latent phase or interval phase is a period when the thoraco-abdominal injuries are asymptomatic after the recovery of the injuries. In this period the ruptured area of the diaphragm is covered by the abdominal organs, which slowly herniate toward the thorax. Ischemia, obstruction, and strangulation findings are observed in this chronic obstructive period. Most of the diagnosis and treatment plans of the patients whose problems couldn't be diagnosed at the acute phase are completed in this period [10]. In our study, all of our patients were diagnosed and treated in the chronic obstructive period after the patients became symptomatic.

It is inevitable to have herniation of the abdominal organs at the unnoticed ruptures in the acute period following the trauma. During the Valsalva maneuver the pressure difference between abdomen and thorax, which is normally 2-10 mmHg, increases to 100 mmHg [11]. The herniated organs may vary depending on the diameter of the defect on the diaphragm and features of the adjacent organs of the defected area. Mostly the stomach, small intestine, and colon, and rarely the liver and spleen, are herniated [12]. After the TDR it is possible to observe stomach or colon herniation together with strangulation or intra-thoracic perforation. This situation leads to increasing morbidity and mortality in the following period [13]. In our patients we observed incarceration at the herniated organs of our patients, but no strangulation.

The optimal treatment for TDR is the repair of defects for the cases of early diagnosis. In this phase the abdominal surgery methods must be chosen considering the possibility of the injury of adjacent organs. When such a method is not applied, then thoraco-abdominal or separate thoracic incision may be required. In recent years the laparoscopic approaches also have been widely applied. The primary repair of the diaphragm with unabsorbed sutures is generally the preferred method. In cases with big defects that are not suitable for primary closure, using an appropriate non-absorbable polypropylene graft or dual graft to close the defect is suggested [14,15].

Conclusion

The most important tool for the diagnosis of traumatic diaphragm injury is to suspect rupture of the diaphragm after the obtuse or penetrating injury of the abdominal thoracic area. During the abdominal surgery of such patients, both hemi-diaphragms must be explored carefully. For patients receiving conservative treatment, diagnostic laparoscopy must be performed before discharge. The diaphragm must be repaired through primary suture and/or by using graft for the patients found to have diaphragm rupture.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consents were obtained from patients who participated in this study.

Competing interests

No conflict of interest was declared by the authors.

Financial Disclosure

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The relationship between tinnitus and mean platelet volume

Tinnitus ve ortalama trombosit hacmi arasındaki ilişki

MPV & tinnitus

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Öz

Amaç: Bu çalışmanın amacı tinnitus ile ortalama trombosit hacmi(OTH) arasındaki ilişkiyi araştırmaktır. Materyal ve Metod: 40 tinnituslu hasta ile 40 kulak patolojisi veya kardiyovasküler hastalığı olmayan sağlıklı birey kontrol grubu olarak çalışmaya dahil edildi. Hastaların değerlendirilmesi detaylı hikaye, tam baş boyun muayenesi, laboratuar kan testleri, OTH, platelet distribution width (PDW) ve platelet count (PC) içermekteydi. Ardından sonuçlar karşılaştırıldı. Bulgular: Gruplar yaş ve cinsiyet bakımından benzerdi (p=0.068, p=0.649). Ortalama OTH değerleri tinnitus grubu ve kontrol grubunda benzerdi (p=0.522). Ayrıca ortalama PDW ve PC değerleri de gruplarda benzer olarak bulundu (p=0.311, p=0.402). Tartışma: Tinnituslu hastalarla sağlıklı bireylerin OTH değerleri arasında anlamlı bir farklılık bulunmadı. OTH değerleri tek başına tinnitus patogenezinde önemli bir rol oynamıyor gibi görünmektedir.

Anahtar Kelimeler

Tinnitus; Ortalama Trombosit Hacmi(OTH); Platelet Distribution Width (PDW) and Platelet Count (PC)

Abstract

Aim: The aim of this study is to investigate the relationship between tinnitus and mean platelet volume (MPV). Material and Method: 40 subjects with tinnitus and 40 healthy subjects as control group with no evidence of ear pathology or cardiovascular diseases were included in the study. The evaluation of the subjects included a detailed history, otorhinolaryngological examination, assessment of laboratory blood parameters, MPV, platelet distribution width (PDW) and platelet count (PC). Then the subjects were compared. Results: The groups were similar in terms of age and gender (p=0.068, p=0.649). The mean MPV values in tinnitus group and control group were similar (p=0.522). Also, the mean PDW and PC values in tinnitus group and control group were similar (p=0.311, p=0.402). Discussion: We found that there was no significant difference in MPV values of patients with tinnitus compared to the control group. MPV values alone do not seem to play a major role in the pathogenesis of tinnitus.

Keywords

Tinnitus; Mean Platelet Volume(MPV); Platelet Distribution Width (PDW) and Platelet Count (PC)

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Introduction

Tinnitus is the perception of sound in ear or head in the absence of external stimulus [1]. Tinnitus affects approximately 17% of general population, and 33% of elderly population [2]. Tinnitus may be classified into two main groups as subjective and objective tinnitus. Subjective tinnitus is also named as nonpulsatile tinnitus whereas objective tinnitus is named as pulsatile tinnitus. Non–pulsatile or subjective tinnitus is the most common form of tinnitus [3].

The most common cause of subjective tinnitus is otological disorders. Otological disorders are acoustic trauma, presbiacusis, otosclerosis, otitis, Meniere's disease, and sudden hearing loss. Drugs, neurological and infectious pathologies are the other causes of subjective tinnitus [4].

Recently many studies about the neurobiological etiology of tinnitus have been conducted. In animal models, it had been shown that tinnitus is generated from the imbalance of excitatory and inhibitory impulses to the auditory neurons. It is declared that this imbalance occurs in the whole auditory system [5].

Mean platelet volume(MPV) is a parameter that reflects the activation and function of platelets. In previous studies, it had been shown that MPV was increased in cardiovascular diseases, diabetes mellitus, hypertension, hypercholesterolemia, obese and smokers [6]. Also, an increase in MPV was reported in vascular diseases such as atherosclerosis, venous or arterial thrombosis, and thromboembolism. On the other hand, an inverse relationship was shown between MPV and the activity of inflammatory bowel diseases, rheumatoid arthritis, and ankylosing spondylitis [7]. In a recent study about the relationship between MPV and hearing loss, MPV was increased in patients with sensorineural hearing loss [7].

There is no previous study about the relationship of MPV and tinnitus. In this study, we aimed to investigate the relationship between MPV and tinnitus.

Material and Method

Study population

40 subjects who referred to the otorhinolaryngology department of Mustafa Kemal University in 2014 with tinnitus were included in the study. The exclusion criteria for the subjects were as follows: pneumonia, diabetes mellitus, hypertension, liver or renal dysfunction, obstructive sleep apnea syndrome, coronary artery disease, chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases, severe anemia or hematological diseases, medication (anticoagulants, anti-inflammatory agents, systemic corticosteroids) and smoking history [7]. The control group included 40 healthy subjects with no evidence of ear pathology or cardiovascular diseases. The evaluation of the subjects included a detailed history, otorhinolaryngologic examination, assessment of laboratory blood parameters. Ethics committee approval was obtained from Mustafa Kemal University and the study was conducted adhering to the Declaration of Helsinki. Informed consent was obtained from all of the participants.

Laboratory evaluation

Venous blood samples were collected into tubes containing calcium ethylen ediamine tetra acetic acid (EDTA). To avoid platelet swelling, measurement of the blood samples were done within 30 min after sampling. MPV, platelet distribution width (PDW) and platelet count (PC) was measured with an automated blood cell counter (Mindray BC-6800, Autohematolgy Analyzer China) in our hospital's central laboratory.

Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) 16.0 Evaluation for Windows. Descriptive statistics were stated as mean ± SD (standard deviation). Average distribution of continues variables were tested with Kolmogorov-Smirnov test. Chi-square test was used for comparisons between categorical variables, and Mann-Whitney U tests were used for continuous variables when comparing the groups. The statistically significant level was accepted as a p value <0.005.

Results

Demographic properties

The mean age of the patients with tinnitus and the control group were 37.52 ± 10.24 and 33.80 ± 7.52 years respectively. 60% of tinnitus group and 65% of a control group were females. The groups were similar in terms of age and gender (p=0.068, p=0.649).

Laboratory evaluation

The mean MPV was 9.43 ± 1.10 in tinnitus group and 9.91 ± 1.36 in the control group. The mean MPV in tinnitus group and control group were similar (p=0.522) (Figure 1).

The mean PDW was 16.13 ± 0.75 in tinnitus group and 19.80 ± 22.74 in the control group. The mean PDW in tinnitus group and control group were similar (p=0.311) (Figure 2).

The mean PC was 278.525 ± 66.735 in tinnitus group and 267.225 ± 52.366 in the control group. The mean PC in tinnitus group and control group were similar (p=0.402) (Figure 3).

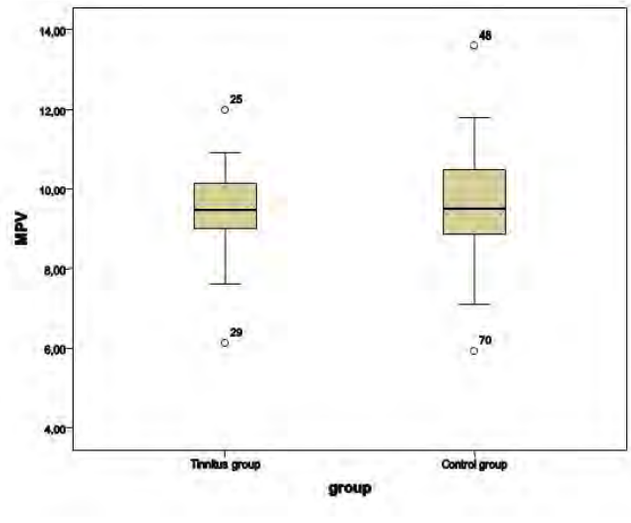


Figure 1. The mean MPV values of tinnitus group and control group

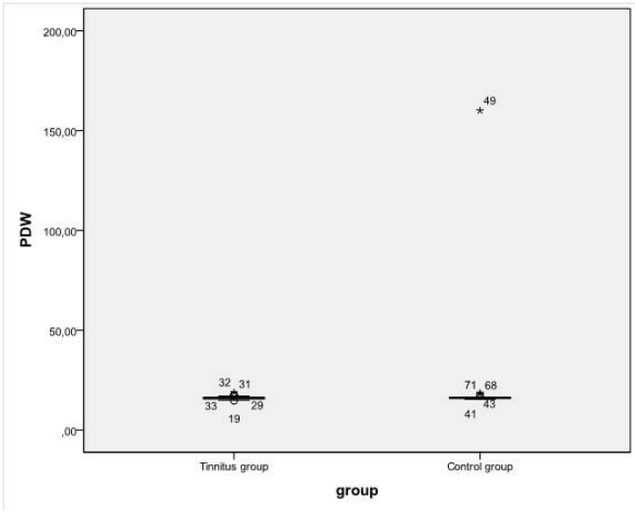


Figure 2. The mean PDW values of tinnitus group and control group

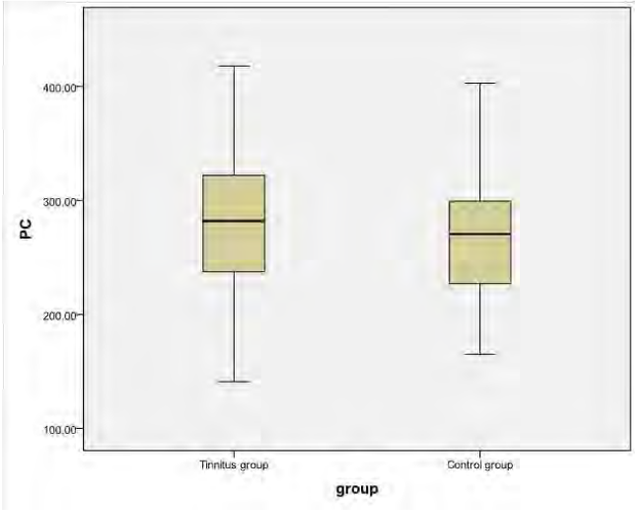


Figure 3. The mean PC values of tinnitus group and control group

Table 1. Demographic and laboratuvary features of the groups

	Tinnitus group (n=40) mean±SD	Control group (n=40) mean±SD	p values
Age, years	37.52± 10.24	33.80± 7.52	0.068
Sex (F/M)	24/16	26/14	0.649
MPV, fL	9.43± 1.10	9.91± 1.36	0.522
PDW, fL	16.13± 0.75	19.80± 22.74	0.311
PC, 10^3/µL	278.52± 66.73	267.22± 52.36	0.402

MPV= mean platelet volume, PDW= platelet distribution width, PC=platelet count, p<0.05 showing statistically significance

Discussion

Mean platelet volume (MPV) is one of a platelet indices parameter and can be measured by readily available routine blood count. It has been used as a marker of platelet activity and function. Its relationship with the pathogenesis of some diseases have been investigated and reported as a prognostic factor in some cardiovascular disorders. In previous studies, increased MPV have been observed in patients with cardiovascular risk factors, such as diabetes mellitus [8], hypertension [9], obesity [10] and smoking [11]. Chu et al. have suggested that increased MPV is associated with mortality due to acute myocardial infarction and restenosis following coronary angioplasty [6]. O'Malley et al. have argued that increased MPV and decreased PC are characteristic laboratory findings in ischemic stroke [12]. In another study, increased MPV have also been reported to be associated with the severity of cerebral damage and mortality [13,14].

There are limited numbers of studies investigating MPV changes in disorders of ear, nose, and throat. In a study, decreased MPV values were detected in patients with nasal polyps [15]. In another study, investigating the relationship between MPV and sensorineural hearing loss, significantly increased MPV values were found in patients with hearing loss. Researchers speculated that ischemia and atherosclerosis might be important in the pathogenesis of idiopathic sudden hearing loss [7].

Tinnitus is a common health problem among older adults. Vascular risk factors are thought to be important in the pathogenesis of tinnitus. In this study, we aimed to investigate the relationship between MPV and tinnitus. The current study showed that there was no significant changes in MPV values of study group compared to control group.

Some researchers have speculated that there is a link between MPV with disease activity and treatment efficacy in chronic inflammatory disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and Crohn's disease [16], whereas some others argue for such a connection [17,18]. In another study Hilal et al. suggested that a single MPV determination was not a reliable indicator for diagnosis of pulmonary embolism and its severity [19].

In conclusion, we found that there was no significant difference in MPV values of patients with tinnitus compared to healthy subjects. MPV values alone do not seem to play an important role in the pathogenesis of tinnitus.

The limitation of the study is the number of cases we studied. Further, more detailed studies with larger numbers exploring the relationship between platelet indices and tinnitus will be beneficial to the literature.

Human studies

'All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.'

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None

Competing interests

The authors declare that they have no competing interests.

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A short survey study in asthma patients related to misperception of the disease

Astım hastalarında yanlış algıya yönelik kısa bir anket çalışması

Disease misperception in asthma patients

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Chest Diseases, Abant Izzet Baysal Univercity, Medicine Faculty, Düzce, Turkey

Öz

Amaç: Astım hastalarında iki temel yanlış algının yaygınlığını değerlendirmek. Gereç ve Yöntem: 18 yaşından büyük, astım tanısı almış ve atım ilaçları kullanan hastalar çalışmaya alındı. Hastalar yazarın ofisine muayene olmak amacıyla gelen hastalar arasından sırası ile çalışmaya alındı. Hastalara 'astım hastalığının bulaşıcı bir hastalık olup olmadığı ve astım ilaçlarının bağımlılık yapıp yapmadığı konularında sorular soruldu. Bulgular: Toplam 1003 hasta çalışmaya alındı. 'Astım bulaşıcı bir hastalıktır' ve 'Astım bulaşıcı bir hastalık değildir' yanıtını veren hastaların oranları sırası ile %15.3 ve %58.0 idi. 'Astım ilaçları bağımlılık yapar' ve 'Astım ilaçları bağımlılık yapmaz' şeklinde cevap veren hastaların oranları ise sırası ile %17.9 and %27.0 idi. Tartışma: Hastaların büyük kısmı mevcut bilimsel gerçeklere uygun cevap vermişlerse de verilen yanlış cevap oranlarının yüksek olduğunu değerlendiriyoruz.

Keywords

Astım; Bulaşıcılık; Bağımlılık Yapma; Anket

Abstract

Aim: To evaluate the extensity of two basic misperceptions in asthma patients. Material and Method: The patients over 18 years of age who had been diagnosed with asthma and using asthma drugs were enrolled in the study. The patients were consecutively selected who examined in the private office of the author. Participants have been asked whether 'asthma is a contagious disease' and whether 'asthma drugs cause addiction'. Results: A total of 1,003 patients were included in the study. The ratios of patients who declared that 'asthma is a contagious disease' or 'asthma is not a contagious disease' were 15.3% and 58.0%, respectively. The ratio of patients who declared that 'asthma drugs cause addiction' and 'asthma drugs do not cause addiction' were 17.9% and 27.0%. Discussion: Although most patients answers were in accordance with scientific facts, the ratios of misperception are thought to be high.

Keywords

Asthma; Contagious; Addiction; Misperception; Questionnaire

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Introduction

Bronchial asthma is a chronic inflammatory disease characterized by airflow limitation that resolves spontaneously or with treatment. It is a serious global health problem that affects people of all backgrounds and ages [1,2]. It is one of the most prevalent chronic diseases worldwide and is the most common indication for hospitalization among children [1]. The 2010 Global Burden of Disease study estimates the current asthma burden to be greater than 334 million which is consistent with previous reports [3-5].

The genetic and environmental factors play a role in the development of asthma. However, all aspects of the etiopathogenesis were not understood fully until today. For this reason, the definition of asthma defines the clinical and pathologic features of the disease [6].

During routine chest diseases practice, patients often ask the author of this study whether asthma is a contagious disease and the addictive potential of asthma drugs. For this reason, the author aimed to investigate the frequency of this perception of asthma among adult patients.

Material and Method

The study was performed in the private office of the author (SK). Consecutive patients above 18-years old who were diagnosed with asthma previously and using asthma medications were included in the study. The patients were given a questionnaire consisting of demographic questions and questions about the perception of asthma disease (Table 1). The study protocol was approved by Sakarya University Medical Faculty Ethics Committee (71522473/050.01.04/192). Signed informed consent was obtained after the interviewer discussed the study details.

Statistical analyses were performed by using SPSS program. Pearson correlation test was used to compare the answers given to the questionnaire according to the gender and age groups. P values less than 0.05 were considered statistically significant.

Table 1. The questionnaire form

Demographic Questions	
Age	
Gender	Male/Female
Marital Status	Married
	Single
	Divorced
Education Level	Illiterate
	Literate
	Primary School
	High School
	University
Questions about the perception of disease	
What is the cause of asthma	Yes, asthma is a contagious disease
	No, asthma is not a contagious disease
	I do not know
Do asthma drugs cause addiction?	Yes, asthma drugs may cause addiction
	No, asthma drugs do not cause addiction
	I do not know

Results

A total of 1003 consecutive patients were included in the study (521 female and 482 male), respectively. The demographic characteristics of the patients (age, the marital and educational status) are presented in Table 2. Most of the patients (74.7%) were between 25-65 years-old. Most of the patients (74.7%) were married and graduated from the primary school (61.7%).

Table 3 shows the results of questions about the perception of the disease. More than half of the patients (58.0%) stated that 'asthma is not a contagious disease'. Again, more than half of the patients (55.1%) stated that they do not know whether asthma medications cause addiction.

Table 2. Demographic data of the participants

Parameter		n	Percentile
Age (years)	18-24	130	12.9%
	25-44	430	42.9%
	45-64	316	31.5%
	≥65	127	12.7%
Marital Status	Married	751	74.9%
	Single	121	12.1%
	Divorced	131	13.0%
Education level	Illiterate	84	8.4%
	Literate	49	4.9%
	Primary School	621	61.9%
	High School	176	17.5%
	University	73	7.3%

Table 3. Comparison of the knowledge level about the questionnaire

Is asthma infectious or microbial?			
Questions	Answers	n	%
What is the cause of asthma?	Yes, asthma is a contagious disease	153	15.3%
	No, asthma is not a contagious disease	582	58.0%
	I do not know	268	26.7%
Do asthma drugs cause addiction?	Yes, asthma drugs cause addiction	180	17.9%
	No, asthma drugs do not cause addiction	271	27.0%
	I do not know	552	55.1%

Discussion

The main physiological characteristic of asthma is airway constriction with airflow limitation [7]. Asthma is a good example of diseases in which the gene-environmental factor interaction appears. The emergence of different clinical presentations of asthma depends on the genetic structure of the person, the environmental factors causing inflammation [8], the contraction of smooth muscles, and the effect of varying rates of edema and airway reconstruction [9]. Asthma is a chronic inflammatory disease that might affect all age groups and cause serious health problems all over the world [7]. Based on standardized methods applied in children and adults, although it is thought that the global prevalence of asthma has changed in communities living in different countries of the world, it is estimated that there are 300 million asthmatic patients all over the world. The prevalence of asthma in our country varies between 5-10% in childhood and 2-6% in adults. Training programs related to asthma therapy improves the level of asthma knowledge and enhance patient compliance with treatment [6].

It is well recognized that questionnaire based definitions of asthma may not necessarily correspond to the clinical definition of asthma, and that there is no universally accepted 'gold standard' definition of asthma for use in epidemiologic studies [10]. In this study, we aimed to investigate the extensity of perception of asthma as 'a contagious disease' and 'the addictive potentials of asthma medications' in a Turkish population. We found that 15.3% of patients perceived asthma as a contagious disease. 58% of patients perceived against that thought.

The purpose of asthma therapy is to provide clinical control and maintain it. Drugs that are used in asthma treatment can be grouped as controlling drugs and symptom-relieving drugs. Controlling drugs are taken every day and for a long time, which are used to control asthma clinically due to its anti-inflammatory properties. This group consists of inhaled and systemic glucocorticosteroids, leukotriene antagonists, long-acting beta-2 agonists used in combination with inhaled glucocorticosteroids, slow releasing theophylline, chromones, and anti-IgE. Inhaled glucocorticosteroids are the most efficient controlling medicines used today[7,11]. In this study, we found that 17.9% of patients perceived asthma medications as addictive drugs. More than half of the patients (55.1%) stated that they do not know whether asthma medications may cause addiction. Only 27% of the patients reported that asthma drugs were not addictive. In a study performed in Brazil, 70% of participants thought that asthma drugs might cause addiction [7].

Misinformation and wrong opinions about asthma treatment might affect treatment compliance and control of asthma therapy, so these assessments will also determine the missing parts in the treatment. There are a variety of validated questionnaires to measure the awareness of the disease, determine the effectiveness of the program, and assess the relationship between awareness-control of asthma [6,12]. Otherwise, there would be more patients who hinder or discontinue their treatment with the misconception of the addictiveness of asthma medicines. Or, those who think that asthma is a contagious disease would hide their illness and might give up their treatment completely. For this reason, awareness caused by our questionnaire becomes more of an issue. The aim of asthma therapy is to maintain and provide clinical control [7]. It is therefore important to inform the patients not to give up their treatments with misperceptions as much as to prescribe the drugs of the patient.

Human Rights Statement: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Animal Rights Statement

Nonapplicable

Conflict of Interest Statement

The authors have no conflict of interest

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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Body mass index related clinical outcomes after knee replacement in overweight and obese patients

Aşırı kilolu ve obez hastalarda diz protezi sonrası klinik sonuçların vücut kitle indeksi ile ilişkisi

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Öz

Amaç: Aşırı kilolu ve obez hastalarda total diz protezi (TDP) sonrası vücut kitle indeksinin (VKİ) fonksiyonel sonuçlara etkisini ortaya koymak. Gereç ve Yöntem: Ocak 2002 ve Aralık 2010 arasında primer TDP yapılan hastalar geriye dönük incelendi. Ortalama takip süresi 7 yıldı. Dizler vücut kitle indeksleri baz alınarak Dünya Sağlık Örgütü sınıflamasına göre gruplara ayrıldı ve aşırı kilolu, 1. derece obez ve 2. derece obez hastalar değerlendirildi. Grupların klinik sonuçları Oxford Diz Skoru (OKS), Görsel ağrı skalası (VAS) ve Kısa Form-36 fiziksel skoru (SF-36 PCS) ile Kısa Form-36 mental skoru (SF-36 MCS) hesaplanarak karşılaştırıldı. Bulgular: En düşük skorlar 2. derece obez hastalarda elde edildi. Fakat gruplar arasında OKS, SF-36 PCS, SF-36 MCS ve VAS skorları arasında istatistiksel olarak anlamlı farka rastlanmadı. Grupların ortalama yaşları sırasıyla 67, 64 ve 62 idi ($p<0.05$). Diğerleri ile karşılaştırıldığında 2. derece obez grubundaki hastaların daha erken yaşta ameliyat edildiği görüldü. Tartışma: Aşırı kilolu, 1. derece obez ve 2. derece obez hastalarda TDP sonrası klinik sonuçların ortalama 7 yıllık takipte VKİ'nden etkilenmediği görüldü.

Anahtar Kelimeler

Artroplasti; Diz; Vücut Kitle İndexi; Klinik Sonuç; Fonksiyonel Skor

Abstract

Aim: To analyze the influence of body mass index (BMI) on functional outcome in overweight and obese patients after total knee replacement (TKR). Material and Method: The patients who underwent primary TKR between January 2002 and December 2010 were retrospectively reviewed. The mean follow-up period was seven years. The knees were divided into the groups according to the World Health Organization classification based on BMIs and overweight, class 1 obese, class 2 obese patients were assessed. The clinical outcomes of the groups were compared by evaluating the Oxford Knee Score (OKS), visual analog scale (VAS), and Short Form-36 physical component summary (SF-36 PCS) and mental component summary (SF-36 MCS) scores. Results: The lowest scores were obtained in class 2 obese group. However, the differences of OKS, SF-36 PCS, and SF-36 MCS and VAS between the groups were not found to be statistically significant. The mean ages of the groups were 67, 64 and 62 respectively ($p<0.05$). Class 2 obese group underwent surgery at a younger age compared to the others. Discussion: Clinical outcome after TKR was not affected by BMI at a mean seven years follow-up in overweight, class 1 obese and class 2 obese patients.

Keywords

Arthroplasty; Knee; Body Mass Index; Clinical Outcome; Function Score

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Introduction

Obesity is a significant health condition associated with multiple comorbidities, including diabetes mellitus, metabolic syndrome, hypertension and coroner artery diseases [1]. The prevalence of obesity has been increasing in both emerging and industrialized countries [2]. It was stated that a 33% increase in obesity prevalence and a 130% increase in severe obesity prevalence are estimated over the next two decades [3].

Obesity is also defined as a risk factor for the development of hip and knee osteoarthritis [4-6]. Recently, the prevalence of overweight and obese individuals has been increasing among orthopedic patients who underwent total knee replacement (TKR) [7]. Furthermore, need for having TKR has been increasing due to increased body mass index (BMI) [8]. Thus, it is not surprising that obese patients are undergoing surgery at a younger age compared with their non-obese counterparts [9,10].

The current literature has divided in opinion of the influence of BMI on clinical outcomes after TKR. Several studies reported that obesity adversely affected the functional scores [11-14]. Others claimed that the effect of BMI on clinical outcomes was not significant after TKR [15-17]. Most of them compared the obese (BMI>30) and non-obese (BMI<30) individuals [13,16,17], or intercalarily morbidly obese (BMI>40) patients [11,12,17]. However, only a few studies have reported subgroup analysis by classifying the overweight and obese patients as recommended by World Health Organization (WHO) [10,18].

The aim of this study was to determine the influence of body mass index on functional outcome among overweight and obese patients after TKR. It was hypothesized that higher BMI is associated with poorer functional scores.

Material and Method

The study was approved by the local Ethics Committee. The patients who underwent primary TKA in a single clinic between January 2002 and December 2010 were reviewed retrospectively. The inclusion criteria for the study were patients with primary osteoarthritis who underwent primary TKA at least five years before their most recent follow-up visit and overweight or obese patients according to their BMIs. Patients who were over 80 years old on their last visit, had prior knee surgery or had <5-year follow-up period were excluded.

The clinicodemographic data including sex, age, operation side and follow-up periods were collated for each patient. The BMIs were calculated for each patient as body weight(kg)/height2(m2) at their most recent follow-up visit, then Function scores and life-quality assessment were obtained. Function assessment was performed using the Oxford Knee Score (OKS). To determine the relief of pain and quality of life, the visual analog scale (VAS) and Short Form 36 (SF-36) health survey questionnaire—both physical component summary (PCS) and mental component summary (MCS)—were used. In bilateral cases, each knee was included into the belonged group according to the BMI. OKS and VAS which reflect the related knee were measured separately for each knee. However, SF-36 scores which reflect the general condition of the patient were the same for both of the knees.

The knees were divided into the groups according to the WHO classification based on BMIs as overweight (25 to 29.99), class 1 obese (30 to 34.99), class 2 obese (35 to 39.99) and class 3 obese (>40) [19]. The function scores of each group were compared using the OKS, VAS, SF-36 PCS, and SF-36 MCS.

Surgical technique

All operations were performed using a conventional approach with applying a tourniquet by three different senior orthopedic surgeons. A standard surgical approach with a medial parapatellar incision and arthrotomy was used. Femoral cuts were performed by intramedullary guides, and extramedullary guides were used for tibial cuts in all cases. Cemented cruciate ligament retaining modern implant designs were used without patellar resurfacing. All patients received antibiotics prophylaxis for 24 hours and, low molecular weight heparin and full-length anti-embolic stockings were applied for deep venous thromboembolism prophylaxis after surgery. The patients were mobilized the next day after surgery, and all patients underwent standardized rehabilitation programs.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM corp., USA. Different categorical data were compared using the chi-square test and Fisher–Freeman–Halton test. The results of normal distributions were compared using one-way ANOVA test, and non-normal distributions were compared using the Kruskal–Wallis test. Statistical significance was set as $p < 0.05$.

Results

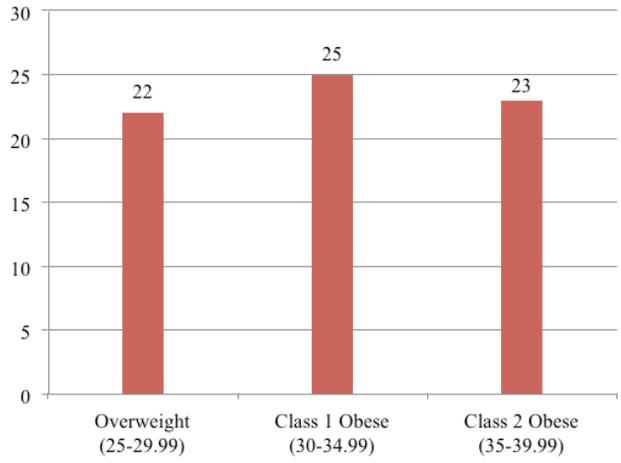
Sufficient data of 237 patients were obtained (preoperative clinicodemographic data, phone number, etc.) from the hospital archives who had proper follow up. Fifty-three of them were over 80 years old at the last follow-up, and 17 of them died. Eighteen patients underwent surgery for seconder osteoarthritis etiology, and 16 of the patients had prior knee surgery. These patients were excluded according to the inclusion and exclusion criteria. Thirty-five patients stated that they had no complaint and did not want to continue follow-ups. The other 45 patients rejected to participate in the study. Remaining 53 patients were included in the survey.

Because there were only two morbidly obese (class 3 obese) patients and the number was not sufficient for statistical comparison, these patients were excluded. A Total of 70 knees of 51 patients were evaluated, and the comparison was performed between overweight (n=22 knees), class 1 obese (n=25 knees) and class 2 obese (n=23 knees) patients. The distribution of the groups based on BMIs are shown in Table 1.

There were no complications, such as wound problem, deep infection, deep venous thrombosis, periprosthetic fracture, or component loosening.

The mean age of the patients at surgery date was 64.8 (range; 56–73), and mean follow-up period was 84.9 months (range; 60–144). The mean ages of the groups were 67, 64 and 62 respectively. The difference in the ages between the groups was statistically significant. It was demonstrated that obese patients underwent surgery at a younger age compared to overweight patients as estimated. On the other hand, the differences were not significant between the groups according to the

Table 1. Distribution of the number of the groups based on BMIs



follow-up periods, gender distribution, or operation sides. The clinicodemographic data of each group was shown in Table 2. The mean OKS of the groups were 35.8, 37.1 and 33.5 respectively (p>0.05). The mean VAS of each group was 2.9, 2.8 and 3.8 respectively (p>0.05). The mean SF-36 PCS of the overweight group was 38.5, and class 1 obese group was 39.9. Class 2 obese group had the lowest SF-36 PCS (35.9). However, the differences were not statistically significant. The SF-36 MCSs of the groups were 46.2, 45.4 and 44.4 respectively (p>0.05). The differences of OKS, VAS, SF-36 PCS and SF-36 MCS between the groups were not found to be statistically significant. The function scores of each group were shown in Table 3.

Discussion

The overall results of the current study support that clinical outcome after TKR is not related to the BMI in overweight and obese individuals at mid-term.

Table 2. Clinicodemographic data of groups

		Overweight	Class 1 Obese	Class 2 Obese	P value
Mean age		67±4.1	64.7±3.3	62.8±3.7	[a]0.02
Mean BMI		27.3±1.3	32.2±1.4	37.9±1	[b]<0.001
Mean Follow-up period (month)		90±13	80.9±13.6	84.5±19.8	[b]0.68
		n	n	n	
Gender	Female	19	21	23	[c]0.14
	Male	3	4	0	
Operation side	Right	11	13	13	[d]0.90
	Left	11	12	10	

[a]One way ANOVA Test, [b]Kruskal Wallis Test, [c]Fisher Freeman-Halton Test, [d]Pearson Chi-Square Test

Table 3. Function scores of the groups

	Overweight	Class 1 Obese	Class 2 Obese	P value
OKS (Mean±Sd)	35.8±7.7	37.1±8.2	33.5±7.4	[b]0.93
VAS (Mean±Sd)	2.9±2.3	2.8±1.8	3.8±2.1	[b]0.14
SF-36 PCS (Mean±Sd)	38.5±10	39.9±9.7	35.9±9.1	[b]0.33
SF-36 MCS (Mean±Sd)	46.2±10.1	45.4±11.5	44.4±11	[a]0.85

[a]One-way ANOVA Test, [b]Kruskal Wallis Test

There is a debate in the literature regarding the influence of BMI on clinical outcomes after TKR. Several short-term studies showed no difference in clinical outcomes between obese and non-obese individuals [20,21]. Other studies with a mid-term or longer follow-up were also unable to demonstrate inferior results in obese patients [15,16,22].

However, Foran et al. reported that obese patients with BMI >30 showed inferior Knee Society Score and higher revision rates at 15 years after TKR [13]. Similarly, Jackson et al. found significantly lower post-operative total clinical scores in obese patients after cementless TKR at mean 9.2 years [14]. On the other hand, a greater decrease in clinical scores was reported in the morbidly obese group, and these patients were advised to lose weight before the surgery [11].

To our knowledge only one study compared the clinical outcomes after TKR by classifying the patients as overweight, class 1 obese, class 2 obese and class 3 obese like our study method as recommended by WHO. O'Neill et al. reviewed 2180 TKR, and in contrast to our results, they demonstrated significantly inferior scores in class 2 obese patients compared to both overweight and class 1 obese patients [18]. Although a small number of the patients limits the power of our study, the results of our study are more reliable when considering our mid-term (84 months=7 years) follow-up period compared to their only mean 19 months follow-up.

Collins et al. also evaluated 445 TKR with considering the overweight patients in non-obese group and dividing the obese group as mildly obese (BMI 30 to 35) and highly obese (BMI>35), then they reported significantly poorer results in highly obese group compared to non-obese and mildly obese group [23]. They used only KSS for clinical evaluation, whereas multiple scores including OKS, VAS, and SF-36 were used for evaluation of clinical outcomes in our study.

The patients who had had a higher BMI needed TKR at a younger age in our study. Similarly, Guanther et al. reported that the overweight, class 1 obese and class 2 obese patients underwent total joint replacement surgery at the mean age of 68, 65 and 64 respectively [10]. Thus, can also provide the evidence that obesity is a risk factor for the development of knee osteoarthritis [4-6].

The major limitation of the current study is its retrospective design. The second limitation can be stated as our mid-term follow-up period. This is particularly important about the development of aseptic loosening, implant failures and subsequent need for revision surgery. Although similar revision rates and good clinical outcomes were reported in both obese and non-obese patients in 10 years follow-up, there is doubt in longer period results [22].

This study only included the obese patients with BMIs between 30 and 40. Our results would be more reliable and powerful whether we could perform the statistical comparison of class 3 obese patients with BMIs over 40. Nevertheless, we revealed that TKR can be carried out in obese whose BMIs between 30 and 40 with results similar to those performed in overweight individuals.

In summary, it was demonstrated that clinical outcome after TKR is not related to patient's BMI at mean seven years follow-up. We recommend starting diet programs with the surgery, instead of denying the obese patients for TKR.

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Conflict of interest

The authors declare that they have no conflict of interest regarding the submission and publication of this manuscript

Animal and human rights statements

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Clinical significance of non-diphtheria corynebacterium in geriatric patients

Geriatrik hastalarda difteri olmayan korineform bakterilerin klinik önemi

Corynebacterium

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Öz

Amaç: Difteri olmayan Korinebakteriumlar; Difteroidler ve Korineformlar, genellikle kolonize yada kontamine olarak değerlendirilirler. Hastanemizin mikrobiyoloji laboratuvarında izole edilen korineform bakterileri hastanın klinik durumu ile birlikte değerlendirerek bu bakterilerin klinik önemini vurgulamayı amaçlıyoruz. Gereç ve Yöntem: Hastanemizin Tıbbi Mikrobiyoloji Laboratuvarına gönderilen çeşitli klinik örnekler Gram boyalı prepatlar ve kültür ekimi ile değerlendirildi. Gram boya mikroskopik incelemesinde polimorfonükleer nötrofiller ve Gram pozitif basiller görülmesi ile kültür plağında saf ve dominant üreme etken olarak değerlendirildi. Kan kültüründe 2 kez yada daha fazla aynı etken üremesi enfeksiyöz ajanlar olarak kabul edilirken, bu kriterlerin karşılanmadığı örnekler kontaminasyon veya kolonizasyon olarak rapor edildi. Hastaların yaş ortalaması 68.46 (47 ile 89 arasında) idi. C. jeikeium, 3 hastadan alınan kan kültürlerinden izole edildi. C. striatum, iki hastanın yara kültürlerinden, iki hastanın bronşiyal aspiratlarında ve bir hastanın kan kültürlerinden izole edildi. C. urealiticum iki hastanın idrar kültüründe (105Cfu/ml) izole edildi. C. amycolatum bir hastanın yarasında, C. minutissimum iki hastanın yarası, bir hastanın kulağı ve bir hastanın kateterinden izole edildi. Bulgular: Hızlı taksonomik değişiklikler nedeniyle Korinebakterium türlerinin belirlenmesi zor olabilir. Bu mikroorganizmaların duyarlılık testleri henüz standart değildir. Ancak giderek artan klinik önemi nedeniyle bu bakteriler hakkındaki veriler toplanmaktadır. Difteri olmayan Korinebakteriumlar özellikle geriatric hastalarda ciddi enfeksiyonlara neden olan önemli patojenler olarak ortaya çıkmıştır.

Anahtar Kelimeler

Korineform Bakteriler; Geriatrik Hastalar

Abstract

Aim: Non-diphtheria corynebacteria are referred as diphtheroid and coryneform, and can be considered as 'colonizers' and contaminants. We aim to evaluate the coryneform bacteria isolated in our hospital's microbiology laboratory together with the patient's clinical status. Material and Method: Various clinical samples sent to our hospital's Medical Microbiology Laboratory were Gram stained and cultured in agars. The strains with polymorphonuclear neutrophils and gram-positive bacilli on Gram stain, dominant or absolute growth in culture and growth in the repeated blood cultures were regarded as infectious agents while bacterial growths are not completing those criteria were reported as contamination or colonization. The mean age of the patients was 68.46 (between 47 and 89). C. jeikeium was isolated from blood cultures from 3 patients. C. striatum was isolated from wound cultures of 2 patients, in the bronchial aspirates of 2 patients and in the blood cultures of 1 patient. C. urealyticum was isolated from pre-diagnosed cystitis from 2 patients (105Cfu/ml). C. amycolatum was isolated from wound cultures of 1 patient, and C. minutissimum was isolated from 2 patient's wounds, one patient's ear and one patient's catheter and wound. Result: Identification of Corynebacterium species can be difficult because of rapid taxonomic changes. Susceptibility testing of these micro-organisms is not yet standardized. However because of their growing clinical importance, data on these bacteria are accumulating. Non-Diphtheria corynebacteria have emerged as important pathogens causing many serious infections.

Keywords

Corynebacterium; Geriatric Patients

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Introduction

Corynebacterium species, or "diphtheroids", are aerobic, non-spore forming, pleomorphic, Gram-positive bacilli. Non-diphtheria corynebacteria are referred to as diphteroids and coryneforms and can be considered as 'colonizers' and contaminants [1,2]. Nevertheless, the ability of these bacteria to cause life-threatening disease is well established, and over the last decade, there have been increasing reports of their pathogenic potential in numerous clinical scenarios. Including bacteremia and endocarditis [1]. Several species such as ***C. xerosis, C. amycolatum, C. striatum, C. minutissimum, C. pseudodiphtheriticum, C. matruchotii, C. aquaticum, C. genitalium***, and ***C. pseudogenitalium*** have been related to human infections. Coryneform bacteria exist commensally in the soil, water, human, and animal mucosa and on the skin. Coryneform bacteria other than Corynebacterium diphtheria are often isolated from clinical samples and regarded as contamination. However, after they began to be identified, it has been realized that they are an agent of important infection of geriatric patients and hospital infections. This study aims to emphasize the clinical significance of coryneform bacteria and to draw attention to the problems arising in microbiological diagnosis because coryneform bacteria mostly are not considered as contamination and ruled out. It is quite difficult to determine whether this bacterium is an agent or contaminant; We aim to evaluate the coryneform bacteria isolated in our hospital's microbiology laboratory together with the patient's clinical status.

Material and Method

Various clinical samples sent to our hospital's Medical Microbiology Laboratory were Gram stained, and cultured in agars. The strains with polymorphonuclear neutrophils and Gram-positive bacilli on Gram stain, dominant or absolute growth in culture and growth in the repeated blood cultures were regarded as infectious agents while bacterial growths are not completing those criteria were reported as contamination or colonization. Isolates of Corynebacterium obtained from catheters (≤15 CFU by the rollingplate method), urine culture (>105 CFU/mL) and predominant culture from wound exudates and bronchial aspirates were considered potentially significant. Identification of the agents at stain level was performed with Vitek MS (bioMerieux, France) system.

Results

The mean age of the patients was 68.46 (between 47 and 89). ***C. jeikeium*** was isolated from blood cultures from 3 patients. ***C. striatum*** was isolated from wound cultures of 2 patients, in the bronchial aspirates of 2 patients and in the blood cultures of 1 patient. ***C. urealyticum*** was isolated from pre-diagnosed cystitis from 2 patients. ***C. amycolatum*** was isolated wound cultures of 1 patient, and ***C. minutissimum*** was isolated from 2 patient's wounds, 1 patient's ear and 1 patient's catheter and wound (Table 1).

Discussion

After much discussion and confusion about their clinical significance, coryneforms have emerged as important pathogens [3]. It is quite difficult to determine whether this bacterium is an agent or contaminant; It must be taken into consideration that coryneform bacteria, which are generally regarded as contamination and as diphtheroids in gram staining, can be an opportunistic pathogen in patients with risk factors such as a compromised immune system and staying in the intensive care unit in addition to a long-term antibiotic treatment history. That the same coryneform bacterium grew in more than one clinical sample and that dense granular leukocyte or intensive shaped leukocyte and coryneform bacteria were seen in Gram staining is an indication that this situation can be clinically significant.

C. striatum survives as a saprophyte on the skin and mucous membranes of asymptomatic individuals. Corynebacterium striatum is an agent of endocarditis and pneumonia and infects surgical wounds. Many hospital-acquired epidemics and osteomyelitis are caused by C. striatum [4]. In addition, meningitis [5], shunt infection [6], endocarditis [7] and peritonitis [8], keratitis [9] cases have been reported [10,11,12]. In a study by Renom et al., ***C. striatum*** was isolated from the sputum samples of 21 patients with a chronic obstructive respiratory disease, and it was reported hat this isolate can colonize the respiratory tracts of chronic obstructive respiratory disease patients and causes hospital-acquired infections by spreading from person to person [12]. Similarly, Tarr et al. detected ***C. striatum*** growth in the bronchoalveolar lavage (BAL) and sputum cultures of a 58-year-old male patient diagnosed with bilateral pneumonia three months after undergoing a heart transplantation; they showed that the pneumonia was reduced after four weeks of vancomycin treatment. While ***C. striatum*** growth is mostly regarded as contamination, one study indicated that it can be considered a pathogen in immunocompromised patients with a prolonged hospitalization history undergoing long-term antibiotic treatment [13]. In general, cell renewal decelerates in geriatric patients, and they tend to be open to various infections. Reunes et al. found the Corynebacterium spp. isolation rate to be 0.6% (1/155) in a study conducted on geriatric patients with bloodstream infections [14]. The agent must be identified at type level in case bacterial growth occurs in blood cultures taken in at least two different periods. That these bacteria were isolated from the respiratory tract and blood samples simultaneously and that the same agent was detected in repeated blood samples for analyzing the bacteremia accompanying the pneumonia observed in one patient made us think that ***C. striatum*** is highly likely to be the agent. Proven infections have been found most commonly in the setting of immunocompromised patients with respiratory infections, recurrent or continuous instrumentation, chronic ulcers or surgery [11,15]. The nosocomial person-to-person spread has been documented twice [16]. Septic arthritis has been reported in the setting of joint replacement surgery and after accidental scalpel laceration [17]. In the case reported here, several factors enhanced the patient's risk of infection with ***C. striatum***, including an immune system compromised by age and failing health, prolonged institutionalization, the presence of chronic ulcers, the occurrence of pneumonia, a reported blunt trauma to the knee when he fell, and osteoarthritis in the involved knee [2,11,15,18]. In this case, the infecting organism is most likely to have gained access to the patient's circulation either through the respiratory tract, perhaps during his pneumonia, or through his persistent and

Table 1. Clinical distribution of patients

Case	Gender	Age	Patient's diagnosis	Clinic	Culture material	Bacterial growth	The number of sets where growing occurred
1	F	64	Lower respiratory tract infection	Intensive Care Unit	Tracheal aspirate 100.000 cfu/ml	C. striatum (Leukocytes and gram-positive bacilli)	
2	M	78	Lower respiratory tract infection	Intensive Care Unit	Tracheal aspirate 100.000 cfu/ml	C. striatum (Leukocytes and gram-positive bacilli)	
3	F	74	Lower respiratory tract infection	Intensive Care Unit	sputum	C. striatum (Leukocytes and gram-positive bacilli)	
4	M	82	DM + soft tissue infection	Infectious Diseases	Wound	C. striatum (agent) (Abundant leukocytes, gram-positive bacilli)	
5	M	62	Acute lymphadenitis	General Surgery	Wound	C. striatum (agent) (Abundant leukocytes, gram-positive bacilli)	
6	F	88	Bowel bypass anastomosis	Surgery site infection	Blood	C. striatum (agent)	2
7	M	47	Lung malignancy	Pulmonology	Blood	C. jeikeium(agent?)	1
8	F	67	DM+ diabetic foot	Internal Diseases	Blood	C. jeikeium (agent?)	1
9	F	89	Pneumonia	Pulmonology	Blood	C. jeikeium (agent?)	1
10	F	66	Cystitis	Urology	Urine	C. urealyticum (agent) 10^5 cfu/ml growth	
11	M	49	Soft tissue infection	Urology	Wound	C. amycolatum (agent) (Abundant leukocytes, gram-positive bacilli)	
12	M	68	DM + osteomyelitis	Infectious Diseases	Wound Culture	C. minutissimum (agent)	
13	F	55	Otitis media	Ear Nose and Throat (ENT)	Ear	C. minutissimum (agent) (Rare leukocytes, epithelial cells, gram-positive bacilli)	
14	F	63	DM + diabetic foot	Infectious Diseases	Wound	C. minutissimum (agent) (Abundant leukocytes, gram-positive bacilli)	
15	F	75	Coronary failure, soft tissue infection	Internal Diseases	Catheter + Wound	C. minutissimum (agent) (Leukocytes and gram-positive bacilli)	

open venostasis ulcers. This case highlights both the growing importance of C. striatum as a nosocomial pathogen, and the difficulty microbiology laboratories may encounter when trying to identify this species. It is likely that the number and range of clinically important infections with this organism have been underestimated. The first recognized spontaneous infection of a natural joint with ***C. striatum*** is reported here, in our study, was isolated from three patients with pulmonary infections, tracheal aspirates were identified as causative pathogen. One patient was isolated from the Diabetic foot wounds. It was isolated from a patient with acute lymphadenitis. Also, a patient has also caused a surgical site infection (Table 1).

C. jeikeium colonizes especially the skin floras of the inguinal, axillar and rectal areas of hospitalized patients. It is evaluated as contamination, but it also plays a role as a slightly pathogenic agent. Various infections caused by ***C. jeikeium*** are septicemia, meningitis, peritonitis, foreign body infections, osteomyelitis, pneumonitis, and endocarditis. ***C. jeikeium*** causes hematologic and catheter infections. Infections are mostly observed in patients with nosocomial infections, those with malignity and neutropenia and in patients who are hospitalized for a prolonged duration [19,20,21,22]. Since it has become possible to identify these isolates, there has been an increase in the occurrence rates of these bacteria [2].

In our study, two geriatric and immunosuppressed patients who had a pulmonary infection had growth on their blood culture. It has also been isolated from diabetic foot wounds (Table 1).

C. amycolatum causes endocarditis, pneumonia, and skin, soft tissue, and catheter infections. It also causes urinary tract infection and the development of kidney stones because of the strong activity of its urease enzyme. In our study, one patient was isolated from the wound tissue of a patient with soft tissue infection (Table 1).

C. urealyticum is a urinary system pathogen and causes the occurrence of kidney stones by producing strong urease. In our study, urinary tract infection was seen as affecting (Table 1).

C. minutissimum causes erythrasma infection in healthy people by colonizing the skin. Although this infection is most frequently formed by ***C. minutissimum***, it can also be caused by other Corynebacterium species. ***C.minutissimum*** can also be an agent of endocarditis, catheter infection, and peritonitis in peritoneal dialysis patients. Invasive ***C. minutissimum*** infection usually occurs in immunocompromised patients and/or patients with skin disruption due to surgery or indwelling devices, such as a central venous catheter or a peritoneal dialysis catheter [23,24]. Although the source of infection was unknown, skin disruption by surgery and a drainage catheter might have contributed to the development of invasive ***C. minutissimum*** infection in this patient. In conclusion, given an increasing number of cases with ***non-diphtheria Corynebacterium*** as an agent of serious opportunistic infection in immunocompromised patients and the more common use of indwelling devices causing a breach in the skin barrier [24,25]. Clinicians would be wise to keep this organism in mind as a rare cause of post-surgical abdominal infection. In our study, it was isolated as an osteomyelitis-affecting effect in a diabetic patient. It was also isolated from a diabetic

foot wound. It was isolated in a wound and catheter culture of a patient with coronary artery insufficiency. Otitis media was also seen as effective (Table 1).

Identification of ***Corynebacterium*** species can be difficult because of rapid taxonomic changes. Susceptibility testing of these micro-organisms is not yet standardized. However because of their growing clinical importance, data on these bacteria are accumulating. After decades of confusion on their clinical significance, non-diphtheria corynebacteria have emerged as important pathogens causing many serious infections.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

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Human Rights Statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Animal Rights Statement

Nonapplicable.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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Evaluation of intensive care performance in hospitals

Hastanelerde yoğun bakım servislerinin performanslarının değerlendirilmesi

Intensive care performance

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Öz

Amaç: Bu çalışmanın amacı, Kocaeli ili merkez ve ilçelerinde yer alan kamu hastanelerinin yoğun bakım servislerinin performansları açısından değerlendirilmesi ve karşılaştırılmasıdır. Gereç ve Yöntem: Bu amacı gerçekleştirmek için toplam 9 hastanenin 2016 yılına ait yoğun bakım verileri gri ilişkisel analiz yöntemiyle değerlendirilmiştir. Bulgular: Yapılan analiz sonucunda; yoğun bakım mortalite oranının en düşük olduğu; ventilatör başına bağlı kalan hasta sayısının, ventilatör başına bağlı kalınan gün sayısının, yoğun bakım yatağı başına yatılan gün sayısının, yoğun bakım yatağı başına taburcu edilen hasta sayısının, hemşire başına yoğun bakımdan taburcu edilen hasta sayısının ve yatak doluluk oranının en yüksek olduğu birinci sıradaki hastane 0,77 gri ilişkisel derece ile A Hastanesi olmuştur. Tartışma: Bu araştırmada kullanılan gri analiz yönteminin farklı hastanelerin yoğun bakım ünitelerinin performanslarını karşılaştırmak için kullanılabileceği gösterilmiştir.

Anahtar Kelimeler

Yoğun Bakım; Performans; Gri İlişkisel Analiz; Hastane

Abstract

Aim: The purpose of this study is to evaluate and compare the performances of intensive care units in public hospitals located in Kocaeli province (its central district and other districts). Material and Method: To this end, the intensive care data of nine hospitals from the year 2016 were evaluated through grey relational analysis method. Results: At end of the analysis, Hospital A was found to have the intensive care with the highest grey relational degree (0.77): the lowest intensive care mortality rate, the biggest number of; patient dependent on each ventilator, days with a patient dependent on each ventilator, days with a patient hospitalized per intensive care bed, patients discharged per intensive care bed, patients discharged from intensive care per nurse, and the highest occupancy rate. Discussion: It was revealed that grey analysis method applied in the present study can be used for comparing the intensive care units of different hospitals as well.

Keywords

Intensive Care; Performance; Grey Relational Analysis; Hospital

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Introduction

An intensive care unit (ICU) is a department of a hospital that uses the most advanced technology for critical patients and high-risk patients and provides aggressive treatments by use of invasive and noninvasive interventions [1]. Recently, a fast, considerable increase has taken place in the number of intensive care beds in Turkey. According to the most recent statistics published by the Ministry of Health, total number of intensive care beds which was 20,977 in 2011 (The Ministry of Health + university + private hospitals) rose to 31,525 in 2015 [2]. Given the current increase and costs, efficient and effective service offered in intensive care units has become a priority issue for health managers, especially in the context of use of resources. Also, performance measurement and financial incentives are highly interrelated in the field of health care services [3-4].

Performance measurement is an instrument used for monitoring and controlling organizational activities for establishments and units to accomplish the predetermined objectives [5]. Performance is measured by evaluating the effectiveness and efficiency of the activities conducted [6]. The present study specifically focuses on performance measurement in intensive care units. The literature review shows that the performance of intensive care units are measured through diagnostic scoring systems such as "Acute Physiology and Chronic Health Evaluation (APACHE)" [7-8]; "Simplified Acute Physiology Score (SAPS)" [9-10-11], or "Mortality Prediction Model (MPM)" [12-13] as well as "Analytical Hierarchy Process (AHP)" [14] and "Data Envelopment Analysis (DEA)" [15-16]. Diagnostic scoring systems involve logistic regression equations that make mortality estimates for case mixes in specific intensive care units. In these studies, the ratio of estimated mortality to observed mortality (standardized mortality ratio - SMR) was used for comparing the performances of different intensive care units [32]. AHP employs a multidimensional quantitative performance measurement model [14]. Apart from these methods, data envelopment analysis, TOPSIS, and grey relational analysis are among the multi-criteria decision-making methods that can be used.

Grey relational analysis technique was deemed suitable for the present study because the number of the variables used was small, and evaluation criteria were based on maximum or minimum rather than input and output approach. Also, grey relational analysis technique is frequently adopted when the sample is small, and there is not enough information about the sample. With the use of this method, the study aimed to evaluate and compare the performances of intensive care units of nine public hospitals providing service in Kocaeli province.

Grey Relational Analysis

Grey relational analysis (GRA) is a relatively new analysis method that was developed by Professor Deng Julong Huazhong in the People's Republic of China based on the grey system theory. The main point of GRA is to find a grey relational order that can be used for defining the relationships between the relevant factors depending on data series. When sample size is not large enough, GRA can be used instead of linear relationship and typical distribution [17].

Systems with imperfect information are defined as grey systems. The application purpose of the grey system is to lay a bridge between social sciences and natural sciences. Thus, it is possible to say that it is a point of intersection for different disciplines. The grey system theory is applied in a variety of fields such as agriculture, ecology, economy, management, history, geography, and law [18]. The number of studies employing grey analysis in the field of heath care services is rapidly increasing as well [17-19-20-21-22].

The grey system theory focuses on problems that have a small sample and involve insufficient information. According to Professor Julong Deng, its founder, the system has six basic principles: information differences, non-uniqueness, minimal information, recognition base, new information priority, and absolute greyness [23]. GRA, which is part of the grey system theory, is a multi-criteria decision-making technique that allows measuring the relationship and ordering depending on the degree of similarity or difference of the trends between the components [24]. The steps to be followed for ordering the alternatives through GRA are presented below [25].

Step 1. Creating the reference series

$$x_0 = \left(x_0(1),\ x_0(2),\ x_0(3) \dots, x_0(j) \dots, x_0(n)\right)$$

j referring to units and x_i referring to comparison series

$$\left(x_i(1),\ x_i(2) \dots, x_i(j) \dots, x_i(n)\right), \text{i= 1,2,3…m}$$

x_i comparison series can be expressed by use of matrix form as follows;

$$X_i = \begin{bmatrix} x_1(1) & \dots & x_1(n) \\ \vdots & \dots & \vdots \\ x_n(1) & \dots & x_m(n) \end{bmatrix}$$

Step 2. Normalizing the dataset

A dataset can be evaluated in three different ways: 1) the approach in which the maximum score is better; 2) the approach in which the minimum score is better; and 3) the approach in which the ideal value is better. There are different formulations of normalization for each type.

max χ_i (j): The maximum value in the unit subject to ordering
max $\chi_i^{(j)}$ (j):: The minimum value in the unit subject to ordering
x 0b (j): The ideal value to be determined for the unit subject to ordering

The conversion formula in which higher scores are accepted better

$$x_i'(j) = \frac{x_i\ \ (j) - \min x_i^{(j)}(j)}{\max x_i^{(j)}(j) - \min x_i^{(j)}(j)} \qquad (1)$$

The conversion formula in which lower scores are accepted better

$$x_i'(j) = \frac{max\ x_i^{(0)}(j) - x_i^{(\ \ )}(j)}{\max x_i{}^j(j) - \min x_i^{(j)}(j)} \qquad (2)$$

The conversion formula in which the ideal score is accepted better

$$x_i'(j) = \frac{x_i^{(0)}(j) - x\,0b \quad (j)}{\max x_i{}^j(j) - \mathrm{x}\,0b \quad (j)} \qquad (3)$$

Also, the reference series values are normalized through the formula mentioned above. Following the normalization process, the data matrix turns out to be as follows:

$$X'_i = \begin{bmatrix} x'_1(1) & \dots & x'_1(n) \\ \vdots & \dots & \vdots \\ x'_n(1) & \dots & x_{,m}(n) \end{bmatrix}$$

Step 3. Creating the absolute value table

In this step, the absolute value Δ_{0i} (j) of the difference between x'_0 and x'_i is calculated.

$$\Delta_{0i}(j) = |x'_0(j) - x'_i(j)|$$

$$= \begin{bmatrix} \Delta_{01}(1) & \dots & \Delta_{01}(n) \\ \vdots & \dots & \vdots \\ \Delta_{0m}(1) & \dots & \Delta_{0m}(n) \end{bmatrix}$$

Step 4. Calculating the grey relational coefficient

The following formula is applied for calculating the grey relational analysis coefficient:

$$\gamma 0i(j) = \frac{\Delta_{min} + \delta\Delta_{max}}{\Delta_{0i}(j) + \delta\Delta_{max\wedge}}$$

Δ max= $\max_i \max_j \Delta_{0i}(j)$, Δ min= $\min_i \min_j \Delta_{0i}(j)$ and $\delta \in [0,1]$

Step 5. Calculating the grey relational degree

$$r(0i) = \frac{1}{n}\sum_{j=1}^{n} \gamma\left(x_0(j), x_i(j)\right)$$

$r(x_0, x_i)$ indicates the grey relational degree between and . The alternative having the highest grey relational degree with the reference series will be the series having the most similarity to the reference series, and so it will be the best option.

If weight is to be applied to evaluation criteria, the formula will be as follows:

$$r(0i) = \sum_{j=1}^{n} [Wi(j) * r0i(j)]$$

Material and Method

The population of the study consists of 11 public hospitals affiliated to Kocaeli Union of Public Hospitals. However, as two of them did not have data about intensive care use, the data of nine hospitals were included in the evaluation. The data of the study cover the period from January 2016 to December 2016. The performance criteria used in the study are as follows:

- the number of patients dependent on each ventilator,
- the number of days with a patient dependent on each ventilator,
- the number of days with a patient hospitalized per intensive care bed,
- the number of patients discharged per intensive care bed,
- the number of patients discharged from intensive care per nurse,
- total number of patients who died in intensive care unit
- intensive care occupancy rate,
- intensive care mortality rate.

Among these criteria, intensive care mortality rate was wished to be low, whereas others were wished to be high or big. The data of the study were analyzed via MS. Office Excel.

Results

Table 1 presents the hospitals whose intensive care units were put in order of performance regarding the criteria determined through the grey system approach and the reference values.

Normalization was made to prevent vast differences between the scores of the hospitals evaluated concerning the comparison criteria. While intensive care mortality rate was normalized through the second formula in Table 2, other criteria were normalized by the first formula.

Table 3 presents the values obtained through calculation of the absolute differences between the normalized reference series value and the normalized alternative values. The formula in the third step was used in calculations.

The values in Table 4 were obtained through the formula in the fourth step.

Δ max = 1 and Δ min = 0

γ coefficient was taken as 0.5 in accordance with the literature.

Table 5 presents the grey relational degree scores obtained through grey relational coefficients and ordering (from large to small) based on these scores. According to the ordering obtained, Hospital A was found to have the intensive care with the highest grey relational degree (0.77): the lowest intensive care mortality rate, the biggest number of; patients dependent on each ventilator, days with a patient dependent on each ventilator, days with a patient hospitalized per intensive care bed,

Table 1. Dataset and reference values of hospitals performance criteria

	Maks	Maks	Maks	Maks	Maks	Maks	Maks	Min
	The number of patients dependent on each ventilator	The number of days with a patient dependent on each ventilator	The number of days with a patient hospitalized per intensive care bed	The number of patients discharged per intensive care bed	The number of patients discharged from intensive care per nurse	Total number of patients who died in intensive care unit	Intensive care occupancy rate	Intensive care mortality rate
Reference	68.28	260.82	371.12	60.67	53.85	595.00	101.68	0.08
Hospital A	68.28	225.12	371.12	49.05	39.79	595.00	101.68	0.24
Hospital B	36.55	245.65	339.12	45.12	26.23	255.00	92.91	0.23
Hospital C	22.18	233.27	331.84	36.42	27.68	128.00	90.92	0.20
Hospital D	24.77	107.85	321.29	45.71	32.00	230.00	88.02	0.38
Hospital E	62.18	260.82	313.37	60.67	37.23	216.00	85.85	0.16
Hospital F	3.00	24.00	74.83	9.33	11.20	7.00	20.50	0.12
Hospital G	0.67	2.33	151.50	23.25	18.60	12.00	41.51	0.12
Hospital H	39.21	38.02	264.42	55.23	53.85	459.00	72.44	0.08

Table 2. Normalized values

	The number of patients dependent on each ventilator	The number of days with a patient dependent on each ventilator	The number of days with a patient hospitalized per intensive care bed	The number of patients discharged per intensive care bed	The number of patients discharged from intensive care per nurse	Total number of patients who died in intensive care unit	Intensive care occupancy rate	Intensive care mortality rate
Reference	1	1	1	1	1	1	1	1
Hospital A	1.00	0.86	1.00	0.77	0.67	1.00	0.00	1.00
Hospital B	0.53	0.94	0.89	0.70	0.35	0.42	0.11	0.53
Hospital C	0.32	0.89	0.87	0.53	0.39	0.21	0.13	0.32
Hospital D	0.36	0.41	0.83	0.71	0.49	0.38	0.17	0.36
Hospital E	0.91	1.00	0.81	1.00	0.61	0.36	0.19	0.91
Hospital F	0.03	0.08	0.00	0.00	0.00	0.00	1.00	0.03
Hospital G	0.00	0.00	0.26	0.27	0.17	0.01	0.74	0.00
Hospital H	0.57	0.14	0.64	0.89	1.00	0.77	0.36	0.57

Table 3. Absolute value table

	The number of patients dependent on each ventilator	The number of days with a patient dependent on each ventilator	The number of days with a patient hospitalized per intensive care bed	The number of patients discharged per intensive care bed	The number of patients discharged from intensive care per nurse	Total number of patients who died in intensive care unit	Intensive care occupancy rate	Intensive care mortality rate
Hospital A	0.00	0.14	0.00	0.23	0.33	0.00	1.00	0.00
Hospital B	0.47	0.06	0.11	0.30	0.65	0.58	0.89	0.47
Hospital C	0.68	0.11	0.13	0.47	0.61	0.79	0.87	0.68
Hospital D	0.64	0.59	0.17	0.29	0.51	0.62	0.83	0.64
Hospital E	0.09	0.00	0.19	0.00	0.39	0.64	0.81	0.09
Hospital F	0.97	0.92	1.00	1.00	1.00	1.00	0.00	0.97
Hospital G	1.00	1.00	0.74	0.73	0.83	0.99	0.26	1.00
Hospital H	0.43	0.86	0.36	0.11	0.00	0.23	0.64	0.43

Table 4. Gray relational data table (criteria equal weighted)

	The number of patients dependent on each ventilator	The number of days with a patient dependent on each ventilator	The number of days with a patient hospitalized per intensive care bed	The number of patients discharged per intensive care bed	The number of patients discharged from intensive care per nurse	Total number of patients who died in intensive care unit	Intensive care occupancy rate	Intensive care mortality rate	The number of patients dependent on each ventilator
Hospital A	1.00	0.78	1.00	0.69	0.60	1.00	0.33	1.00	0.77
Hospital B	0.52	0.89	0.82	0.62	0.44	0.46	0.36	0.52	0.59
Hospital C	0.42	0.82	0.79	0.51	0,45	0.39	0.37	0.42	0.54
Hospital D	0.44	0.46	0.75	0.63	0.49	0.45	0.38	0.44	0.51
Hospital E	0.85	1.00	0.72	1.00	0.56	0.44	0.38	0.85	0.71
Hospital F	0.34	0.35	0.33	0.33	0.33	0.33	1.00	0.34	0.43
Hospital G	0.33	0.33	0.40	0.41	0.38	0.34	0.66	0.33	0.41
Hospital H	0.54	0.37	0.58	0.83	1.00	0.68	0.44	0.54	0.63

Table 5. Sort of hospitals by gray relational Degree

	Grey relational degree	Sorting
Hospital A	0.77	1
Hospital B	0.59	4
Hospital C	0.54	5
Hospital D	0.51	6
Hospital E	0.71	2
Hospital F	0.43	7
Hospital G	0.41	8
Hospital H	0.63	3

patients discharged per intensive care bed, patients discharged from intensive care per nurse, and the highest occupancy rate. The hospital with the lowest grey relational degree (0.41) was found to be Hospital G. No weighting was done as equal importance was attached to all the performance criteria during ordering.

Discussion

In health care services, effectiveness is the measure of to what extent patients' needs are met, while efficiency is the measure of how economically the resources of an establishment are used for ensuring a particular level of patient satisfaction; that is, efficiency is about the use of resources and costs, whereas effectiveness is about reaching the best clinical results in the units where patients are served. Measures of effectiveness and efficiency are two important parts of performance evaluation. In the present study, the performances of the intensive care units of hospitals providing service in Kocaeli province were evaluated and compared regarding clinical results and use of resources.

Duration of hospitalization in a hospital or intensive care is a suitable measure of use of resources, which is commonly employed [26-27-28-29-30]. Examining mortality rates and durations of staying in intensive care together brings synergy to the evaluation of the effectiveness of intensive care units. Mortality rates may stand as an indicator of clinical performance, and a patient's duration of staying in intensive care may be an indicator of use of resources. When they are evaluated together, the efficiency of a unit may be showed [30]. In the present study, in addition to the measures of duration of staying in intensive care as to the use of resources (the number of days with a patient hospitalized per intensive care bed, the number of patients discharged per intensive care bed, intensive care occupancy rate), the use of ventilator in intensive care (the number of patients dependent on each ventilator) and the number of nurses (the number of patients discharged from intensive care per nurse) were included in evaluation. Moreover, as a negative value, mortality rates were examined for each intensive care unit. The data from the last one-year period were analyzed for each intensive care unit.

According to the results obtained from the analyses, when the performances of the intensive care units were ordered in terms of the criteria determined, Hospital A was seen to rank first with the biggest number of; patients dependent on each ventilator, days with a patient dependent on each ventilator, days with a patient hospitalized per intensive care bed, patients discharged per intensive care bed, patients discharged from intensive care

per nurse, the highest occupancy rate, and the lowest mortality rate (grey relational degree: 0.77).

As the results of the present study allow the comparison of the performances of intensive care units of health establishments, they will be guiding for future efforts for improvement and development. Furthermore, these kinds of studies provide information to establishments providing health care services and their managers so that they can check and monitor the performances of intensive care units. As grey analysis was adopted for data evaluation in the present study, the case mix of the patients admitted to intensive care and the differences in institutional factors were not taken into consideration, and no risk adjustments were made for them. We recommend making these kinds of risk adjustments for mortality rates that are to be used for evaluating intensive care performance in future research.

The main purpose of performance measurement system is to ensure continuous improvement and enhance organizational performance. Choosing appropriate factors (sub-factors and factors under them), using a suitable quantitative measurement framework, and employing clear methodological steps for practices are critically important to achieve success in this regard. It was revealed that grey analysis method applied in the present study can be used for comparing the intensive care units of different hospitals as well.

The results of this study have limitations on generalization to all intensive care units. The sample of the study consists of intensive care units in public hospitals and Kocaeli province. And also, the research only covers one year period. Future studies with larger samples and wider time periods are expected to produce more effective results.

Compliance with Ethical Standards

Funding: None

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

Ethical Approval

Not required for this study. However written permission was received from Kocaeli Union of Public Hospitals before the investigation.

Competing interests

The authors declare that they have no competing interests.

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Effect of palmatine on periodontal tissue destruction in experimental periodontitis rat model

Deneysel periodontitis rat modelinde palmatinin periodontal doku yıkımı üzerine etkisi

Effect of palmatine on periodontium

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Öz

Amaç: Bu çalışmanın amacı deneysel periodontitis (DP) rat modelinde oral olarak uygulanan palmatinin periodonsiyum üzerindeki etkilerini incelemektir. Gereç ve Yöntem: Toplam 40 sıçan, DP oluşturulmayan ve palmatin uygulanmayan (grup 1, CTRL); DP oluşturulan ama palmatin uygulanmayan (grup 2, EP); DP oluşturulan ve 5 mg / kg palmatin uygulanan (grup 3, EP-5P); DP oluşturulan ve 10 mg / kg palmatin uygulanan (grup 4, EP-10P) olmak üzere dört gruba ayrıldı. Deneysel periodontitis, sıçanların sağ mandibular birinci molar dişlerinin servikal kenarlarına 3.0 ipek dikiş yerleştirilerek elde edildi. Alveoler kemik seviyesi (AKS), ataşman seviyesi (AS) ve alveolar kemik alanı (AKA) histomorfometrik yöntem ile incelendi. Receptor activator of nuclear factor kappa-B ligand (RANKL) ve Osteoprotegerin (OPG) immünoreaktivitesi ve RANKL/OPG oranları immünhistokimyasal analiz ile değerlendirildi. Bulgular: Palmatin gruplarındaki alveolar kemik alanı değerleri, EP grubuna göre istatistiksel olarak daha yüksek tespit edildi ($p<0.05$). AKS ve AS değerleri, palmatin gruplarında EP grubuna göre anlamlı olarak daha düşük bulundu ($p<0.05$). AKS, AS ve AKA değerleri için, EP-5P ve EP-10P grupları arasında anlamlı bir fark bulunmadı ($p>0.05$). RANKL / OPG oranı, deney süresi boyunca palmatin ile tedavi edilen gruplarda belirgin olarak daha düşük gözlendi ($p<0.05$). Buna ek olarak, RANKL / OPG oranına göre EP-5P ve EP-10P arasında anlamlı bir fark bulunmadı ($p>0.05$). Tartışma: Palmatinin periodontal hastalıkta alveoler kemik kaybı ve bağ dokusu yıkımı üzerine koruyucu etkisi olabilir.

Anahtar Kelimeler

Periodontal Hastalık; Palmatin; Alveolar Kemik Kaybı

Abstract

Aim: The aim of this study is to examine the effects of orally administered palmatine on periodontium in an experimental periodontitis (EP) rat model. Material and Method: A total of 40 rats were divided into 4 groups as group 1, no EP and no palmatine (CTRL); group 2, EP and no palmatine (EP); group 3, EP and 5mg/kg of palmatine (EP-5P); group 4, EP and 10mg/kg palmatine (EP-10P). Experimental periodontitis was achieved by placing 3.0 silk sutures on the cervical margins of the right mandibular first molar teeth of the rats. The alveolar bone loss, attachment loss and alveolar bone area were evaluated by histomorphometric evaluation. Immunohistochemical evaluation was used to assess the Receptor activator of nuclear factor kappa-B ligand (RANKL) ve osteoprotegerin (OPG) immunoreactivity and RANKL/OPG ratio. Results: Alveolar bone area (ABA) values in palmatine groups were statistically higher than EP group ($p<0.05$). Alveolar bone level (ABL) and attachment level (AL) values were significantly lower in palmatine groups than EP group ($p<0.05$). For ABA, ABL and AL values, no significant difference was found between groups EP-5P and EP-10P ($p>0.05$). According to the RANKL / OPG ratio, a significant decrease was observed in the palmatine-treated groups during the experimental period ($p<0.05$). In addition, there was no significant difference between EP-5P and EP-10P according to RANKL/OPG ratio ($p>0.05$). Discussion: Palmatine might have protective effects on alveolar bone loss and connective tissue destruction in periodontal disease.

Keywords

Periodontal Disease; Palmatine; Alveolar Bone Loss

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Introduction

Periodontal disease (PD) is a chronic inflammatory disease of teeth supporting tissues[1]. Although microbial dental plaque is considered as the primary etiologic factor, the onset and progression of the disease is the result of the inflammatory response of the host. PD is characterized by gingival inflammation, periodontal pocket formation, connective tissue attachment loss, and alveolar bone resorption that may result in tooth loss [2-4].

The osteoclast-derived bone resorption pathway is related to the interaction of the TNF superfamily. As members of this family, Nuclear factor-kB ligand receptor activator (RANKL); its receptor, RANK; and the decoy receptor, osteoprotegerin (OPG). RANK is a cell surface receptor of osteoclast precursor cells and osteoclasts[5]. RANKL is a potent osteoclastogenic factor synthesized by osteoblasts, fibroblasts, lymphocytes, and osteocytes[5,6]. By directly binding to RANK, it leads to osteoclast differentiation and activation, and initiates bone destruction[6,7]. RANKL activity is regulated by OPG produced by bone marrow stromal cells, osteoblasts, and osteocytes[5-7]. OPG binds to RANKL and inhibits RANKL + RANK composition, thus inhibiting osteoclastogenesis and bone destruction[7].

Palmatine is a yellow, protoberberine alkaloid derived from some plants like *Cortex phellodendri* and *Rhizoma coptidis [8]* and is structurally similar to berberine inhibiting bone destruction in osteoporotic models. Palmatine is used in the treatment of hypertension, acute and chronic inflammation, and liver related diseases[9]. By affecting serum RANKL and OPG levels, palmatine is believed to reduce bone destruction due to the anti-resorptive effect[10].

This study is based on the hypothesis that the antiresorptive effect of palmatine may reduce alveolar bone destruction in the periodontal inflammation process and may have a protective effect on periodontal inflammation. The purpose of this study was to investigate the effects of orally administered palmatine on periodontium by evaluating the alveolar bone loss, attachment loss and alveolar bone area and changes in the RANKL/OPG ratio in a ligature-induced experimental periodontitis (EP) model in rats.

Material and Method

Experimental Design:

Study protocol was approved at Bulent Ecevit University Animal Experiments local ethics committee number: 2016-01-06/01. 40 male Sprague-Dawley (SD) rats aged 6-8 weeks (200-250 grams) were used. The weekly weight checks were followed to prevent the rats from not feeding enough. The rats were housed in separate plastic cages in a room with temperature control and a standard lighting cycle, and fed with sufficient water and food. The rats were divided into 5 groups. Accordingly, the groups were organized as; group 1, no EP and no palmatine delivery (control-CTRL); group 2, EP and no palmatine delivery (EP); group 3, EP and 5mg/kg of palmatine (EP-5P); group 4, EP and 10mg/kg palmatine (EP-10P).

Induction of experimental periodontitis:

General anesthesia was administered with intramuscular injection of 3 mg / kg Xylazine HCl (Rompuns; Bayer Leverkusen, Germany) and 35 mg / kg Ketamine HCl (10% Ketasol; Richter Pharma AG, Wels, Austria) to the rats scheduled to develop EP. EP was accomplished by placing 3.0 silk sutures on the cervical margins of the right mandibular first molar teeth of the rats in groups 2, 3 and 4. The experimental period ended with the sacrificing rats under general anesthesia.

Administration of palmatine:

Palmatine was applied for 15 days starting the day before the insertion of the ligatures in group 3 and group 4 in doses of 5 mg/kg and 10 mg/kg, respectively. Palmatine was given by gavage once a day by dissolving in distilled water.

Histological analysis:

10% buffered formalin was used to fix the right side of the removed mandibles. For decalcification of the samples 10% formic acid (Merck Millipore Corporation; Darmstadt, Germany) at room temperature (pH 7.2) was used. Next the samples were embedded in paraffin (Agar, Cambridge, UK). Serial paraffin sections were taken mesiodistally along the mandibular first molar using a rotary microtome (Leica RM 2135; Leica Instruments, Nussloch, Germany). Three sections were selected and were stained with hematoxylin and eosin (H&E) representing the center of each tooth. The alveolar bone level (ABL) of the first molar tooth, alveolar bone area (ABA) and the attachment level (AL) were evaluated in all sections. A light microscope (BX50 research microscope, Olympus, Tokyo, Japan) was used for the histometric analysis. Images of the sections are digitized using a camera (DP26 Digital Camera, Olympus, Tokyo, Japan). The evaluations were performed with the OLYMPUS DP2-BSW application software. The ABL of the first molar tooth were measured from the cemento-enamel junction (CEJ) to alveolar bone crest (ABC). The furcation area was detected using an imaginary line located between the roots. The sum of the trabecular bone area and the bone marrow area were considered as the alveolar bone area. Attachment level (AL) was determined by calculating the area between the CEJ and the most coronal portion of connective tissue attachment (CTA) to cementum (Figure 1). All analysis were performed by a calibrated examiner who is blinded to the study design with respect.

Immunohistochemical analysis:

A streptavidin-biotin complex (Abcam, Cambridge, MA, USA) was used for immunohistochemical evaluation. The polyclonal anti-RANKL and anti-OPG (Boster Biological Technology Ltd., Fremant, USA) were used for detection. The endogenous peroxidase was treated with 3% hydrogen peroxide for 10 minutes at 25 ° C. Sections were incubated with the primary antibody overnight at 4 ° C in a humidified chamber. Subsequently, sections were washed with 1% PBS / BSA and incubated with biotinylated secondary antibodies (Abcam, Cambridge, Mass., USA) for 60 min at room temperature. HRP / AEC chromogen kit (Abcam, Cambridge, Mass., USA) was used and sections were stained with Mayer's hematoxylin (Sigma, Saint Louis, USA). Positive cells were painted brown. Immunoactivity was scored using HScore[11]. Immunohistochemical density scoring was evaluated as 0 (none), 1 (weak), 2 (moderate), 3 (intense). The following formula was used in the calculation: HSCORE = ΣPi (i + 1). According to the formula, i represents intensity scores, Pi percentage of stained cells, and 1 is the correction factor.

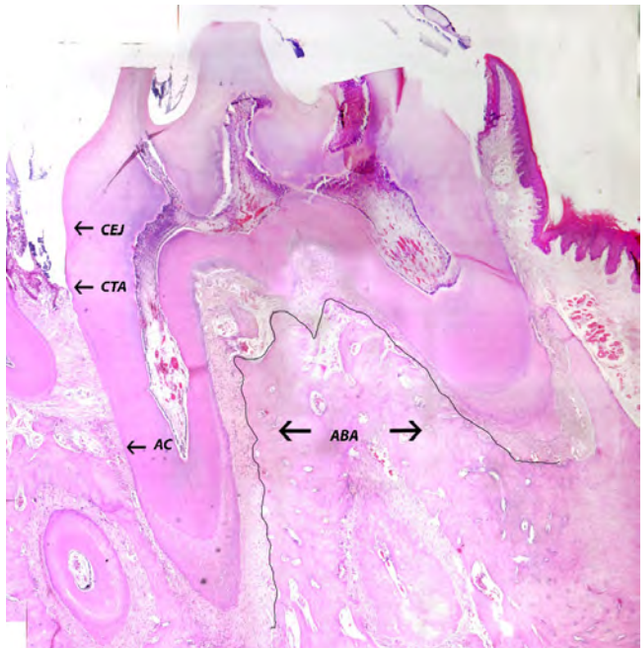


Figure 1. Histologic presentation of alveolar bone area, alveolar bone level, and the attachment level.
Sections from the mesio-distal aspects throughout the mandibular first molars and the reference areas for histomorphometric analysis (H&E, 4×). CEJ: cemento-enamel junction, CTA: connective tissue attachment, AC: alveolar crest, ABA: alveolar bone area.

Statistical analysis:

Statistical analyzes were performed using a computer software (SPSS 19.0). One-way Anova test (posthoc test, Tukey's) was applied for intergroup comparison for normal distribution data. Non-parametric tests were evaluated using the Kruskall-Wallis test. Data are presented as mean ± SD and the statistical significance value was accepted as $p<0.05$.

Results

All rats given palmatine were able to tolerate the alkaloid. No rats died during the experimental period. Although weight loss was seen, it did not reach the size that would affect the life functions. In EP group, alveolar bone and attachment loss were significantly higher than control group ($p<0.05$).

Histomorphometric results:

ABA, ABL and AL values are shown in table 1. ABA values in palmatine groups were statistically higher than control and EP groups ($p<0.05$). However, no significant difference was found between groups EP-5P and EP-10P, in which palmatine was administered at different doses throughout the course of the experiment ($p>0.05$). ABL and AL values were significantly lower in palmatine groups than EP group ($p<0.05$). For both ABL and AL values, no significant difference was found between groups EP-5P and EP-10P given palmatine during the study period ($p>0.05$).

Table 1. Alveolar bone area, alveolar bone level, and the attachment level among groups.

GROUPS	ABA (%)	ABL (µm)	AL (µm)
Group 1. CTRL	71.39±4.01	664.02±13.90	337,97±30.10
Group 2. EP	49.37±1.08[a]	1111.90±64.78[a]	1016,94±73.55[a]
Group 3. EP-5P	60.94±3.97[a,b]	898.00±56.30[a,b]	878,29±21.73[a,b]
Group 4. EP-10P	65.43±2.76[a,b]	849.99±8.78[a,b]	852,28±15.15[a,b]

Data are expressed as the mean ± SD
ABL: Alveolar bone level, ABA: alveolar bone area, AL: attachment level, CTRL: control group, EP: Experimental periodontitis group, EP-5P: 5 mg/kg palmatin administrated group, EP-10P: 10 mg/kg palmatin administrated group.
[a]significantly different from CTRL group ($p<0.05$)
[b]significantly different from EP group ($p<0.05$)

Immunohistochemical results:

Table 2 shows the OPG and RANKL immunoreactivity scores. There was a significant difference between EP and CTRL groups in terms of OPG and RANKL scores ($p<0.05$). RANKL immunoreactivity was significantly increased in EP group when compared with control group ($p<0.05$). The RANKL immunoreactivity was found significantly lower in the palmatine treated groups compared with EP group during the experimental period ($p<0.05$). There was also a significant difference between CTRL and palmatine treated groups ($p<0.05$). However, no significant difference was found between EP-5P and EP-10P ($p>0.05$). OPG immunoreactivity was significantly decreased in the EP group when compared with control group ($p<0.05$). OPG immunoreactivity was significantly increased in palmatine treated groups than EP group ($p<0.05$). There was a significant difference between groups EP-5P and CTRL ($p<0.05$), but there was no difference between groups EP-10P and CTRL ($p>0.05$). In contrast to RANKL results, a significant difference was also found between EP-5P and EP-10P ($p<0.05$). Furthermore, no significant difference was observed between CTRL and EP-10P groups ($p>0.05$). According to the RANKL / OPG ratio, the EP group was found to be significantly higher than the CTRL group, and a significant decrease was observed in the palmatine-treated groups during the experimental period ($p<0.05$). In addition, there was no significant difference between EP-5P and EP-10P according to RANKL/OPG ratio ($p>0.05$).

Discussion

The aim of the study is to investigate the protective effect of palmatine on tissue destruction during periodontitis formation. Periodontitis is a disease characterized by tooth supporting tissue destruction by the direct effect of microorganisms in the plaque and indirectly through the immune-inflammatory host response[1-3]. Various cytokines, proteases are involved in the host response[3]. Another important system for osteoclastic activity is the RANK / RANKL / OPG system. RANK is a receptor expressed by osteoclast progenitor cells. RANKL and OPG are cytokines produced from osteoblasts and bone marrow stromal cells bound to the TNF family[5-7]. The RANKL RANK compound causes active osteoclast production whereas the OPG RANKL compound inhibits the osteo-

Table 2. The HSCORE values of OPG and RANKL immunoreactivity among groups.

GROUPS	RANKL	OPG	RANKL/OPG
Group 1. CTRL	115,81±5.59	244,61±7.73	0,47±0.03
Group 2. EP	254,84±8.99[a]	148,20±10.22[a]	1,73±0.15[a]
Group 3. EP-5P	187,61±10.00[a,b]	218,00±5.49[a,b]	0,86±0.06[a,b]
Group 4. EP-10P	176,86±4.60[a,b]	231,86±2.43[b,c]	0,76±0.02[a,b]

Data are expressed as the mean ± SD
CTRL: control group, EP: Experimental periodontitis group, EP-5P: 5 mg/kg palmatin administrated group, EP-10P: 10 mg/kg palmatin administrated group.
[a]significantly different from CTRL group ($p<0.05$)
[b]significantly different from EP group ($p<0.05$)
[c]significantly different from EP-5P group ($p<0.05$)

clast differentiation process[7]. Hence, the high ratio of RANKL / OPG is associated with the destruction process in periodontal disease. RANKL / OPG ratio was evaluated immunohistochemically for the evaluation of osteoclastic activity[7].

Animal models have advantages such as easier formation of the disease to be examined and providing important information on the pathogenesis of the disease[12]. Rat ligature method is a method in which silk suture is placed in the sulcus of the first molar teeth. As a result of plaque accumulation in the region, ulceration of the epithelium, connective tissue invasion and periodontal tissue loss are expected. It is an easy and inexpensive method[13]. Due to these advantages, SD wistar rats were used in our study and experimental periodontitis was created by ligature method. Different information about the period of experimental periodontitis formation is mentioned in the literature[11,14,15]. Previously, it was determined that ligament-induced bone destruction occurred within 15 days[16]. Therefore, the experimental period in this study was completed on day 15.

Palmatine is a protobarberine alkaloid and has many biological properties such as antipyretic, antibacterial, antioxidative and anti-inflammatory properties [17-19]. In the literature, it has been shown that palatinin has anti-resorptive effect[8,10]. It has also been shown to reduce bone resorption in osteoporotic models [10]. It is shown that palmatine plays an important role in osteoclast apoptosis via the nitric oxide synthase (NOS) system in osteoclasts [20]. Also, it is indicated that palmatine inhibits the expression of the RANKL gene in osteoblastic cells [8]. In addition, palmatine has been reported to decrease RANKL / OPG ratio by decreasing both OPG and RANKL levels [10]. This research was based on the hypothesis that palmatine would reduce tissue destruction during periodontitis formation due to the anti-inflammatory and antiresorptive effects.

A recent study has shown that doses of palmatine 1 mg / kg and 10 mg / kg are safe and do not have toxic effects [10]. So, doses of 5 mg / kg and 10 mg / kg were found suitable to use in our study and it was investigated which doses are more effective and sufficient for suppression of periodontal inflammation.

In the present study, the results were evaluated histomorphometrically and immunohistochemically. To our knowledge, this is the first study to investigate the protective effect of palmatine on bone attachment in the experimental periodontitis model. So, we cannot compare ABL and AL values with another study using palmatine. However, the bone and attachment levels in the dental periphery are the data used in the evaluation of the effects of many new biologically active substances [11]. In our results, according to the control group in EP group, ABL and AL are higher and ABA is lower. This shows that experimental periodontitis has developed. According to the histological results of our study, ABL and AL were less in the palmatine applied groups than in the EP group and ABA was found to be higher in the palmatine applied groups than in the EP group. This result indicates that palmatine has a protective effect on the periodontal inflammation formation and destruction process. We can characterize this effect as an antiresorptive effect in accordance with the literature[8,10]. We cannot mention about bone regeneration as we cannot comment for therapeutic purposes because we did not apply after experimental periodontitis; but our results suggest that palmatine reduces the severity of periodontal destruction when applied to rats during experimental periodontitis.

A recent study showed that palmatine (10 μM) significantly reduced RANKL and OPG levels in the culture supernatant of MC3T3-E1 cells and in serum and stated that the RANKL/OPG ratio also decreased depending on the concentration of palmatine [10]. Another study revealed that the inhibitory effect of palmatine on osteoclastogenesis was due to inhibition of the RANKL gene expression [8]. According to our immunohistochemical results, RANKL immunereactivities increased and OPG scores decreased in the experimental periodontitis group compared to the control group. In the palmatine treated groups, it was determined that RANKL scores decreased with respect to periodontitis group. Contrary to the previous study[10], there was an increase in OPG scores after palmatine administration in our study and most importantly RANKL / OPG ratio decreased with palmatine treatment. This can theoretically result from both the decrease in RANKL scores and the increase in OPG scores.

Another aim of our study is to examine which dose will be more effective and sufficient. In a previous study, administration of palmatine at 10 mg / kg was found to have antiresorptive effect [10]. We investigated in this study whether the dose of 5mg / kg would be sufficient to reduce periodontal destruction in an experimental periodontitis model. When the given doses of 5 mg / kg and 10 mg / kg were compared, there was no significant difference between the two doses in terms of RANKL immunoreactivity, but a significant difference was observed between 5 mg / kg and 10 mg / kg in terms of OPG immunoreactivity. However, when the RANKL / OPG ratio was evaluated, there was no significant difference between the two doses. According to the histological results of our study, no significant difference was observed when ABA, ABL and AL levels were evaluated between 5 mg / kg and 10 mg / kg palmatine given groups. As a result, oral administration of palmatine at a dose of 5 mg / kg is considered to be sufficient to reduce periodontal inflammation and destruction.

In conclusion, new biological substances are being studied for the prevention and treatment of periodontal inflammation. The clinical significance of this study is the reduction of periodontal tissue destruction by using palmatine. On the other hand, while we know that these doses are not harmful to rats, we cannot comment on the appropriate dose that should be used in humans. Clinical trials are therefore needed to determine the appropriate dose of palmatine that can be used in humans.

Ethical Responsibilities

All institutional and national guidelines for the care and use of laboratory animals were followed.

Conflict of Interest:

No potential conflict of interest relevant to this article was reported.

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Association between chronic obstructive pulmonary disease and blood types

Kronik obstruktif akciğer hastalığı ile kan grubu arasındaki ilişki

Copd and blood types

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Öz

Amaç: Bu çalışma Şırnak il merkezinde kronik obstruktif akciğer hastalığı (KOAH) olan hastalarda KOAH ile kan grupları arasındaki ilişkiyi ortaya koymak amacıyla yapılmıştır. Gereç ve Yöntem: Şırnak il merkezinde oturan ve 30 yaş üzerinde olan 1000 hastada solunum fonksiyon testleri yapılmıştır. 570 hasta (%57) erkek, 430 hasta (%43) kadın idi. Bulgular: Global Obstruktif Akciğer Hastalığı (GOAH) kriterleri ile birlikte değerlendirildiğinde, KOAH prevalansı %10.1 (101 hasta) olarak saptandı. Hastalık evresi %1.98 hastada hafif, %27.72 hastada orta ve %43.56 hastada şiddetli ve %26.74 hastada ise çok şiddetli olarak saptandı. KOAH çalışmaya katılan erkeklerin %11.92'sinde (68 hasta), kadınların ise %7.67'sinde (33 hasta) saptandı. KOAH tanısı konulan 101 hastadan 93'ünün kan gruplarına hastane kayıtlarından ulaşıldı. Hastalar ABO kan gruplarına göre sınıflandırıldı. Sonuç olarak KOAH en sık olarak A kan grubunda saptandı. ABO kan gruplarına göre KOAH hastalığı olanlarda görülen gruplar şu şekilde idi: A kan grubunda 39 hasta (%42), B kan grubunda 26 hasta (%28), AB kan grubunda 17 hasta (%18) ve 0 kan grubunda ise 11 hasta (%12). Tartışma: Mevcut tıbbi literatürle uyumlu olarak KOAH hastalığı kan grupları ile ilişkili bulunmuştur.

Anahtar Kelimeler

Kronik Obstruktif Akciğer Hastalığı; Kan Grubu; Risk Faktörü

Abstract

Aim: This research was performed on patients diagnosed with chronic obstructive pulmonary disease (COPD) in Şırnak province center to explore the relation between COPD and blood types. Material and Method: Pulmonary function tests were performed on 1000 patients over the age of 30 who were randomly selected from the patients residing in the city center of Şırnak. 570 (57%) of the participants were male and 430 (43%) were female. Results: When combined with the Global Obstructive Lung Disease (GOLD) criteria, the prevalence of COPD was 10.1% (101 patients). Disease stages were mild in 1.98%; moderate in 27.72%; severe in 43.56%; and very severe in 26.74% of COPD patients. COPD was diagnosed in 11.92% (68 patients) of men and 7.67% (33 patients) of women participating in the study. The blood types of 93 patients with COPD from the group of 101 were retrospectively reached from hospital records. Patients were classified according to ABO blood type data. As a result, it was found that COPD was more common in patients with blood type A. According to ABO blood types distribution of our cases with COPD were as follows: 39 patients (42%) were type A, 26 patients (28%) were type B, 17 patients (18%) were type AB and 11 patients (12%) were type O. Discussion: A conclusion is reached revealing the association of blood type with COPD risk factors, which was mentioned in much of the corpus of medical literature.

Keywords

Chronic Obstructive Pulmonary Disease; Blood Type; Risk Factor

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Introduction

Chronic Obstructive Pulmonary Disease (COPD), a common, preventable, and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles and gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1]. COPD prevalence may vary according to countries, geographical regions, lifestyle, sociocultural structure, age, and sex [2].

Genetic, environmental factors and especially smoking play an important role as COPD risk factors. Many risk factors such as smoking, occupational dust exposure, air pollution, biomass exposure may cause the development of COPD. Atopy, low birth weight, blood type A, non-secretory Ig A deficiency are among the risk factors of COPD [3].

The purpose of this study is to prove an association between blood type and COPD, for although mentioned in the literature as among the risk factors for COPD, there are not enough conclusive studies that establish the relation between blood type and COPD. In our study we presented, in accordance with the literature, that blood type A is seen more commonly among COPD patients than other blood types.

Material and Method

This study was planned randomly in order to investigate which blood type was detected more commonly among COPD patients in Şırnak province center. It was retrospectively performed using the data from the hospital patient records.

The population in our study was composed of 1000 patients who were randomly selected from patients admitted to the hospital and were over 30 years old.

The data for the study was collected between May 2010 and May 2011. We performed the study with a study group of 1000 randomly selected patients. At the same time standardized measurements (respiratory function test, height, weight) were recorded.

Respiratory function tests were performed at least 3 times for each individual and the highest values were recorded. Individuals with obstruction of respiratory function according to GOLD criteria were accepted as COPD [4]. Blood types of patients with COPD were obtained retrospectively from the hospital registry

The obtained data and pulmonary function test values were evaluated by coding in software program "SPSS for Windows version 11.0 (SPSS Inc, Chicago, USA)". Data was presented with mean values and standard deviation (mean ± SD) for the groups. T test was used in the comparison of measurement-based variables between groups for two mediums in the independent groups. A chi-square analysis was performed to examine the distributional differences of categorical variables. Analysis results were evaluated at 95% confidence interval. The level of significance was based on $p < 0.05$ value. Pulmonary function test results were evaluated together with GOLD criteria [4,5].

Results

The study group consisted of 570 males and 430 females. Distribution of individuals by sex, age, height, and body weight characteristics are given in Table 1. Our cases with COPD were mostly GOLD stage 3 (severe COPD) (Table 3). The blood types of 93 patients with COPD from the group of 101 were retrospectively reached from hospital records. Patients were classified according to ABO blood type data. As a result, blood type A was detected most frequently in COPD cases.

In COPD cases; there was no significant difference between Rh + and Rh - (p value: 0.059).

Discussion

This study showed that the prevalence of COPD in Şırnak province center was 10.1% in a population of 30 years old and more. COPD was found in 11,92% of men and in 7,67% of women who participated in our study. It was noteworthy that, while a relationship with blood type A and COPD has been mentioned in previous publications, there was limited evidence of this association in Turkish populations. Among the risk factors of COPD, the blood type association frequently occurs

Table 2. Diagnosis, obstruction parameters of COPD patients in the study group

	Female (COPD female patients) n: 33	Male (COPD male patients) n: 68	Total (COPD cases) n: 101
COPD prevalence	33 (%7.67)	68 (%11.92)	101(%10.1)
Previous COPD diagnosis	11 (%3.9)	19 (%3.3)	30 (%3)

Table 3. Distribution of our cases with COPD according to COPD stages.

	Number	Percentage (%)
Stage 1 (Mild COPD)	2	1,98
Stage 2 (Moderate COPD)	28	27,72
Stage 3 (Severe COPD)	44	43,56
Stage 4 (Very severe COPD)	27	26,74
Total	101	100

Table 4. Distribution of our COPD patients according to ABO blood types.

Blood type A	Blood type B	Blood type AB	Blood type O
39 patients	26 patients	17 patients	11 patients
%42	%28	%18	%12

Table 5. Distribution of our COPD cases by Rh factor.

Rh+	Rh-
49 patients (%52.7)	44 patients (%47.3)

Table 1. General characteristics of the research group.

	Male 570 patients (%57)			Female 430 patients (%43)			Total 1000 (%100)		
	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean
Age (Year)	30	89	64.9±16.16	30	77	51.36±14.35	30	89	63.40±15.16
Height (cm)	163	189	167.92±8.78	141	174	155.34±7.24	141	189	166.22±8.20
Body Weight (kg)	53	101	75.4±14.05	40	104	69.7±13.66	40	104	71.9±14.69

in many publications [3,6]. Therefore, we wanted to make up for the lack of studies in our country. In order to reveal scientific data, we conducted this study.

Studies on the epidemiological characteristics of COPD encounter two important problems. One is selection of the observation group and the other one is sampling errors [7,8]. The spirometric criteria on which we base the diagnosis of COPD are the widely accepted GOLD criteria. The most common symptoms of the disease are shortness of breath, chronic cough, and chronic sputum production. Spirometry is necessary for the diagnosis of the disease. In elderly-middle aged adults with chronic symptoms and exposure to risk factors, spirometric findings of airflow obstruction (post-bronchodilator FEV1 / FVC <70%) were confirmed [9].

Özlü and his colleagues investigated the prevalence of COPD in Trabzon in 2004 and in people over the age of 30. This study is one of the first prevalence studies based on the criteria of GOLD and ATS COPD Guidelines. In this study, face to face interviews and respiratory function tests were applied to 613 people over the age of 30 in Trabzon city center and its provinces. The prevalence of COPD was 0.98% according to the GOLD criteria [5]. This rate is 1.7% for males and 0.3% for females. When ATS criteria are considered, the prevalence of COPD is reported to be 4% in males, 1.6% in females and 2.8% in total. The prevalence of COPD found by Özlü and his colleagues is well below both our prevalence findings and the expected prevalence in our country.

The frequency of COPD was assessed in a study conducted in a population between 40-69 years, living in the Konak Health Group in İzmir, between February and May 2003. 1.404 respiratory function tests were performed and at the same time the questionnaire was applied. According to the GOLD criteria, the frequency of COPD was 10.2%, which was reported as 13.3% in men and 7.3% in women [9,10]. The most important risk factor for developing COPD is smoking [11]. Smoking is responsible for 90% of COPD risk in developed countries [3]. In addition to many risk factors such as smoking, occupational dust exposure, air pollution, and exposure to biomass, atopy, low birth weight, blood type A, non-secretory IgA deficiency are also among the risk factors for COPD. These lead to the development of COPD [3,6].

In a study conducted, a 5-year follow-up showed that people with blood type A had an accelerated decline in pulmonary function values compared to people with other blood types [12]. Cohen BH. and colleagues demonstrated and emphasized the association between COPD and blood type [13]. In our study, 11.92% (68 patients) of the participating men and 7.67% (33 patients) of women were found to have COPD. The blood types of 93 patients with COPD from the group of 101 were retrospectively reached from hospital records. Patients were classified according to ABO blood type data. As a result, it was found that COPD was more common in blood type A. Distribution of our cases with COPD according to ABO blood types: 39 were identified as blood type A (42%), 26 as blood type B (28%), 17 as blood type AB (18%) and 11 as blood type O (12%). Our results were in concordance with previous studies, which showed an association with blood type A and COPD. There was no difference in the distribution of our COPD cases with respect to Rh factor.

In many countries, an increase in COPD mortality is observed. The international mortality of COPD varies widely among different countries [14,15]. The reasons for this discrepancy may be differences in smoking behavior, environmental factors, genetic factors, and infections. The data we obtained regarding the prevalence of COPD in Şırnak province center is important for the prevalence statistics of COPD in our country. Even more importantly; our study has significant importance since it constitutes an example for the association of blood type and COPD. Many important publications accept blood type A as a risk factor for COPD [3,6,13]. Therefore, we also aimed to investigate this information. In the data, we obtained; blood type A was the most common group among COPD patients by 42%.

Human Rights Statement:

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Animal Rights Statement:

Nonapplicable.

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Studying the polymorphism of TNF- and TNF- genes among people suffering from helicobacter pylori infection

Helicobacter pylori infection

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Abstract

Aim: One of the most important risk factors proposed for gastric cancer is Helicobacter pylori; however, the correlation between polymorphism of TNF-αα and TNFββ with Helicobacter infection has never been studied. The present research seeks to examine the correlation between polymorphism of these two genes in Helicobacter pylori infection and gastric cancer among those suffering from infection with this bacteria. Material and Method: This is a case-control research seeking to study the polymorphism of TNF-α and TNF-β genes among those suffering from Helicobacter pylori infection and compare it to healthy people. Polymorphism genotype of TNF-α-308 and TNF-α+254 genes was studied in 31 healthy cases, 50 cases with H. pylori, and 23 cases with Helicobacter pylori and gastric cancer using ARMS & PCR-RFLP polymerase chain reaction method. Results: According to the results obtained in this research, there is a significant correlation between TNF-308 A/A homozygote genotype and A allele in TNF-308 with H pylori. In other words, there is a correlation between TNF-308 A/A and the possibility of affliction with infection ($P < 0.05$). The correlation between TNF-308 G/A genotype and TNF-308 A/A genotype and TNF-308 An allele with affliction with cancer and H pylori was also significant ($P < 0.05$). Discussion: TNF-308 A/A homozygote genotype has a significant correlation with gastric cancer and H pylori. As a matter of fact, TNF-308 A/A has increased the possibility of affliction with H pylori and gastric cancer. A significant correlation was also observed between TNF-308 G/A genotype and TNF-308 A/A and TNF-308 An allele with affliction with gastric cancer and H pylori.

Keywords

Helicobacter Pylori; Gastric Cancer; Polymorphism

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Introduction

The genetic differences of people in each population are the major factor determining allergy towards various diseases, whether these diseases are infectious and contagious (like viral hepatitis) or non-contagious (like cancer) [1]. Furthermore, as cancer is caused by multiple factors, it is possible that genetic polymorphisms have a simultaneous interaction with environmental and other genetic factors affecting allergy on affliction with it [2, 3].

Helicobacter pylori is a growing microaerophilic gram-negative microorganism found in the stomach and duodenum, and it is associated with some diseases of stomach and duodenum. One of the most important risk factors playing a major role in causing gastric cancer is Helicobacter pylori bacteria. The role of this bacteria in this disease is so important it has come to be introduced as Class 1 carcinogenic factor by WHO [4]. By producing Cag A protein and entering it into epithelial cells of the stomach, the expression of various genes in these cells undergoes a major change thus affecting the hosting factors and making the individual prone to cancer [5]. Ever since a correlation has been established between Helicobacter pylori infection and gastric cancer, further researchers have sought to study the possibility of an infectious origin for other types of cancer. However, no case with such high level of influence like Helicobacter pylori has ever been introduced. The initial infection with Helicobacter pylori causes mild gastritis, and the resulting inflammation may end in an ulcer. If the pathogenic procedure continues and no measures are taken for appropriate treatment of ulcer, it will cause atrophic gastritis. People suffering from this inflammation are exposed to the danger of malignancy and cancer [6, 7].

Nowadays, various large-scale studies have been conducted on the correlation between genetic changes such as polymorphisms and the risk of affliction with various types of cancer [8]. Polymorphisms have their effect by increasing or decreasing the risk of a disease through several ways [9]. Polymorphisms may play a major role in making people prone to cancer [2]. Necrosis factor of an alpha tumor is an intracellular signaling protein that intervenes in the inflammatory system. The primary role of TNF is to adjust immunity cells. TNF may cause fever, an apoptotic death of the cell, and inflammation. It may also harness viral replication tumor. Failing to adjust TNF production (or lack of accurate correctness of its protein structure) may cause cancer, Alzheimer and bladder inflammation. Beta tumor necrosis factor is a multifunctional Cytokine protein mostly produced by T lymphocytes induced by mitogens or leukocytes. The range of TNF-α and TNF-β activities are identical, although the beta type has fewer capabilities. TNF-β induces interleukin-1 synthesis, collagenase and prostaglandin E2 in fibroblasts. TNF-α and TNF-β have cytotoxic and cytolytic effects on most tumor cells with the only difference being in their level of influence [10].

Dr. Hadi Ghafrani et al. (2003) conducted a research titled "Studying the role of Helicobacter pylori in Gastric Adenocarcinoma in terms of anatomic site" and found no significant difference in prevalence of Helicobacter pylori in cardiac and non-cardiac cancer (70% vs. 73.3%) [11].

A research by Shahrokh Iravani (2013) titled "gastric cancer as a multifactorial disease" found that Helicobacter pylori infection, genetic background and environmental factors such as nutrition and sanity are considered risk factors that cause gastric cancer [12].

In a research by Saito et al. (2000), the effects of eradicating Helicobacter pylori on malignancy of Gastric adenoma was studied. It was finally concluded that eradication of Helicobacter pylori may prevent gastric adenoma from developing into gastric cancer [13].

As the correlation between polymorphisms of TNF-α and TNF-β genes and Helicobacter pylori infection has not been studied so far, the present research seeks to examine the correlation between the two above said factors to find proper molecular markers for predicting and preventing gastric cancer among those suffering from this bacteria's infection.

Material and Method

This is a control-case research studying the polymorphism of TNF-α and TNF-β genes among those suffering from Helicobacter pylori infection as the case and healthy people as control group. The statistical population included all the patients with Helicobacter pylori infection resorting to Omid, Ghaem, and Imam Reza hospitals of Mashhad and private clinic of Dr. Hadi Mohammad Doust and Imam Reza Hospital of Bojnourd. As many as 31 healthy cases, 50 cases with positive Helicobacter pylori, and 23 with both gastric cancer and positive Helicobacter pylori were selected for sampling through convenient sampling method. The informed consent of the individuals was obtained, and their demographic information (including age and gender) were asked. Using patients' files fro the hospital, their histopathological information was also written in the questionnaires.

In the next phase, blood samples were made in the above-said therapeutic centers with DNA PCR and Electrophoresis tests conducted on them. Next, polymorphism of TNF-α and TNF-β genes was determined according to RFLP-Restriction Fragment Length (polymorphism) and ARMS (Amplification refractory mutation system) methods in order to determine allele frequency of genotype in case and control groups. The H. pylori level was also determined and recorded in serum samples of patients. The collected information was then analyzed using SPSS v.20.

Results

There were 31 healthy participants in control group, while 50 people with H pylori infection and 23 with gastric cancer and H pylori infection were in case group. Table 1 shows distribution of age frequency. Table 2 represents the health status of the participants. Table 3 shows distribution of age groups in terms of health status.

Table 1. Distribution of the age frequency of participants

Average age	Frequency	Percentage
20 to 35	23	22.17
35 to 50	24	23.07
50 to 65	28	26.9
65 to 80	27	25.9
Older than 80	1	0.96
Total	104	100

Table 2. Health status of the participants

Health status	Frequency	Percent
Healthy	31	29.8
Positive H pylori	50	48.1
Positive cancer and H pylori	23	22.1
Total	104	100

Table 3. Distribution of age groups according to their health status

Health status	20 to 35	35 to 50	50 to 65	65 to 80	Older than 80	Total
Healthy	2	5	12	11	0	30
Positive H pylori	10	15	9	16	0	50
Cancer and positive H pylori	11	4	7	0	0	22
Total	23	24	28	27	0	102

While analyzing the research, two participants disappeared (one healthy person and one with both diseases)

Table 4 shows the frequency distribution of genotype and alleles of -305 G>A polymorphism in TNF gene promoter (TNF-α) and 252 A>G in the first intron of LTA (TNF-β) gene among patients with Helicobacter pylori infection and healthy control people in Khorasan province of Iran.

Table 4. Frequency distribution of genotypes and alleles of -308 G>A polymorphism in (TNF-α) TNF promoter and 252 A>G in the first intron of LTA (TNF-β) gene

	H-Pylori, n=50 (%)	Healthy Controls, n=30 (%)	P Value	OR (95% CI)
Genotypes				
TNF-308 G/G	30(60.00)	23(74.2)	-	-
TNF-308 G/A	4(8.00)	3(.679)	0.88	1.12 (0.77–1.34)
TNF-308 A/A	16(32.00)	5(16.13)	0.045	2.03 (0.65–2.12)
LTA 252 A/A	27(54.00)	17(54.8)	-	-
LTA 252 A/G	13(26.00)	9(29)	0.69	1.07 (0.63–1.84)
LTA 252 G/G	10(20.00)	8(25.8)	0.59	1.07 (0.63–1.84)
Alleles				
TNF-308 G	34(68.00)	26(83.87)	-	-
TNF-308 A	20(40.00)	8(25.8)	0.02	1.96 (0.80–1.91)
LTA 252 A	40(80.00)	26(83.87)	-	-
LTA 252 G	23(46.00)	17(54.83)	0.43	0.67 (0.54–1.65)

According to Table 5, TNF-308 A/A homozygote genotype and A allele have a significant correlation with H pylori in TNF-308. As a matter of fact, there is a correlation between TNF-308 A/A and the possibility of affliction with infection ($P < 0.05$).

Table 5 represents the frequency distribution of genotype and alleles of -308 G>A polymorphisms in TNF (TNF-α) gene promoter and 252 A>G in the first LTA intron of (TNF-β) gene among patients suffering from Helicobacter pylori infection and gastric cancer and healthy control participants in Khorasan province.

According to Table 5, the correlation between TNF-308 G/A genotype and TNF-308 A/A genotype and TNF-308 A allele with affliction with gastric cancer and H pylori is significant ($P < 0.05$).

Table 5. Frequency distribution of genotype and alleles of G>A -308 polymorphisms in TNF (TNF-α) gene promoter and 252 A>G in the first LTA intron of (TNF-β) gene

	H-Pylori, n=23 (%)	Healthy Controls, n=30 (%)	P Value	OR (95% CI)
Genotypes				
TNF-308 G/G	13(56.52)	23 (74.2)	-	-
TNF-308 G/A	5(21.7)	3 (9.67)	0.004	1.98 (0.76–2.02)
TNF-308 A/A	5 (21.7)	5 (16.13)	0.043	1.77 (0.83–1.90)
LTA 252 A/A	9(68.7)	17 (54.8)	-	-
LTA 252 A/G	8 (29.6)	9 (29.03)	0.98	1.05 (0.74–1.54)
LTA 252 G/G	6 (29.6)	8(25.8)	0.069	1.17 (0.45–1.32)
Alleles				
TNF-308 G	18 (78.26)	26 (83.87)	-	-
TNF-308 A	10(43.47)	8 (25.8)	0.005	2.85 (0.56–1.71)
LTA 252 A	17 (73.9)	26 (83.87)	-	-
LTA 252 G	14 (60.86)	17 (54.83)	0.064	1.27 (0.66–1.94)

Discussion

Helicobacter pylori and polymorphisms of the genes of some cytokines such as TNF increase the level of relevant proteins and cause surface inflammation of the stomach [10]. Atrophy of the gastric mucosa is another factor that contributes to cancer [10]. Keeping in mind the fact that the next step in causing cancer is chronic gastritis, it becomes clear that inflammation and inflammatory responses play a major role in various types of gastric cancer. Thus, the present research sought to study the polymorphism of various TNF and LTA genotypes in order to find the correlation between these inflammation mediators in Iranian race in Razavi Khorasan and Northern Khorasan provinces of Iran. As for the analysis of –TNFα polymorphism, the patients were divided into the positive and negative H pylori groups. The frequency of AA and A allele of TNF gene polymorphism among the patients who have gastric cancer with positive H pylori is significantly more common than healthy people. As a result, this polymorphism has had a greater influence on the possibility of affliction with cancer among people suffering from infection. But this state has not been observed for polymorphism studied by LTA. As a matter of fact, polymorphism of this gene has had no influence on the possibility of affliction with cancer whether with infection or without it.

Various researches have pointed to the fact that genetic changes in the area adjusting cytokine genes are associated with affliction with various diseases [5, 8]. For example, a change from G to A in -308 positios in α-TNF promoter increases the density of α-TNF and affliction of the individual with various diseases including gastric cancer. Although molecular mechanisms showing how genetic polymorphism influences cytokine gene is not mostly available, different researches show that -380 polymorphism can influence the connection between transcription factors and increase TNF-α gene expression [14]. Infection with Helicobacter pylori studied in this research indicates that effect of TNF-α in the presence of A308- allele in causing cancer is much more than G308-. This result highlights the importance of this region in adjusting α-TNF gene.

In 2001, a case-control study by Macron et al. on a Portuguese population of 252 cases of gastric cancer compared to 220 people in control group investigated polymorphisms of α-TNF

promoter in -238 and -308 positions in Helicobacter pylori. An analysis of +ureA versus –ureA showed that -308 polymorphism had no significant correlation with Helicobacter pylori infection [15]. This is in line with the results of the current research. However, other researchers have recently shown that a genotype change in -308 position from α-TNF position is more prominent among those patients with positive Helicobacter pylori than those with negative Helicobacter pylori [16, 17]. Therefore, the results may have been influenced by the difference between samples. If the correlation between these polymorphisms and Helicobacter pylori and gastric cancer is proved accurately, the polymorphism of the genes studied in this research is recommended to be taken into consideration as markers and used in clinical examinations.

Conclusion

On the strength of the present research, it can be concluded that the effect of α-TNF in the presence of –A308 allele on causing cancer is much more than that of –G308. A rise in the density of α-TNF as a result of –A308 polymorphism can change the defensive reaction of the body and prepare it for gastric infections such as Helicobacter pylori.

Human Rights Statement:

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Animal Rights Statement: Nonapplicable.

Conflict of Interest Statement:

The authors have no conflict of interest.

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Compare impulsivity between traditional and industrial drug-dependent people and healthy people

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Abstract

Aim: This study compares the impulsivity in patients addicted to industrial and traditional narcotics and healthy people. Material and Method: In this comparative study, 40 people addicted to traditional narcotics (20 males and 20 females), 40 patients addicted to industrial narcotics (20 males and 20 females) and 40 healthy subjects (20 males and 20 females) were evaluated and selected by convenience sampling method from all male and female patients addicted to traditional and industrial narcotics at Shahid Modarres hospital of Najafabad in Isfahan during September 2016 to January 2017. Barratt's revised scale was individually used to collect data. Kolmogorov-Smirnov test was applied to analyze normality of data. Multivariate analysis of variance (MANOVA) was used to compare variance. Results: Based on the results of Kolmogorov-Smirnov test, distribution of all data was normal ($0.051<P<1.000$) and there was not any significant difference between the industrial-traditional narcotics consuming people in terms of impulsivity subscales [attention ($P=0.539$), mobility (0.196), self-control ($P=0.051$), recognition plexus ($P=0.077$), assiduity ($P=0.133$), and personality instability ($P=0.116$)]. However, there was a significant difference between healthy people regarding these variables. Discussion: Based on the results of this study, it seems that there is an appropriate relationship between impulsivity and industrial and traditional narcotics consumption.

Keywords

Impulsivity; Industrial Narcotics; Traditional Narcotics

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Introduction

Drug addiction can be considered as a brain injury [1] which is associated with cognitive impairment. A part of the prefrontal cortex (for instance the orbitofrontal cortex) plays a role in the process of drug addiction by reducing the inhibition of impulsive behavior [2]. Impulsivity is defined as the cause of unplanned and rapid response to internal or external stimuli regardless of negative consequences for ourselves and others [3]. Impulsivity plays a major role in the diagnosis of a variety of clinical disorders such as drug dependence [4]. The drug consumers are less sensitive to adverse consequences of their activities [5] and are less able to use negative feedback of their behavior for adaption of future behavior [6]. Impaired decision-making can be considered as one of the most fundamental mechanisms of impulsivity compulsive behavior and addiction. Its diagnosis can estimate the actual incidence of the disorder. The neural imaging studies support a variety of abnormalities in the prefrontal cortex of people who consume drugs such as amphetamines [7]. The excitement and impulsivity are very important in patients who consume industrial and traditional narcotics. Emotions are the models of organism reaction to internal and external stimuli, and they are manifested in pleasant-unpleasant (proximity-avoidance), and irritation-inhibition dimensions and they are gradually distinct from motives. According to the literature review on impulsivity, the impulsive behavior is the core of numerous mental disorders such as attention-deficit/ hyperactivity, conduct disorder, impulse control disorders, drug abuse, bulimia, suicidal behavior, and some personality disorders [8].

Several studies have been conducted on the relationship between impulsivity and drug abuse disorder, and they consider the impulsive behavior as one of the risks and persisting factors of this disorder, and also as the determinant of the type of narcotics consumed by addicts such as the tendency to use stimulants [9, 10]. This study seeks to compare impulsivity in patients with impaired use of traditional and industrial narcotics and healthy individuals.

Material and Method

This research is casual-comparative and performs a retrospective comparison of impulsivity in healthy subjects and all male and female patients addicted to traditional and industrial narcotics in Modarres Hospital of Najafabad in Isfahan between October and February 2015. The healthy population included all healthy males and females in Isfahan, and they were compared regarding gender, age, and educational level, and they were selected from people admitted to Shahid Modarres Hospital of Najafabad in Isfahan by convenience sampling. 120 participants were randomly selected: 40 subjects were addicted to traditional narcotics (20 males and 20 females), 40 subjects were addicted to industrial narcotics (20 males and 20 females), and 40 healthy subjects were (20 males and 20 females). In this research, the criteria for patient inclusion were as follows: lack of DSM-IV diagnostic criteria for the risk of any mental illness without comorbidity or suffering from disorders axes 1 and 2 of DSM-IV according to clinical psychologist or psychiatrist's diagnosis; at least 18 years of age; at least literacy (primary-school degree); lack of concurrent use of traditional and industrial narcotics; and the ability to respond to questionnaire. The exclusion criteria were: Utilization of DSM-IV diagnostic criteria for the risk of any mental illness without comorbidity or suffering from disorders axes 1 and 2 of DSM-IV according to clinical psychologist or psychiatrist's diagnosis; lack of at least 18 years of age; lack of literacy (primary-school degree); background of concurrent use of traditional and industrial narcotics; and lack of ability to respond to questionnaire. The impulsivity as considered as the dependent variable; and the patients addicted to narcotics (traditional and industrial) were considered as the independent variables. This research was conducted by receiving a referral from the Islamic Azad University of Najafabad to Shahid Modarres Psychiatric Hospital of Najafabad in Isfahan of patients, and then by investigating the patient records according to psychiatrist's diagnosis and structured diagnostic interview, and selecting the target samples based on the research conditions. Finally, Barratt Impulsiveness Scale (BIS) was individually implemented at the hospital by the researcher. The demographic characteristics were studied based on the level of education, marital status and duration of drug consumption separately for those addicted to traditional and industrial narcotics and healthy people.

The axis-1 disorders of DSM-IV were diagnosed through a diagnostic interview by psychiatrists or psychologists. Barratt Impulsiveness Scale (BIS): This questionnaire (eleventh edition) was introduced by Ernest Barratt. Its validity and reliability are examined by Ekhtiari et al. in 2008 [11]. It is based on Barratt's theory of personality and consists of 30 questions and evaluates six factors (attention, mobility, self-control, recognition plexus, assiduity, and personality instability). The questions are multiple-choice and ranked from rare to almost always. The highest obtained score will be 120. The results indicate the appropriate reliability and validity of the questionnaire. Barratt concludes that the impulsiveness scale is a proper tool with high validity for investigating the impulsivity in people.

The statistical analysis was performed at the level of descriptive statistics in terms of frequency percentage, frequency, mean and standard deviation, and the research hypotheses were confirmed by the inferential statistics through multivariate analysis of variance (MANOVA). Statistical results were analyzed using SPSS20 software. First, the normality of data distribution was examined by Kolmogorov-Smirnov test. The MANOVA was used to compare variances. Data of those variables, which had significant difference according to comparison test of variance was evaluated by Tukey post hoc test to find the variance of which groups had a significant difference and which groups had a statistical significant difference.

Results

All studied subjects in Shahid Modarres hospital of Najafabad were classified into three groups as;the people addicted to; traditional narcotics, industrial narcotics and healthy subjects. Their demographic information is presented in Table 1. 50% of subjects were male, and other 50% were female. As shown, the number of males and females were equal to 50% in all three groups. Among people addicted to traditional narcotics, 35% (n=14) had primary school degrees, 30% (n = 12) had secondary school degrees, and 35% (n= 14) had high school diploma or associate degrees. Among people addicted to traditional nar-

cotics, 30% (n=12) had primary school degrees, 37.5% (n=15) had secondary school degrees, 30% (n=12) had high school diploma or associate degrees, and 27.5% (n=11) had bachelor or master's degrees. According to Table 1, 2.5% (n= 1) of healthy people had bachelor or master's degrees. 35% (n=14) of people addicted to industrial narcotics were married and 65% (n=26) were single. 40% (n= 16) of people addicted to traditional narcotics were married and 60% (n=24) were single. However, 32% of healthy people (n= 13) were married, and 67.5% (n=27) were single as shown in Figure 1.

Table 1. Demographic data of studied subjects based on the frequency and relative frequency

Demographic characteristics		Industrial consumer		Traditional consumer		Healthy people	
		Frequency	Relative frequency	Frequency	Relative frequency	Frequency	Relative frequency
Gender	Male	20	50	20	50	20	50
	Female	20	50	20	50	20	50
Educational level	Primary school	14	35.0	12	30.0	13	32.5
	Secondary school	12	30.0	15	37.5	15	37.5
	High school diploma/ Associate degree	14	35.0	12	30.0	11	27.5
	Bachelor/ master's degree	0	0	1	2.5	1	2.5
Marital status	Single	26	65	24	40	27	67.5
	Married	14	35	16	60	13	32.5

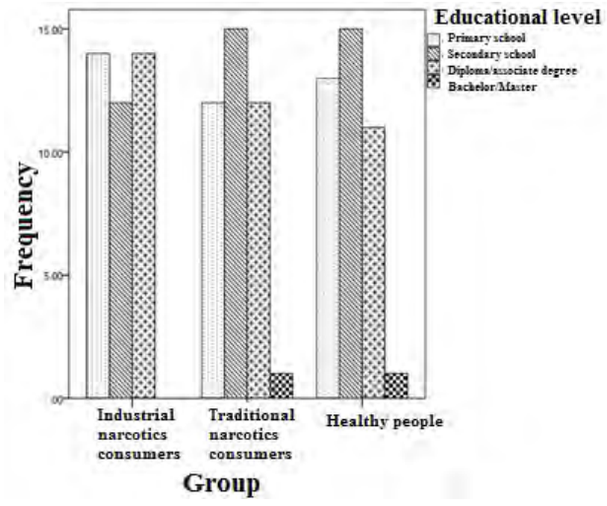


Figure 1. Bar graph of educational level separated for individual groups

Furthermore, the information about the average duration of traditional and industrial narcotics consumption in years is presented in Table 2.

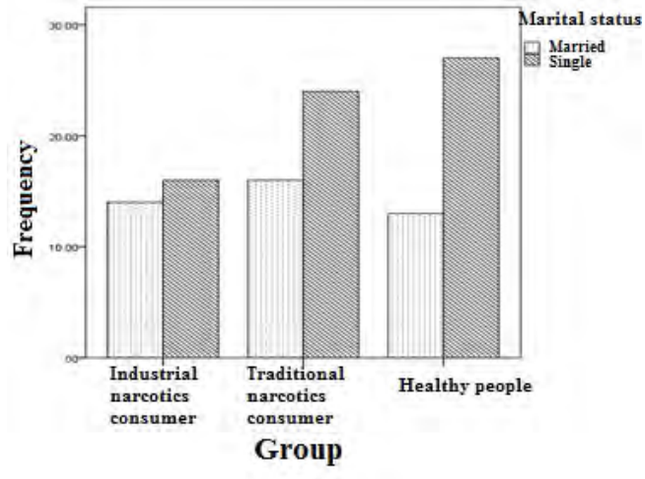


Figure 2. Bar graph of marital status for individual groups

Table 2. Average age and duration of narcotics consumption in research participants in 2015-16

Samples' age				Narcotics consumption duration			
Industrial narcotics consumers		Traditional narcotics consumers		Industrial narcotics consumers		Traditional narcotics consumers	
Mean	standard deviation	Mean	standard deviation	Mean	standard deviation	Mean	standard deviation
35.48	9.12	39.51	8.32	11	7.56	9.43	7.18

According to the obtained mean values, the mean consumption in samples of traditional narcotics group is less than the mean consumption in samples of industrial narcotics group, while the traditional narcotics consumers' age is higher than the industrial narcotics users.

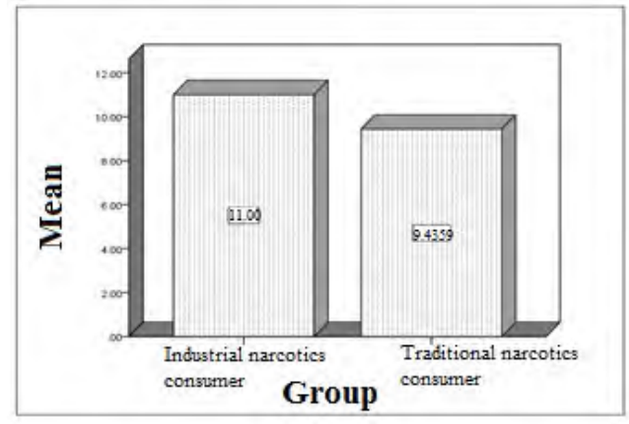


Figure 3. Bar graph of narcotics consumption duration for individual groups

Table 3 presents the descriptive information including the mean and standard deviation, minimum and maximum for subscales of attention, mobility, self-control, recognition plexus, assiduity, and personality instability.

Table 3. Descriptive statistics of impulsivity variable and its subscales

	Group	Mean	Standard deviation	Minimum	Maximum
Attention	Industrial narcotics consumers	2.09	0.66	1.0	3.40
	Traditional narcotics consumers	2.50	0.63	1.0	3.60
	Healthy people	3.50	0.41	2.60	4.0
Mobility	Industrial narcotics consumers	1.94	0.36	1.14	2.57
	Traditional narcotics consumers	2.29	0.66	1.14	3.57
	Healthy people	3.40	0.52	2.0	4.0
Self-control	Industrial narcotics consumers	2.15	0.72	1.33	3.33
	Traditional narcotics consumers	2.68	0.59	1.50	3.67
	Healthy people	3.45	0.42	2.33	4.0
Recognition plexus	Industrial narcotics consumers	2.04	0.69	1.0	3.40
	Traditional narcotics consumers	2.21	0.61	1.0	3.40
	Healthy people	2.72	0.46	1.60	3.60
Assiduity	Industrial narcotics consumers	2.31	0.80	1.25	4.0
	Traditional narcotics consumers	2.93	0.53	1.75	4.0
	Healthy people	3.32	0.33	2.50	4.0
Personality instability	Industrial narcotics consumers	2.15	0.68	1.0	3.0
	Traditional narcotics consumers	2.49	0.82	1.0	4.0
	Healthy people	3.11	0.64	1.67	4.0

According to Kolmogorov-Smirnov test, distribution of all data is normal (P>0.05).

Table 4. Kolmogorov-Smirnov on research variables

	Attention	Mobility	Self-control	Recognition plexus	Assiduity	Personality instability
Z Test statistics	1.04	1.03	1.35	1.13	1.15	1.30
Significance level	0.23	0.24	0.051	0.153	0.14	0.067

The multivariate analysis of variance (MANOVA) was also performed on impulsivity variables in three groups and both genders according to Table 5.

Table 5. Results of MANOVA in impulsivity variable

Independent variable	Name of test	Value	Degree of freedom for hypothesis	Degree of freedom for error	F-test	Significance level
Group	Pillai's trace test	0.806	12	156	8.776	0.000
	Wilks' lambda test	0.237	12	154	13.53	0.000
	Hotelling trace test	3.04	12	152	19.25	0.000
	Roy's largest root	2.979	6	78	38.72	0.000
Gender	Pillai's trace test	0.022	6	77	0.291	0.94
	Wilks' lambda test	0.978	6	77	0.291	0.94
	Hotelling trace test	0.023	6	77	0.291	0.94
	Roy's largest root	0.023	6	77	0.291	0.94

There is a significant difference between the industrial and traditional narcotics consumers and healthy people at least in one of the variables namely the attention, mobility, self-control, recognition plexus, assiduity, and personality instability (P=0.000), but there is not any significant difference between the both female and male genders in terms of above-mentioned variables (P=0.94). According to results for mobility and personality instability, there is a significant difference between the interaction of gender and groups, but there is not any significant interaction between gender and group.

Conclusion

In group variable (industrial narcotics consumers, traditional narcotics consumers, and healthy subjects), the significance levels of all tests are less than 0.05 indicating that there is a significance difference between the industrial narcotics consumers, traditional narcotics consumers, and healthy subjects at least in one of the dependent variables (Attention, mobility, self-control, recognition plexus, assiduity, and personality instability) (P<0.001). According to this finding, there is a significance difference between the industrial narcotics consumers, traditional narcotics consumers, and healthy subjects in terms of all impulsivity subscales (P<0.001), but there is not any significance difference between the industrial narcotics consumers and traditional narcotics consumers in all studied variables, but there is a significance difference between narcotics consumers and healthy subjects. The mean value for healthy subjects is significantly higher than the mean value for narcotics consumers. Results of this research are consistent with research by Fox and Bergquist who studied the procedure of emotions and impulsivity in cocaine consumers [12], Mokri and Ekhtiari who studied the relationship between impulsivity indices and risk-seeking behavior with craving for in narcotics consumption in different groups of opiate addicts [13], Haddadi who compared the effects of Risperidone and Fluoxetine in combination with treatment group of impulse control on improving the impulsivity and slip in crack-heroin addicts under the Methadone maintenance treatment (MMT) [14], and Azami et al who investigated the effect of emotion regulation training based on Gross model on reduction of impulsivity in drug-dependent individuals [15]. The variety of causes, which can lead to impulsive behavior, is the complicated point in the study of impulsive behavior. Impulsivity is the main core of numerous kinds of social harm such as drug abuse, pathological gambling, and crime [16]. According to results, there is a significant difference between narcotics consumers and healthy subjects. The mean value for healthy subjects is significantly higher than the mean value for narcotics consumers. In general, the results of this research are consistent with previous findings confirming that both groups of traditional and industrial narcotics consumers have higher impulsivity than normal people. However, there is not any difference between these two groups in any aspect of impulsivity according to evaluation by impulsivity test. Following the explanation of these results, for instance, a narcotics consumer may show such impulsive behavior due to the tendency to risk-taking behaviors, much attention to incentives, neglect of harm, interest in experiencing the new issues, or other psychological traits. Furthermore, the impulsive behavior is different from the com-

pulsive behavior under which the person is aware of the behavior, and the purpose of behavior is not pleasure but generally avoidance of anxiety. Furthermore, it is different from behavior caused by a failure in judgment and decision-making; and the person is in fact at the disorder judgment stage.

Suggestions

Since the quantitative measurement of human behavior has been always affected by mental background such as feelings, emotions, attitudes and perceptions, and the use of questionnaire as a self-report tool cannot determine the exact status of subjects, and the research has this restriction, this study is conducted on a small population; hence, the generalization of its results to other population members should be done with caution.

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Competing interests

The authors declare that they have no competing interests.

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Developing a scoring system to select cases requiring chest radiography following catheterization of the central venous

Catheterization of the central venous

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Abstract

Aim: Central venous catheterization (CVC) is a standard intervention with various side effects such as pneumothorax. The principle of routine chest radiography following catheterization has been recently challenged. The present research seeks to develop a scoring system to select patients requiring radiography following central venous catheterization. Material and Method: As many as 210 patients requiring central venous catheterization participated in this cross-sectional research. They were assessed and studied concerning pneumothorax risk factors including a body mass above 30, history of emphysematous disease or neck and chest cage surgery, a history of catheterization, number of punctures, inappropriate position during CVC, treatment with a ventilator. Finally, the pre- and post-catheterization chest radiographs were compared to one another, and the sensitivity and specificity of the scoring system were measured. Results: A frequency of 5.24% was reported for pneumothorax. There was a significant correlation between the number of punctures, patient's position and history of catheterization with the occurrence of pneumothorax ($P < 0.001$). A frequency of 80% was observed for pneumothorax with a score above 4. This frequency was significantly more than what was noted in the group with a score less than 4 ($P < 0.001$; OR: 174.2). The sensitivity and specificity of the scoring system used for the score above 2 were 81.8% and 87.9% respectively. Discussion: According to the results achieved in this research, the possibility of pneumothorax among patients with an overall score less than 2 is insignificant, and the routine radiography of the chest following the catheterization is not necessary. However in cases with a score of more than 4, the possibility of pneumothorax is higher, and it is necessary to conduct radiography with short intervals and even more than once.

Keywords

Central Venous Catheterization; Chest Cage Radiography; Pneumothorax; Scoring System

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Introduction

Central venous catheterization (CVC) has become a common intervention in many therapeutic centers, particularly in ICU [1, 2]. The central venous catheterization usually seeks to study hemodynamic variables, prescribe different liquids, medicines, blood products, and parenteral nutrition in critically ill patients. This intervention has serious side effects including pneumothorax, hemothorax, cardiac tamponade, sepsis and thrombosis [1-4]. These side effects are life-threatening even in the best hospitals and with the best equipment [3, 4].

The prevalence of pneumothorax for experienced doctors in 1.5 to 3% [5]. Considering the uncommon yet significant side effects of catheterization, chest cage radiography is routine and mandatory.

Various researches have been conducted recently to study the importance and usefulness of preparing routine chest radiography [6, 7] highlighting its little value. Moulgard et al. pointed to the fact that in simple routine radiographs of the chest cage usually prepared with a low quality increases the possibility of making mistakes and ignoring small pneumothoraxes. On the other hand, iatrogenic pneumothoraxes have no symptoms at first, and air leakage is so slow in critically ill patients undergoing treatment with positive-pressure ventilator, and this will result in delayed pneumothorax. The researchers of the current paper demand the omission of the law which requires routine preparation of radiographs after catheterization [6]. In a 4-year research which studied 2230 cases of catheterization, Pickor et al. showed that all cases of pneumothorax were marked prior to radiography and 48% of all radiographs were unnecessary [8].

Considering the dispute among the researchers and doctors concerning the routine chest radiograph after central venous catheterization, the present research seeks to develop a scoring system for patients requiring chest radiography following the central venous catheterization among the patients hospitalized in the ICU.

Material and Method

This is a cross-sectional research conducted on 210 patients hospitalized in the surgery and intensive care units of Vali Asr (PBUH) Hospital pf Arak city.

Need for central venous catheterization for any reason, a minimum stay of at least four days in the unit, no existence of chest tube and completion of informed consent certificate were the inclusion criteria defined for this research. Patient's death, intervention by other doctors, patient's desire to leave the research and any reason rendering the preparation of radiography impossible were the exclusion criteria of the research.

Obtaining the informed consent of the patient or his protector, all clinical information of the patient including his age, gender, body mass index, background diseases, and history of previous operations were recorded, and the score of each patient was determined based upon the scoring system recommended by the research. Two chest radiographs were made before and after catheterization for each patient. Except for the marked cases which required immediate tracking and timely treatment, the second radiograph of all patients was conducted 8 hours after catheterization. All processes of catheterization were carried out by a senior general surgery resident.

The scoring system used in the research is presented in Table 1. Finally, SPSS software and Chi-Square and Mann-Whitney U and logistic regression tests were used to analyze the data. ROC curve was also utilized to calculate the sensitivity and specificity of the test.

Table 1. The scoring system used in the research

Variable	Variable status	Score
BMI	30 <	1
	30 >	0
Number of punctures	3 <	2
	1-3	1
Appropriate position	Yes	1
	No	2
Emphysematous disease history	Yes	1
	No	0
Neck and chest surgery history	Yes	1
	No	0
Catheterization history	Yes	1
	No	0
Under ventilator	Yes	1
	No	0

Results

As many as 136 male (64.8%) and 74 female (35.2%) patients were studied in this research. The average age of the patients was 49.22 ± 95.146 years. The clinical information of the patients is presented in Table 2.

Table 2. The clinical information of the patients studied during catheterization

Variable		Frequency	percentage
History of Emphysematous	Yes	39	18.6
	No	171	0.4
History of neck or chest surgery	Yes	6	2.9
	No	204	97.1
Hospitalization unit	ICU	52	24.8
	Other units	158	75.23
Reason of catheterization	Access to central venous	102	48.57
	Need for complete parenteral nutrition	26	12.39
	Central venous blood pressure control	75	35.71
	Plasmapheresis	3	1.43
Catheterization site	Subclavian vein	199	94.76
	Jugular vein	5	2.38

The average length of preparing chest radiography after catheterization was 7.313 ± 2.11 hours (range: 1-24). Of all the patients undergoing catheterization for various reasons, 11 cases of pneumothorax (5.24%) and 1 case of hemothorax (0.5%) were observed, and ten patients underwent treatment using chest tube. The diagnosis of all cases suspicious of pneumothorax and hemothorax in the clinical examination was proved by preparing chest radiography.

As hemothorax was observed in only one patient in this

research, it was by no means possible to statistically study the correlation between the occurrence of hemothorax and the risk factors discussed in the current paper.

Of all the patients studied, 103 cases were under ventilator where 5 cases of pneumothorax were observed. No significant correlation was observed between ventilator and occurrence of pneumothorax (P = 0.807).

As it is shown in Table 3, there is a significant correlation between thenumber of punctures, patient's position (appropriate position), and history of catheterization with the occurrence of pneumothorax.

Table 3. Studying the correlation between the factors influencing the scoring system and occurrence of pneumothorax

Variable	Pneumothorax		
		Total (positive cases of pneumothorax)	P
BMI	30 >	188 (9)	0.391
	30 <	22 (2)	
Number of punctures	1-3	194 (2)	< 0.001
	3 <	16 (9)	
Patient's position	Appropriate	197 (3)	< 0.001
	Inappropriate	13 (8)	
History of Emphysematous	Yes	39 (4)	0.119
	No	171 (7)	
History of neck or chest operation	Yes	6 (0)	0.559
	No	204 (11)	
History of catheterization	Yes	5 (2)	< 0.001
	No	205 (9)	
Treatment with ventilator	Yes	103 (5)	0.807
	No	107 (6)	

Using the recommended scoring system (Table 1), an individual score ranging from 1 to 6 was calculated for each patient. Initially, a score of 1 to 4 was designated as low risk for occurrence of pneumothorax, and a score of 4 ≤ was considered highly risky. The occurrence of pneumothorax among patients with a score of 4 ≤ was significantly more (P < 0.001). According to the present research, the possibility of pneumothorax is 80% if the score exceeds 4.

Logistic regression method was also utilized to analyze the data. In logistic regression according to Enter's method, the following chance of pneumothorax occurrence in number of punctures with OR:4.26 ($CI_{95\%}$: 2.24-8.093 & P < 0.001), patient's position with OR: 103.47 ($CI_{95\%}$: 20.963-510.675 & P < 0.001) and history of catheterization with OR:14.519 ($CI_{95\%}$: 2.98-15.033 & P < 0.006) were reported.

Logistic regression according to Enter method was also conducted for patient's score based upon the above-said categorization. In this research, the chance of pneumothorax occurrence in the group with a high risk of pneumothorax (a score of 4 or more) and OR:174.2 ($CI_{95\%}$: 30.290-1002 & P < 0.001) was calculated.

The sensitivity and specificity of the scoring system used in this research were calculated by drawing ROC curve to determine the risk of pneumothorax occurrence. These two variables for a score of 2.5 or more were 81.8% and 87.9%, respectively.

Discussion

Based on the results of the present research, more than three punctures, inappropriate patient's position, and the previous history of catheterization have a significant correlation with the occurrence of pneumothorax. The higher number of punctures, inappropriate patient's position and the previous history of catheterization increase the chance of pneumothorax 4, 103 and 14 times respectively.

On the other hand, drawing a division between the scores obtained from the scoring system and dividing them into low risk (1 to 4) and high risk (4 or more) indicates a higher chance of pneumothorax in the high-risk group.

Utilization of portable method in preparing the radiography of some patients and the low quality of some radiographs were the limitations of this research, and a lot of efforts were made to keep these cases at the minimum level. The small number of hemothorax occurrence rendered the statistical analysis impossible.

According to the results of the present research, if the score obtained through the scoring system is less than 2, the possibility of pneumothorax occurrence will be very little (approximately 0), and the routine radiography of the chest will not be necessary. If the resulting score exceeds 4, the possibility of pneumothorax will be high, and chest radiography will be necessary more than once and with short intervals. In the present research, catheterization by trained and skillful people is described as a safe intervention [6].

In a research by Pickor et al., where 2230 cases of catheterization were studied, the prevalence of pneumothorax was 0.58% which was much less than the occurrence rate in the current research. This probably indicates the importance of the intervening doctor's skill. The present research found 48% of post-catheterization radiographs useless [8].

On the other hand, as all 11 cases of pneumothorax occurrence and 1 case of hemothorax were initially reported based upon suspicious clinical symptoms and later proved by chest radiography, the value of routine chest radiography is still disputed. In Pickor's research, all cases of pneumothorax were initially diagnosed by clinical symptoms. In his research, he has reaffirmed the importance of paying attention to clinical symptoms if it is necessary to prepare radiography [8]. Simultaneous attention to the score and clinical symptoms of the patient is necessary to decide about radiography.

Because a rise in the score of the patient and the effective variables results in the higher risk of pneumothorax, interventions in patients with a score of 4 or more is recommended to be conducted under sonographic or fluoroscopic guide to reduce the chance of pneumothorax occurrence. Interventions by an experienced physician is a useful method to reduce the possibility of influential complications.

Recent studies and guidelines have recommended catheterization under sonographic or fluoroscopic guide in adults as well as children. This intervention has been described as a factor which reduces the possibility of pneumothorax and other complications of catheterization [9-11].

Conclusion

The acceptable sensitivity and specificity of the scoring system used in this research and its simple utilization can help us in making decisions to prepare chest radiography following catheterization. We recommend further researches in various centers to measure the validity of the present system of scoring so that preparation of chest radiography after catheterization becomes purposeful and less time and equipment be wasted.

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Human Rights Statement: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Animal Rights Statement: Nonapplicable

Conflict of Interest Statement:

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Original Research
JCAM

An MRI study of various parts of pons

MRI study

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Abstract

Aim: In the field of neuroanatomy, morphometric studies on many parts of the brain are still not accessible. The appearance of magnetic Resonance Imaging (MRI) method has made it possible to reply many questions in this field. Material and Method: The dimensions of target parts were calculated by the MRI-associated measuring system and recorded along with the height of the patients. Results: The data showed a significant correlation between diverse parts of pons and the height in men ($p<0.05$). Among women, except for the length of tegmentum and the height of basal part of pons, significant correlations were found between height and the dimensions obtained for other parts of the pons ($p<0.05$). Discussion: The dimensions of different parts of pons in tall men and women were bigger than those in short ones.

Keywords

Magnetic Resonance Imaging; Pons; Height

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Introduction

With the advent of MRI and the possibility of producing precise and wonderful images from human brain at different planes, it is now possible to reply many unclear questions related with the effect of various factors such as height on human brain [1]. In the field of anatomy, mainly neuroanatomy, morphometric studies on many parts of the body are still not accessible and this maybe has been associated with the absence or unavailability of such equipments to previous scientists. Present data in neuroanatomy texts regarding the dimensions of different parts of the brain is restricted to major parts and usually one dimensional and little information on details of different sizes is available [2]. As the previous morphometric studies were done on cadavers through open brain surgeries and because of postmortem changes especially atrophy, and also inaccessibility to many parts of the brain in three-dimensional form in a live person, it is essential the current information attained from alive and healthy individual using new method to be compared with previously recorded cases. Hence, in present study effort has been made to study different dimensions of some parts of the pons in more details. This leads to generation of data associated with the size of these parts and further comparison of these values with height will give rise to results which can help broadening the horizon of the knowledge of anatomy. Since many pathologic cases including, syndromes, drugs and toxic agents can cause alterations in size of these parts [3], the present study could be helpful in identifying the racial difference regarding the size of target parts, difference in size of pons in live and dead humans and lastly, determining the size of different parts of pons in accordance with height. Previous works has mostly focused on the volume of pons [4 and 5] without reference to dimensions of several parts of this organ and only concentrated on the volume of some parts of the pons in men and women at different ages [6,7,8 and 9]. Considering the functions of pons, the importance of lesions involving this organ [10 and 11], and lack of information, it seems that performing morphometric studies on pons to determine and record the dimensions of different parts and also the effect of height on dimensions of these parts, to be crucial in enlightening such information.

Material and Method

This was an experimental study carried out on three hundred peoples referred to MRI center at Imam Reza hospital in Kermanshah (Iran). Forms were used to collect data from patients with demands for brain MRI. The data including height, history of earlier diseases were documented. However, only the patients with no history of any kind of diseases and with normal state of health were included in our study. The patient was located in a supine position while the subject's jaw was as close as possible to the chest and the Orbito Metal Base Line (OMBL) in a position vertical to bed surface. This is of major importance to make comparable investigations in different people. The MRI tool used in our study was a Phillips product (Netherlands), version 2009, a 20-inch LCD monitor, with an intensity of 2 Tessla, 4mm thickness at posterior cavity and 0.7 mm GAP. Following imaging process, morphometric studies were carried out using images with no rotation and artifacts selected based on evidence obtained through forms and also the report of MRI specialist on health state of brain for each patient. At next step, following the preparation of various sagittal, coronal, and axial views, the best T1 views, based on standard researches were selected for anatomical studies [11 and 12]. Using the device measuring system and also marking the image ends at two different points, the measurements were measured in mm (Fig1).



Figure 1. The axial view for morphometric study of transverse length of pons.

Regarding the lack of symmetry and regular geometric shape in parts under study, measurements were done at diverse directions and the biggest value was taken as the actual length. Repeating this procedure on other sections gave rise in generation of values, among those, the largest ones were adopted as real height, length, and width for the structure under study (Fig 2).

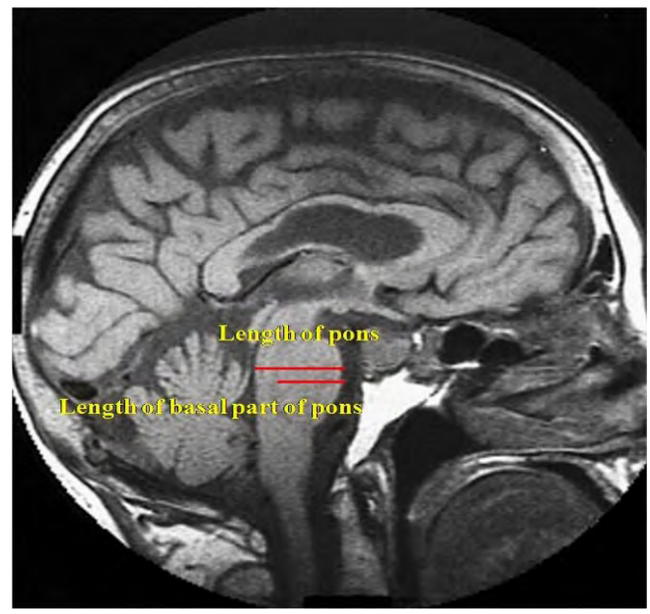


Figure 2. The Midsagital view for morphometric study of length of pons and basal part of pons.

Efforts were made to perform the same type of study on different persons using clear anatomical sections such as midsagital ones particularly in morphometric studies of pons (Fig 3).

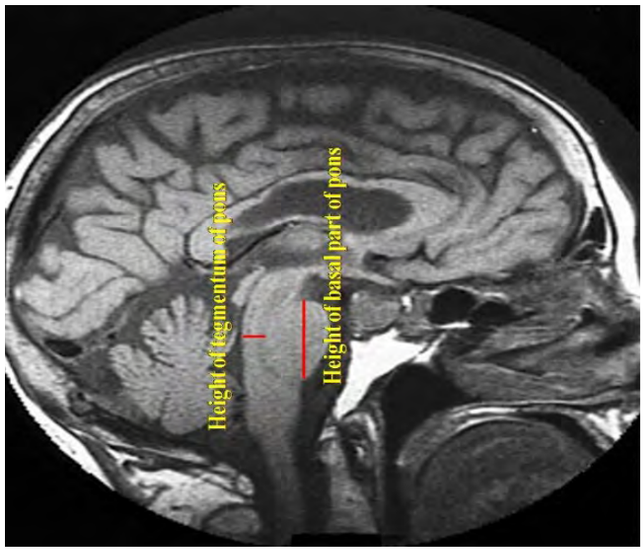


Figure 3. The Midsagital view for morphometric study of the height of basal and tegmentum part of pons.

Considering all preconditions, the patient was allowed to be included in our study. Thus, out of many patients, three hundred cases meeting all the requirements were involved in our study. Regarding the ethical considerations, special codes were used instead of actual names when filling forms or studying MRI images. Furthermore, all patients provided the study group with individually signed consensus forms while no obligation or extra costs were imposed.

Statistical examines were performed by using t test, Pearson's correlation coefficient and regression. Differences between groups with P value of 0.05 or less to be considered as significant.

Results

A total of three hundred healthy peoples including 124 males (41.3%) and 176 females (58.7%) aged between one and eighty-five years, were studied. The patients were divided into five groups Based on their height (table 1).

Table 1. Distribution of study groups based on their height

Height (cm)	49-149	150-159	160-169	170-179	180-200
Number of people	27	54	102	87	30
Percentage	8.7	18	34	29	10.3

Following the necessary investigations on study groups, the dimensions of different parts were obtained in millimeter. The size of various parts in five height groups is presented in table 2.

The information showed that there was significant correlation between different parts of pons and the height in men ($p<0.05$). Among women, except for the length of tegmentum and the height of basal part of pons, significant correlations were found between height and the dimensions obtained for other parts of the pons ($p<0.05$). Correlation and regression coefficients for those parts of the pons showing significant relationship with height were as follows: Height of tegmentum of pons: 15.10+0.03× (body height). Length of pons: 15.16+0.04× (body height). Length of basilar of pons: 11.55+0.03× (body height). Transverse length of pons: 17.84+0.06× (body height). Length of tegmentum of pons: 3.76+0.00× (body height). Height of basal of pons: 16.59+0.05× (body height). It means that when height increases by 1 mm, a value of 0.03 mm will be added to the Height of tegmentum of pons.

Discussion

The current study which was aimed to morphometrically investigate the pons and evaluating the effects of height on dimensions of pons, resulted in determination of sizes of different parts of the pons in accordance with height; a set of information unavailable in current reference anatomical texts so far. Furthermore, our data are suggestive of the presence of a size-associated correlation between the dimensions of various parts of pons with height as shown by the greater values for totally parts of pons in tall men compared to short ones. This relationship was only significant in few parts of pons in women and no significant correlation between the length of tegmentum, height of basilar of pons and the height of body was recognized. In general, the size of pons in tall individuals is bigger than that of shorter ones. Studies on healthy people pons using MRI only equated the volume of basilar of pons between two sexes considering the effect of age with no refer-

Table 2. Dimensions of different parts of pons in mm in different height groups (figures in brackets stand for standard deviation)

Height (cm)	Part of pons	49-149	150-159	160-169	170-179	180-200
Transverse length of pons	Male	23.94 (2.689)	26.83 (1.185)	26.99 (1.259)	27.51 (1.375)	27.91 (1.240)
	Female	22.45 (2.834)	26.34 (1.564)	26.89 (1.234)	27.11 (1.98)	27.26 (1.321)
Length of tegmentum of pons	Male	4.33 (0.485)	4.51 (0.621)	4.41 (0.574)	4.58 (4.70)	4.70 (0.47)
	Female	4.13 (0.53)	4.11 (0.78)	4.151 (0.186)	4.08 (4.66)	4.50 (0.12)
Length of basal part of pons	Male	14.83 (1.043)	16.85 (1.318)	17.01 (1.242)	17.8 (1.114)	17.43 (0.992)
	Female	13.13 (1.145)	16.56 (1.225)	16.88 (1.170)	17.63 (1.112)	17.03 (0.920)
Length of pons	Male	19.33 (1.495)	21.15 (1.122)	21.35 (1.367)	21.68 (1.233)	22.09 (1.164)
	Female	18.73 (1.528)	20.34 (1.409)	21.11 (1.225)	21.41 (1.175)	21.55 (1.99)
Height of basal part of pons	Male	22.06 (2.287)	23.81 (1.056)	24.42 (1.190)	24.65 (1.277)	25.7 (1.490)
	Female	21.12 (2.342)	21.01 (1.112)	22.22 (1.576)	21.05 (1088)	23.22 (1.481)
Height of tegmentum of pons	Male	19.06 (1.862)	20.43 (1.098)	20.81 (1.123)	20.96 (1.050)	21.65 (1.369)
	Female	18.22 (1.155)	19.78 (1.132)	20.34 (1.170)	20.86 (1.070)	20.98 (1.144)

ence to sizes of pons [11, 12 and 13], while the present study bears such information. In agreement with the study mentioned above, following morphometric study of different parts of pons by MRI and further comparison of results according to age and sex in healthy people, showed that some parts of pons such as transverse length, length of tegmentum, height of basilar, and height of tegmentum were larger than those of women with a significant correlation between some parts of pons and age increase [14], but no reference to possible relationship between dimensions of different parts of pons and height of individuals was made. A study of Koh et al, on Korean healthy youths, revealed that there is a direct relationship between the volume of brain and their height, confirmed by the data obtained in our study [15]. Also, they emphasized on lack of an obvious relationship between height and the volume of brain in women, consistent with data found in present work. The result of Raz et al., show that effect of body size, in particular the height, on different parts of pons, completed and supported by our findings [16]. In studies on basketball players by MRI, stressed on volume increase in some parts of their brains compared to normal people which could be attributed to higher height among those players supporting our data [17]. Several other studies related with pons have been carried out using MRI in which evaluations were made between healthy people and those with pathologic lesions such as multiple sclerosis [18 and 19], and further diseases [20 and 21], thus, the outcomes of present study due to its characteristics could help diagnosing such diseases more efficiently mainly those producing changes in dimension of pons [22]. The reason for changes in size of pons in accordance with age among men and lack of such effects in women is not clear as there are many uncertainties regarding the precise function of different parts of pons and also the association of these parts with genetic, sex and hormonal and hence needs further investigations. Finally, according to the findings of this study, it seems that the current study to be a distinctive work in which regardless of different factors including, genetic, hormonal, and environmental conditions not only provides information on sizes of diverse parts of pons, but also investigates the possible relationship between sizes of pons and height increase among two sexes. Moreover, concerning enormous ambiguities on exact function of different parts of pons and also the role and diversity of effectors, further studies are of prime urgency and the present work could be regarded as an opening to such investigations.

Conclusion

The sizes of different parts of pons in tall men were bigger than those in short ones. Among females, except for the length of tegmentum and the height of basal part of pons, the dimensions for other parts of pons in tall women were bigger that those obtained for short women.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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Effects of a novel seven-species probiotic against oropharyngeal bacterial infestation in adult trauma intensive care unit patients

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Abstract

Aim: Ventilator-associated pneumonia results from invasion of the lower respiratory tract and lung parenchyma by microorganisms. Our study aimed to investigate the efficacy of a new probiotic combination containing 7 bacterial species against oropharyngeal bacterial infestation in adult trauma intensive care unit patients. Material and Method: One hundred and fifty patients were placed in the two treatment groups by computerized random allocation in a 1:1 ratio and received either probiotics or placebo. Oropharyngeal cultures were taken on the 1st (before the intervention), 4th, and 6th days of admission. Results: The culture results of the 1st, 4th, and 6th days were comparable, and no statistically significant difference was noticed in the two arms of the study. Discussion: Based on the results of our study, administration of probiotics to alter early oropharyngeal cavity infestation with a potentially pathogenic microorganism in adult trauma patients admitted in Intensive Care Unit appears to be non-efficacious, even when a 7- species combination is used.

Keywords

Probiotics; Bacteria; Culture; Trauma; Intensive Care Unit

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Introduction

Nosocomial pneumonia is the second most common hospital-acquired infection and the primary cause of death among these infections [1]. One of the largest researches investigating the prevalence of intensive care unit (ICU) acquired infections is the EPIC study [2]. It was conducted in 1417 ICUs and included 10,038 patients. The prevalence of ICU acquired infections in this study was 21%, and 47% of these patients had nosocomial pneumonia. The underlying disease process, as well as the severity of the disease, can affect the risk of developing a nosocomial infection. Patients with a primary diagnosis of trauma are at an increased risk because of altered immune responses making them more susceptible to developing infection [2-4].

Ventilator-associated pneumonia (VAP) is considered a type of pneumonia that develops 48 hours or longer after application of mechanical ventilation through an endotracheal or tracheostomy tube. It results from invasion of the lower respiratory tract and lung parenchyma by microorganisms. Intubation compromises the integrity of the oropharynx and trachea and allows oral and gastric secretions to enter the lower airways. This complication occurs in 8%-28% of intubated patients in the ICUs and causes 24% to 76% mortality [5-7].

Many factors increase the susceptibility of critically ill patients to VAP including diminished defense mechanisms due to effects of critical illness and medical therapy, alteration of normal host microbial flora by antibiotic therapy, interference with normal clearance mechanisms due to lack of ciliary reflex, and changes in pH of gastric secretions as a result of proton pump inhibitors and H2 blockers administration [8].

Various preventive measurements have been employed to reduce the incidence of VAP among which, use of probiotics is a novel approach. Probiotics are live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host [9]. This approach is based on the theory that because of previously mentioned reasons, during an acute illness the normal gastrointestinal tract flora is replaced by a potentially pathogenic microorganism (PPM). Probiotics can potentially reduce the incidence of VAP through various systemic and local effects including reduced growth of PPM, improved immune function, improved gut mucosal barrier function, and reduced bacterial translocation [10-13].

Although there are some studies on the effects of 1-3 species-based probiotics on reducing the oropharyngeal pathogenic bacteria of mechanically ventilated patients, we evaluated the efficacy of a new probiotic combination containing 7 bacteria applied both in oral cavity and stomach in this setting.

Material and Method

The study was conducted in four academic adult trauma ICUs. The university ethical review board approved the study protocol (ID: CT_P_9341_4681), and it was registered in Iranian Registry of Clinical Trials (IRCT ID: 2014051417691N1). Written informed consent was taken from patients' surrogates. The intensivist supervised the screening process. Patients were eligible for the study if they were at least 18 years old, informed consent could be taken from the patient's surrogate, there was a high likelihood that the patient would remain intubated for the next 4 days. The exclusion criteria included: pregnancy, immunosuppression, previous prosthetic cardiac valve replacement or vascular grafts, cardiac trauma, history of rheumatic fever, endocarditis or congenital cardiac anomalies, traumas to the aerodigestive tract, tracheostomy, pancreatitis, and base of skull fracture.

Patients were divided into two groups by computerized random allocation in a 1:1 ratio. The doctors, nurses, and laboratory personnel were blinded to the group assignments. All patients continued to receive the routine oral care procedures (cleansed with swabs moistened with 1 mg/ml chlorhexidine (CHX) solution) and the same amount of anti-acid treatment (pantoprazole 40 mg daily).

The probiotic we used was lactocare provided as a capsule containing 1010 colony-forming units (cfu) of 7 probiotics in an inulin base. Included probiotics were; Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophiles, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, and Lactobacillus bulgaricus. It was manufactured by the Zist Takhmir Tehran Company, Tehran, Iran. The placebo capsules were made from dried milk powder by the same company in similar capsules.

The probiotics were administered as follows: each capsule (probiotic or placebo) was suspended in 20 cc of distilled water, and sterile gauze was soaked in the suspension and was rubbed in the oropharyngeal cavity by a trained nurse. The process was repeated every 12 hours, one hour before mouthwash and two hours before feeding. The cultures were taken before the daily oral health care and nasogastric feedings on the 1st (before the intervention), 4th, and 6th days of admission. For this, the patient's tongue was restricted with a tongue blade, and a sterile swab was rubbed against the oropharyngeal cavity and behind the uvula. The swab was then placed in a test tube considering sterile measurements and sent to the central lab within half an hour to be cultured on macconkey agar media. Culture results were categorized according to the number of colonies per high power field as follows: rare (<2 colonies), few (2-15 colonies), moderate (15-50 colonies), and many (> 50 colonies). The culture results were then compared between groups at the end of the study.

Statistical Analysis

Descriptive statistics were used to report the results. Also, t-test and its alternative Mann–Whitney U test, and chi-square tests were employed for analysis and comparing the results between two groups.

Results

Five hundred and eighteen patients were admitted in our trauma ICUs during the study period (Feb. 2014 – Sept. 2014), but only 150 were eligible for the study. One hundred and thirty-two cases were excluded because no relative was available during the first 24 hours of ICU admission, and 236 of cases were further omitted according to other exclusion criteria. After randomization, 10 patients from the probiotic group and 1 patient from the placebo group were excluded from the study due to incomplete data or occurrence of exclusion criteria. Finally, there were 65 patients in the probiotic and 74 patients in the placebo arms left "Figure 1".

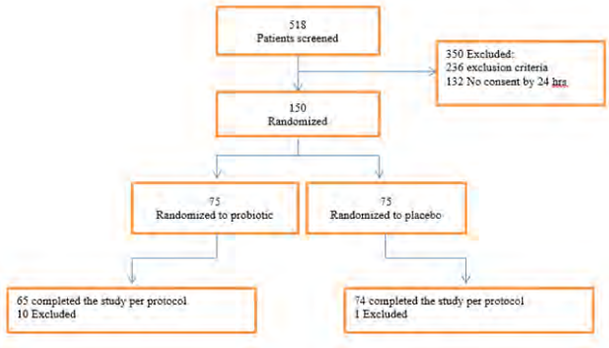


Figure 1. Study participants.

There were no refusals of consent for participation if victims were accompanied by a surrogate.

The demographic characteristics of the two groups and the culture results of the 1st, 4th, and 6th days were comparable, and no statistically significant difference was noticed in the two arms of the study "Table 1 and 2."

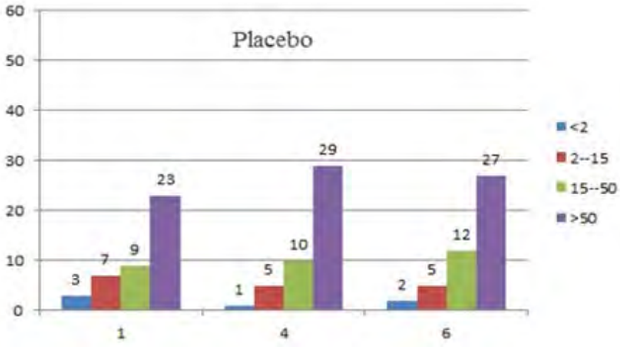
Table 1. Demographic characteristics of the patients in the two groups.

	Probiotic	Placebo	P-value
Number of patients	65	74	
Age, mean±SD	37.90±17.95	39.98±20.04	0.82
Male sex	49	52	0.50

Table 2. Comparison of oropharyngeal culture results between the two groups before (1st day) and after (4th and 6th days) the intervention.

		<2 colonies	2-15 colonies	16-50 colonies	>50 colonies	P-value
Positive 1st day culture	Probiotic	1	2	9	23	0.36
	Placebo	3	7	9	23	
Positive 4th day culture	Probiotic	3	1	10	31	0.29
	Placebo	1	5	10	29	
Positive 6th day culture	Probiotic	1	2	10	35	0.25
	Placebo	2	5	12	27	

Types of bacterial species did not statistically differ significantly between the two groups "Figure 2".



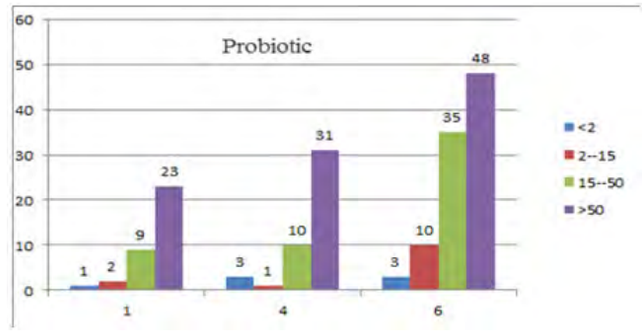


Figure 2. Comparison of bacterial growth in the 1st, 4th, and 6th days between the two groups.

Besides the probiotics had no effects on inhibition of PPM growth when compared by individual species, or as gram-positive and gram-negative groups "Table 3".

Table 3. Types of bacterial species involvement did not differ statistically significant between the two groups.

Bacteria	Probiotic	Placebo	P-value
MSSA	3	5	0.71
Pseudomonas aeruginosa	11	7	0.49
Enterobacteriaceae	4	3	1.00
Acinetobacter	13	12	1.00
Klebsiella	0	4	0.11
Proteus spp.	2	0	0.49
Escherichia coli	3	4	1.00
Citrobacter spp.	2	1	1.00
BHS	0	1	1.00
Serratia spp.	1	0	1.00
Hafnia spp.	0	1	1.00
Pneumococci spp.	0	2	0.49
Candida spp.	0	2	0.49
Normal flora	9	10	0.78
No growth	3	1	0.61
Gram negative bacteria	51	49	0.35
Gram positive bacteria	3	5	0.35

Abbreviations; MSSA: Methicillin Sensitive Staphylococcus Aureus. BHS: Beta Hemolytic Streptococcus.

Discussion

Adult trauma ICU patients are often young with no or minor underlying diseases; however, they are at risk for developing nosocomial infections due to the destruction of natural body barriers, trauma-induced pathophysiologic changes, and intubation in critical medical situations.

VAP is an important cause of increased morbidity, mortality, prolonged ICU stays, and increased health care costs in critically ill patients [14-16]. Early VAP is applied when the disease appears in less than 5 days after the admission and is generally caused by endogenous community-acquired pathogens. Late VAP-responsible pathogens include potentially multidrug-resistant nosocomial organisms residing in oropharyngeal or gastric contents [14, 17]. In the majority of ICUs, Staphylococcus aureus, Pseudomonas aeruginosa, and Acinetobacter baumannii are the most common organisms isolated in VAP; however, causative organisms vary between and within hospitals [18].

In 2008, Rice introduced a coterie of microorganisms that could

escape the effects of antibacterial drugs and had the greatest share of nosocomial infections under the acronym 'ESKAPE' (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species). They termed them as the 'top six bugs' [19]. However, other authors [20, 21] have proposed moving forward the term 'ESKAPE' to a more inclusive acronym termed 'ESCAPE' in order to represent Clostridium difficile (as the new C) and Enterobacteriaceae (as the new final E), encompassing more fully all the current problem pathogens that challenge the efficacious treatment of infectious diseases.

One of the methods applied in providing oral care for the intubated patients in the ICU is the use of CHX. It was proved to reduce the oropharyngeal pathogens and the incidence of VAP in these patients [22, 23]. However, CHX is associated with various side effects ranging from teeth discoloration, irritation of oral mucosa, and burning sensation of the tongue [24, 25] to a more serious adverse effect of allergic reactions in the oropharynx. Moreover, CHX has little effect on gram-negative bacteria [26], and its regular use can result in increased risk for emergence of resistant microorganisms.

A novel approach to decrease the incidence of VAP is the application of probiotics. The World Health Organization's 2001 definition of probiotics is "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" [27]. Use of probiotics does not eradicate the PPM, but it delays the colonization process while the patient is intubated. It also helps boost the patients' immune system and gut mucosal barrier function [28-31].

While all the previous studies had used 1-3 species of bacteria in the form of probiotics, with Lactobacillus as the main species, we decided to use a 7-species combination of probiotics with the concept that the use of a wider range of species can have greater effects on diminishing the colonization of oropharynx with PPM. However, we did not find any benefits in the application of the 7 species probiotic, as it did not alter the rate of PPM growth. This finding is in agreement with a previous study conducted in 2008 with a Lactobacillus based probiotic [32]. Although we used a combination of 7 species, the probiotic was still inefficient [33].

In fact, although not statistically significant, the growth rates were higher towards the end of the study in the probiotic arm (Figure 2). This finding can imply that probiotics might even provide a proper setting for the further growth of PPM and further increase the risk of nosocomial infections.

The results of our study indicate that gram-negative bacteria were more prevalent compared to gram-positive species (92.5% vs. 7.5%) and Acinetobacter was the most common PPM in both groups (24.0 % in the probiotic group and 22.2% in the placebo arm).

However, our study has some limitations; the ICUs this study was conducted in, are mainly trauma-based units and most of the admitted patients are young and without underlying medical diseases. The long list of exclusion criteria also limits our study to a selected group of patients. Hence, further large-scale studies including wider ranges of patients are needed to confirm our findings.

Conclusion

Administration of probiotics to alter early oropharyngeal cavity infestation with PPM in adult trauma patients admitted in ICU appears to be non-efficacious, even when a 7- species combination is used.

Conflict of interest

The authors declare no conflict of interest.

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Investigating the causes of hand paresthesia in the patients admitted to the electrodiagnostic center of martyr Sadoughi Hospital in Yazd

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Abstract

Aim: Paresthesia is an abnormal sensation in the hands characterized by tingling and numbness of the hands. Neuropathy is the most common neurological condition that causes peripheral nervous system involvement and creates tingling and numbness. Carpal tunnel syndrome is the most common neuropathy in the upper organs. Medical history and physical examination are the basic methods for the detection of neuropathies, and electrodiagnostic studies make a decisive diagnosis. The aim of this study was to investigate the causes of paresthesia in patients admitted to Martyr Sadoughi Hospital in Yazd. Material and Method: This is a cross-sectional descriptive study. Sampling in this study was as a census of all patients admitted during the study. A total of 660 patients (512 females and 148 males) were enrolled in the study based on the inclusion criteria from April 2014 to June 2015. After the history and physical examination, x-rays and electrodiagnostic tests were performed for the patients. Afterward, required questionnaires for the patients were completed and analyzed by SPSS software using chi-square test. All probabilities less than 0.05 were considered as statistically significant. Results: Most patients were housewives (69.1%) in the age group of 40-49years (33.3%) who had referred while complaining paresthesia in both hands (54.6%). Median nerve sensory disorder was common and had happened typically in 26.1% of patients. Women with carpal tunnel syndrome comprised 66.4% of the cases. One-sided and two-sided carpal tunnel syndrome, respectively, were recorded in 15.2% and 43.6% of patients. The second cause of paresthesia was cervical spondylosis occurring in 25.5% of patients being more common in the age group of 60-80 years. Discussion: Carpal tunnel syndrome was the most common cause of paresthesia in the patients of our study.

Keywords

Carpal Tunnel Syndrome; Paresthesia; Electrodiagnostic Studies

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Introduction

Paresthesia is an abnormal sensation in the hands characterized by tingling and numbness of the hands. This impairment is caused by the discharge of large sensory fibers that can be created by compression, hypokalemia, and a variety of nervous diseases. In addition, nerve root lesions or isolated peripheral nerves may be the cause of paresthesia [1]. The healing ability of nerves is lost with aging, which leads to the occurrence of progressive destruction of sensory perception [1]. Physical examination is sufficient to determine the cause of paresthesia in most cases. However, the use of electrodiagnostic testing such as Electromyography (EMG) and Nerve Conduction Velocity (NCV) raise the accuracy of diagnosis and reduce plausible differential diagnoses [1]. Compressive neuropathy occurs in certain predictable regions of the upper organs, and the different types can be evaluated with the same methods of likely similar pathophysiology. Neuropathy and localization of nerve compression are detected by the use of clinical examination, electrodiagnostic tests, and according to common places of pressure on the nerve [2]. Carpal tunnel syndrome, which involves the median nerve in the wrist is the most common compressive neuropathy in humans. This disease was first introduced by Foix Marie (1913) as a clinical disease in patients with two-sided thenar atrophy. The incidence of carpal tunnel syndrome is estimated to be 125/100,000. It occurs in women 1.52-2 times more than men. It is observed in people who use their hands frequently in their daily activities; the dominant hand is often involved being two-sided in at least 10% of patients [3].

Any person who has paresthesia and muscle atrophy within a peripheral nerve should suspect the entrapment of peripheral nerve. The involvement mechanism changes in accordance with the relationship between the nerve anatomy and the incoming mechanical force [13]. Intense and annoying paresthesia is often caused by polyneuropathy [4]. Cervical spondylosis (as a cause of hand paresthesia) is the destructive disease of the cervical vertebra that is extremely common in adults and becomes more prevalent with aging. The most common surface of cervical destruction is between the spaces C6-C7, C5-C6, which lead to radiculopathy of C7 and C6 nerve roots.

In spite of physical strength, many patients are incapable of doing things due to the involvement of the one of the most important organ, i.e., the hands. Some patients are not even able to perform everyday tasks, and a group suffers from psychological complications. A faster diagnosis can be reached through the knowledge of age, gender, and common cause. Early diagnosis and proper treatment can solve a lot of problems with patients. Due to these reasons, this study investigated the causes of hand paresthesia in patients admitted to martyr Sadoughi Hospital in the city of Yazd.

Paresthesias

Paresthesias are abnormal sensations experienced in the absence of specific stimuli [5]. These sensations are usually described as burning, tingling or numb feelings, although they may be described as feelings of cold, warmth, prickling, pins and needles, skin crawling or itching. The most common locations of paresthesias are the hands, arms, legs, and feet, although paresthesias can be present anywhere on the body. Paresthesias are contrasted with dysesthesias, which are abnormal interpretations of appropriate stimuli [6]. Paresthesias are common presenting complaints, and diagnosis is usually assisted by knowing the specific clinical presentations associated with various paresthetic syndromes.

The basic pathophysiology of paresthesias is an altered nerve or nerve pathway function. Paresthesias are thought to represent abnormal showers of impulses generated from an ectopic focus [7] and can arise from an abnormality anywhere along the sensory pathway, from the peripheral nerves to the sensory cortex [8]. Paresthesias can be caused by central nervous system or peripheral nervous system abnormalities. Central nervous system causes include ischemia, obstruction, compression, infection, inflammation, and degenerative conditions.

Diagnostic approach

Paraesthesias can be caused by a wide range of conditions affecting the nervous system at any level. Most patients have peripheral neuropathy, but all causes should be considered. The clinical history and physical examination narrow the differential diagnosis and guide the need for further investigations. The aim of the examination is to determine whether the pathology is likely to be affecting the peripheral nerves, plexuses, dorsal spinal roots, spinal cord, or brain, and to identify additional signs of the underlying cause.

Diabetic neuropathy, hypocalcemia, vitamin deficiencies, drug toxicity, and minor infections such as shingles or HSV can usually be diagnosed clinically or with laboratory testing. All other peripheral neuropathies require EMG with nerve conduction studies to confirm and characterize the neuropathy. If the history and examination suggest a plexopathy, a radiculopathy, or a lesion affecting the spinal cord, brainstem, or brain, imaging is required [9].

Characteristics of the paraesthesias

Description: It is important to characterize the paraesthesias being experienced by the patients. The patients should be encouraged to describe their symptoms in detail in their own words. Common descriptions include burning, stabbing, pins and needles, prickling, stinging, and sharp shooting pains. It is important to establish if there is an associated loss of sensation and if it is in the same area as the paraesthesias. Painful paraesthesias suggest an inflammatory or ischemic process such as vasculitis. Shooting pains are characteristic of nerve entrapment. Burning pains are characteristic of paraesthesias affecting small unmyelinated fibers. Paraesthesias may occur as part of a migraine aura or have an onset at the same time as the headache, and they typically last <1 hour from the onset of the headache.

Onset: It is important to reveal if the symptoms had a sudden onset or if they evolved over seconds, minutes, hours, days, or weeks. A sudden onset suggests stroke or trauma. Symptoms that evolve over several seconds suggest epilepsy. Symptoms that evolve over minutes suggest a migraine, panic attack, or fish poisoning (if the patient has ingested fish within the previous 8 hours). An insidious onset is characteristic of inherited neuropathies.

Duration and severity: The patient should be asked whether the symptoms are constant or relapsing and remitting and whether there has been any symptom progression. A history of similar previous symptoms should be sought. Muscle pain, atrophy, or weakness in the same anatomical distribution as the paraesthesias indicates a sensorimotor peripheral neuropathy (often a sign of more advanced disease).

Localization: The location of the symptoms indicates the level of the lesion. Localized symptoms indicate a peripheral mononeuropathy or a plexopathy if in the distribution of one or more peripheral nerves, or a radiculopathy if in the distribution of a dermatome. If symptoms suggest a peripheral mononeuropathy, a more detailed history should be taken to assess for focal nerve entrapment syndromes. Paraesthesias affecting the first 3 digits of the affected hand suggest carpal tunnel syndrome. Symptoms are usually worse at night (awakening patient from sleep) and exacerbated by prolonged wrist extension such as driving, typing on a keyboard, or reading a newspaper. Patients may also have pain in the wrist or hand possibly extending into the forearm, elbow, or shoulder.

Paraesthesias affecting the fourth and fifth digits suggest ulnar neuropathy, which may be induced by prolonged or repetitive flexion of the elbow or repetitive leaning on the elbow. Paraesthesias in the lateral leg or dorsal foot may indicate fibular (peroneal) neuropathy. Patients may also have a foot drop. The nerve compression is usually due to the repetitive crossing of the knees or prolonged kneeling, crouching, or squatting, but a history of trauma or previous knee surgery may also be present. Paraesthesias in the medial aspect of the foot suggest tibial neuropathy, which is relatively rare. Burning paraesthesias with increased sensitivity to touch or pressure in the anterolateral thigh region suggest meralgia paraesthetica, produced by compression of the lateral cutaneous nerve of the thigh. Paraesthesias characterized by persistent itching, localized unilaterally on the upper back, are called notalgia-paraesthetica. Symptoms may also include pain, tingling, numbness, or increased sensitivity to light touch in the affected area. Notalgiaparaesthetica is thought to be due to compression of the dorsal or sensory branches of the spinal nerves, from dermatomes T2 to T6, by paraspinal muscle spasm or by bony degenerative changes in the spine at these levels [9].

Material and Method

This study was a descriptive study conducted through case series method. The population in this study were all patients complaining hand paresthesia referred to the neurology clinic and electrodiagnostic center of Martyr Sadoughi Hospital in Yazd during the study period (April 2014 to June 2015). Samples were selected by census from the population based on clinical observations (signs and symptoms), clinical measures (electrodiagnostic tests of EMG, NCV) and cervical radiography during the fifteen-month period of the study, in which 660 patients were examined.

First, detailed histories were taken from the patients by questioning about the presence of complaints such as numbness, tingling, numbness, and tingling of the hands and weaknesses in everyday tasks, which was followed by a necessary physical examination. Then NCV, EMG, and radiography was performed for all patients and questionnaires were completed containing information such as age, gender, occupation, involved hand, nerve inspections (sensory and motor impairments), neck radiologic findings, EMG and NCV. The results of the questionnaire were analyzed using chi-square test. All probabilities less than 0.05 were considered as significant.

Results

In this study, a total of 660 patients (512 females and 148 males) participated who complained about hand paresthesia and referred to the neurology clinic and electrodiagnostic center of Martyr Sadoughi Hospital in Yazd during the study period (April 2014 to June 2015). They were divided into four groups of 19-39, 40-49, 50-59, and 60-80 years. The age group of 40-49 years was of greatest abundance (33.3%) among the patients.

Among the patients, 456 (69.1%), 80 (18.8%), and 80 (12.1%) individuals, respectively, were housewives, self-employed, and employees. The numbers of patients complaining about paresthesia in the right, left, and both hands were 180 (27.2%), 120 (18.2%), and 360 (54.6%) individuals, respectively. Groups of 18 (27.2%), 120 (18.2%), and 360 (54.6%) patients, respectively, complained about paresthesia in the right, left, and both hands. Most of the patients (89.8%) with hand paresthesia were not affected by hand movement disorder. In the inspection of totaling 420 patients (63.7%), none of them showed hand sensory disorder; the majority of these patients were women in the age group of 50-59 years. From a population of 512 female patients, 132 (25.8%)and 32 (6/2%) individuals, respectively, displayed median and ulnar nerve sensory impairments with the former being more common in the age group of 19-39 years. Sensory abnormality in the radial nerve pathway was observed in none of the patients, and 0.6% of patients exhibited sensory dysfunction in the pathway of all three nerves (median, ulnar, and radial).

A total of 388 (58.8%) patients had carpal tunnel syndrome in the electrodiagnostic test examinations with the highest prevalence in the age group of 50-59 years (72.2%). One hundred (15.2%) of our patients with an average age of 45.6 years experienced one-sided carpal tunnel syndrome and 288 (43.6%) of the samples with an average age of 50.3 years endured two-sided carpal tunnel syndrome. The numbers of females and males with carpal tunnel syndrome equaled 340 (66.4%) and 48 (32.4%), respectively. No significant differences were found between the mean ages of patients ($p = 0.267$) nor between the duration of symptoms in the patients ($p = 0.467$) based on the results of electrodiagnostic tests.

According to the neck cleavage and profile, the prevalence of cervical spondylosis increased with aging, so that the majority of patients with cervical spondylosis were in the age group of 60-80 years. The electrodiagnostic tests revealed radiculopathy in 44 patients. The numbers of patients with C6, C7, and C8 nerve root radiculopathy, respectively, were 28 (4.2%), 12 (1.8%), and 4 (0.6%) individuals with average ages of 44.8, 48.6, and 46 years. The radiculopathy of C6 nerve root was the most common type of radiculopathy, and this disorder was more frequent in men than in women, most of which lied in the age group of 40-49 years. Polyneuropathy was detected in 12 (1.8%) of patients studied. Six percent of the patients had ulnar

nerve compression with the elbow as the most common place of compression (cubital tunnel syndrome), which was more prevalent in the males of 40-49 age group. There were no relationships between the duration of symptoms and the results of electrodiagnostic tests.

Discussion

The most common cause of hand paresthesia in the studied patients was carpal tunnel syndrome (58.8%). Most of our patients were housewives (69.1%). The patients aged between 19-80 years. Similarly, Kouyoundjian reported patients' ages of 17-83 years [10]. The highest prevalence of carpal tunnel syndrome was found in the age group of 50-59 years (72.2%). Nakasalto et al. (2003) also reported similar results [11]. The prevalence of carpal tunnel syndrome was greater in the population of women than in that of men. Likewise, of 388 patients with carpal tunnel syndrome in our study, 340 (87.6%) individuals were females. In a study by Kouyoundjian on 668 patients with carpal tunnel syndrome, 91.3% of patients were females [10].

Bekkeund et al. (2001) reported the prevalence of carpal tunnel syndrome in a public population to be around 3%, which was more prevailing in women and people who performed handwork. The job difference between men and women can explain the increased prevalence of carpal tunnel syndrome in women [12]. In most of the patients studied (54.6%), both hands were involved with the right hand more impaired than the left one. These results are similar to those of Kouyoundjian, in which 72% of patients complained about two-sided impairments [10]. Moreover, Stevens et al. (1988) concluded that 75% of patients with carpal tunnel syndrome showed more severe symptoms in their dominant hand and a half of them had two-sided impairments [13]. The duration of symptoms in the patients was 1-120 months, which is similar to that reported by Kouyoundjian [10].

Ulnar nerve compression was more prevalent in our male samples as was also recorded by Richardson et al. (2001). The results of neck radiography indicated a direct relationship of cervical spondylosis with aging such that it was recorded in 108 (90%) out of 120 patients in the age group of 60-80; this finding corroborates those noted in literature in which the prevalence of cervical spondylosis was reported to be 5-10%, 50%, and over 90%, respectively, in a population aged 20-30, up to 45, and over 60 years [14].

Conclusion

The most common cause of hand paresthesia was the involvement of median nerve in the form of carpal tunnel syndrome, which mainly occurred in the housewives. It is, therefore, recommended that women work with both hands as far as possible and avoid folding and keeping the hands in flexion for a long time in order to prevent the disease. Any patient with paresthesia of both hands, especially in the age group 50-59 years and also females, should first be provided with clinical measures in order to verify the confirmation or rejection of carpal tunnel syndrome and, in case it was disapproved, other paresthesia causes should be looked for. Cervical spondylosis in old age should also be considered as one of the common reasons of paresthesia and neck radiography (cleavage profile) has to be accomplished for the diagnosis.

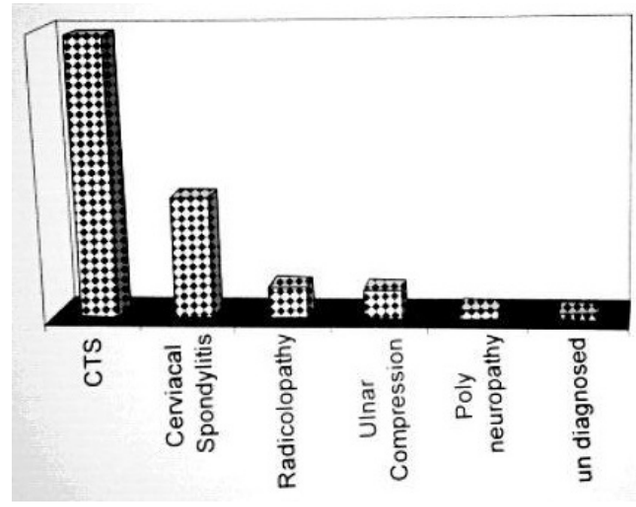


Figure 1. Distribution of factors causing hand paresthesia in the studied patients

Table 1. Distribution of hand disorder by age in the studied patients

Disorder / Age group	No sensory impairment		Median sensory impairment		Ulna sensory impairment		Involvement of three nerves		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
19-39	92	52.3	64	36.3	20	11.4	0	0	176	100
40-49	140	63.6	52	23.6	24	10.9	4	0.6	220	100
50-59	112	77.8	24	16.7	8	5.6	0	0	144	100
60-80	76	36.3	172	26.6	12	10	0	0	120	100
Total	420	63.6	172	26.1	64	9.7	4	0.6	660	100

Table 2. Distribution of average ages in the studied patients based on the results of electrodiagnostic tests

Patients' age Results of electrodiagnostic tests	Number	Average	Standard deviation
Normal	176	44.7	12.8
One-sided carpal tunnel syndrome	100	54.6	11.19
Two-sided carpal tunnel syndrome	288	50.3	13.21
Radiculopathy of Root C6	28	44.8	14.57
Radiculopathy of Root C7	12	48.6	14.57
Radiculopathy of Root C8	4	46	-
Cubital tunnel syndrome	16	33.7	10.04
Ulna compression in the shoulder	4	40	-
Polyneuropathy	12	52.6	15.94
Ulna compression in the arm	12	45.6	6.02
Ulna compression in the forearm	4	43	-
Ulna compression in the wrist	4	59	-
Total	660	47.3	12.62

Competing interests

The authors declare that they have no competing interests.

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Comparing and studying post-rhinoplasty operation sore throat

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Abstract

Aim: Rhinoplasty is one of the most common types of plastic surgery. The recent years in Iran have witnessed a significant growth in the number of rhinoplastic surgeries. As a result, putting this country in the top global ranking. Bleeding and sore throat are the most common complications during and after rhinoplasty. Sore throat is a common post-operation complaint among patients. This sore throat is probably caused as result of different techniques utilized by anesthesiologists. The present research seeks to compare the frequency and level of sore throat in the oral-pharyngeal pack and nasopharyngeal pack methods among patients undergoing an elective rhinoplastic operation. Material and Method: This is a clinical trial research where as many as 76 female patients older than 18 who had resorted to private operation centers for elective rhinoplastic surgery were studied. Having determined the exclusion and inclusion criteria for the participants, they were divided into two equal groups. Pain measurement numerical scale system was used to measure pain score in recovery, while direct questioning was utilized 12 hours later. Complications such as coughing, vomiting and nausea and patient's status during the recovery period and 12 hours after operation were also documented. The results were analyzed using SPSS v.17. Chi-square test (a non-parametric statistical test) was utilized to study the data. The level of significance in this research (P-value) was set below 0.05. Results: The results indicate a statistically significant difference between different types of packs used in rhinoplasty in terms of clinical complications such as the level of sore throat, coughing, nausea, and vomiting (p-Value < 0.05). According to the results achieved in this research, it turned out that utilizing nasopharynx could result in a significant reduction of coughs, sore throat, nausea, and vomiting among those patients undergoing rhinoplastic surgery. Furthermore, a better state of recovery was observed among those individuals utilizing nasopharynx compared to those who had used oral-pharyngeal pack. Discussion: Considering the results achieved in this research, it is concluded that nasopharynx pack has a better performance in preventing severe sore throats and other complications of rhinoplastic surgery.

Keywords

Rhinoplasty; Sore Throat; Anesthesia; Oral-Pharyngeal Pack; Nasopharynx Pack.

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Introduction

Rhinoplastic surgery is one of the most common types of facial cosmetic surgeries, and it plays a major role in changing cosmetic proportions of the face [1]. Rhinoplasty is one of the most common types of plastic surgeries. Nose plastic surgery is a detailed job where the difference between good and bad may be 1 to 2 mm [2, 3]. We may say that rhinoplasty or nose plastic surgery is one of the most accurate and difficult types of plastic surgeries [4, 5]. The word rhinoplasty is formed by *rhino* meaning nose and *plasty* meaning reform or beautification. As many as 276 thousand cosmetic nose surgeries were reported in the US in 1998 [6]. Closer accounts report as many as 201 thousand cases of rhinoplasty in this country as of 2005 [7]. Rhinoplasty has experienced significant growth in Iran over the last few years putting this country on top rank in the world. According to statistics, there were as many as 35 thousand cases of rhinoplasty only in Tehran in 2006, while the total number of this surgery in the same year in England was only 6 thousand cases [8]. Bleeding and sore throat are the most common complications during and after rhinoplasty. Sore throat is considered to be a common post-operation complaint. The prevalence of sore throat after tracheal intubation was 14.4 to 50 percent [1-8] while using pharyngeal mask reduced this number to 5.8 to 34 percent [9-11, 5]. This great difference in prevalence is probably caused by different techniques used by anesthesiologists and differences between anesthesiologists and patients in terms of their description of the sore throat. Using an oral-pharyngeal pack or stomach suction at the end of operation can help reduce post-operation nausea and vomiting. Nasal packing is one of the therapeutic measures taken in order to control nose bleeding caused by injuries, post-paranasal sinus, and nasal cavity surgery bleedings [9]. The purpose of using a tampon in rhinoplasty is to control post-operation bleeding, prevent the formation of a hematoma in the septum, fix nasal septum in a direct line after the operation, and correct deviations [10]. Various materials such as strip gases (meshed or regular tampon) impregnated with antibiotic ointment, merocel, and ativan. Most strip gases used to pack the patient's nose are impregnated with Vaseline or antibiotic ointment [10]. Several researches have been conducted over this issue, and we will have a brief review of them. Elyassi et al. (2011) studied the prevalence of sore throat after rhinoplasty in two groups who had undergone general anesthesia (GA) and conscious sedation (CS). They utilized a numeric rating scale in a clinical trial in order to stud and assess the level of sore throat at the end of operation and 4, 12, and 24 hours after it. The prevalence of sore throat after operation and 4, 12, and 24 hours after rhinoplasty in CS group compared to GA group is reported here respectively: 34.9% and 34.9% (P = 0.99), 27% and 33.3% (P = 0.27), 14.3% and 22.2% (P = 0.10), and 10.3% and 15.9% (P = 0.19). They arrived at the conclusion that general anesthesia plays no independent role in controlling sore throat. The results of their researches also showed that using sedatives may increase the risk of post-operation sore throat. Thus, none of these two anesthetic methods are superior to the other one in terms of reducing levels of sore throat [11]. Turan et al. (2004) studied the efficiency and safety of using Gabapentin for those patients who had undergone rhinoplasty or sinus endoscopy. In this research, Gabapentin or placebo was used for patients one hour before the operation. 25 people in each group received Propofol, fentanyl, and local anesthesia. The pain and sedation scores within the 5th, 15th, 30th, 45th, and 60th minutes of operation and within 2, 4, 6, 8, 12, 16, 20, and 24 hours after operation were measured. An intramuscular injection of Diclofenac (75 mg) as an Analgesic was prescribed for everyone. They reported significantly lower pain scores during operation and within the 45th and 60th minutes of operation in the group who had received gabapentin. Compared to placebo, they reported a significant reduction of pain during and after operation as a result of utilizing gabapentin among those patients undergoing rhinoplasty or sinus endoscopy surgery. As a result, dizziness may be considered as a setback of this medicine [12]. Various experiences have pointed to the fact that the type of pack used in rhinoplasty can also influence the control or intensification of sore throat or other complications of surgery. The present research also seeks to study and compare the level of sore throat in oral-pharyngeal pack and nasopharynx pack methods for those patients undergoing elective rhinoplasty.

Material and Method

This is a clinical trial research conducted in order to measure and compare the level of sore throat in oral-pharyngeal pack and nasopharynx pack methods among patients undergoing elective rhinoplastic surgery. For this purpose 76 female patients older than 18 years who had applied for elective rhinoplastic surgery took part in the research. The patients were divided into 2 groups, each one composed of 36 people. An oral-pharyngeal pack was used for one group, while nasopharynx pack was used for the other. These patients who were in two classes of ASA 1 and 2 underwent GA. The following inclusion criteria were defined: no pre-operation sore throat, not smoking cigarettes, no previous history of head and neck trauma or surgery, no known cardiac, pulmonary, or digestive diseases or endocrine, no history of sensitivity or reaction to sedatives or anesthesia. Those with Mallampati 3 & 4 and laryngospasm during general anesthesia or CS and laryngoscopy were excluded from the research. Different criteria were studied by questionnaires including patient's age, sore throat, the length and existence of nausea and vomiting in recovery and 12 hours after surgery. All the information was registered in pre-defined papers by an anesthesiologist. GA was conducted by anesthesiologists. It should be noted that different surgeons performed the operations. In GA group, the patients had a supine position in operation room. Levels of saturated oxygen, pulse and the respiratory state of the patients were constantly monitored and studied in the operation room. The heart rate and non-invasive blood pressure of patients were also constantly monitored. Intravenous injections of 2-3 µg/kg Fentanyl, 0.05 mg/kg Midazolam, and 1-1.5 mg/k Lidocaine were conducted before anesthesia. Thiopental 5 mg/kg and Atracurium 0.5 mg/kg were used for anesthesia. Then low-cuff pressure PVC tracheal tube with a high volume (7-7.5 size based on the size of patient's glottis) was used for intubation (the cuff of trachea tube was filled by air with a pressure of 15-20 cm H_2O in order to have the minimum amount of leakage). An 85-bladed laryngoscope and Magill forceps were used to fix the wet pharyngeal

pack and nasopharynx pack. Anesthesia was maintained with a repetitive dose of Atracurium and minimum alveolar concentration of isoflurane (MAC 1-0.8). Systolic blood pressure was restricted to 75 to 100 mm, and intravenous nitroglycerin and propranolol were also used if necessary. When rhinoplasty was over, Atropine (0.02 mg/kg) and Neostigmine (0.04 mg/kg) were used to reverse muscle relaxants. After removal of pharyngeal pack and nasopharynx pack, the patients were completely extubated in awakened state. Using numeric rating scale, the level of post-operation sore throat was studied and measured. The raw data was analyzed by SPSS v.19. The normality of data was then studied for all variables, and appropriate statistical tests were used based on the normality status. Chi-Square (a non-parametric statistical test) was used to study and analyze the data. The level of significance in this research (P-value) was set less than 0.05.

Results

The present research studied 76 female patients who had resorted to a private operation center for face rhinoplasty. Different parameters were studied, and the following results were achieved. The participants in this research were equally divided into oral-pharyngeal pack and nasopharynx pack groups. The distribution of sore throat among patients in nasopharynx pack compared to those in oral pack in recovery was as follows: 42.2% compared to 22.2% slight sore throat, 47.5% compared to 55.6% moderate sore throat, 10% compared to 22.2% severe sore throat. Levels of sore throat were measured 12 hours after operation where no significant difference was observed with recovery stage. The following comparison was made in level of sore throat between those who had received nasopharynx pack and those who had utilized oral pack 12 hours after operation: 54% compared to 25% slight sore throat, 37% compared to 57% moderate sore throat, 8% compared to 17% severe sore throat [Figure 1]. These studies pointed to the fact that a significant interaction existed between the type of pack (oral-pharyngeal pack and nasopharynx pack) and sore throat in both the recovery phase and within 12 hours after operation ($p = 0.013$). A comprehensive study of the data derived from numeric frequency analysis of sore throat points to the conclusion that nasopharynx pack has had a better performance in preventing severe sore throats, and most participants in this group experience only slight and moderate pains.

We also studied coughing among the participants in the recovery phase and 12 hours after operation and classified it as slight, moderate, and severe. A comparison of the frequency of this complication in nasopharyngeal pack group and oral-pharyngeal pack group is as follows: 68% to 32% slight cough, 18% to 25% moderate cough, and 12% to 42% severe cough. According to the result, using nasopharynx pack in recovery phase can significantly prevent coughing among those undergoing rhinoplasty ($p < 0.05$). The frequency of coughing was also studied 12 hours after operation in both groups where a noticeable difference from recovery phase was observed. A comparison of the frequency of coughing in nasopharyngeal pack group and oral-pharyngeal pack group 12 hours after operation is as follows: 66% to 46% slight cough, 25% to 35% moderate cough, and 8% to 17% severe cough. Statistical tests failed to show that utilizing different packs could cause a significant difference in preventing coughs 12 hours after operation ($p > 0.05$). The results show that all participants in nasopharyngeal pack had a good recovery, while the recovery of those using oral-pharyngeal pack was far from being satisfactory (P-value < 0.05). Statistical tests could find a significant correlation between the type of pack (oral-pharyngeal pack and nasopharyngeal pack) and nausea-vomiting in both states of the patient (recovery phase and 12 hours after operation) ($p< 0.05$). In the recovery phase; 17.5% of the patients with nasopharyngeal pack and 69.4% with oral-pharyngeal pack experienced nausea and vomiting. Patients' status in both groups 12 hours after operation showed not much difference with recovery phase.). Twelve hours after operation 13% of the patients with nasopharyngeal pack and 60% of those with oral-pharyngeal pack were experiencing nausea and vomiting. The results showed that utilizing nasopharyngeal pack plays a major role in preventing nausea and vomiting.

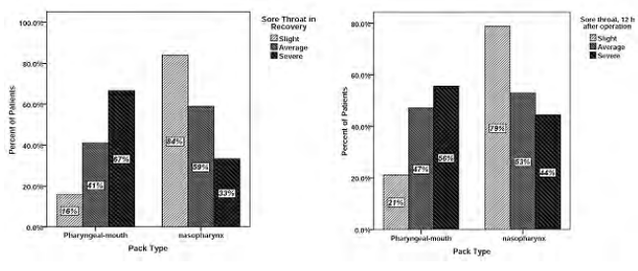


Figure 1. Frequency of the level of sore throat among patients in oral-pharyngeal pack and nasopharynx pack in recovery phase (left) and 12 hours after operation (right)

Discussion

Just like any other type of surgery, rhinoplasty is not without its side effects. The difference between these patients and other patients lies in the fact that rhinoplasty is conducted for the sake of beauty where complications must be prevented as much as possible [5]. Sore throat is a common minor side effect of anesthesia. Most applicants of rhinoplasty are very sensitive. Hence a minor complication might have an adverse effect on their satisfaction with surgery. Thus, preventing or solving this issue can boost patients' satisfaction. Various studies have dealt with sore throat. A study by Christensen et al. (1994) has studied complaints of sore throat within 6 to 24 hours after tracheal intubation. They arrived at the conclusion that occurrence of sore throat after Thyroid surgery among women is significantly more than what is observed among men (17% compared to 90%). They also reported a higher frequency of sore throat after intubation [13]. Jorgensen (1987) studied the effect of using suxamethonium in endotracheal anesthesia on occurrence of sore throat after operation. Sixty patients were selected for this purpose and divided into 2 equal groups (A & B). Anesthesia was accomplished using Fentanyl, Droperidol, N2O, Pancuronium. Participants in groups A were given Pancuronium before endotracheal intubation, while those in group B were given suxamethonium. No difference was observed between the two groups in terms of the intensity and occurrence of sore throat 20 to 30 hours after operation. They finally said their results were not in line with other researches which claimed a deterio-

rating effect for suxamethonium on sore throat [14]. In 1992, Herlevsen et al. conducted a research in order to study the effect of lidocaine aerosol on sore throat, hoarseness and cough correlated with endotracheal intubation. It was a double-blind randomized research conducted on 193 patients candidated for surgery divided into two classes of ASA I-II. The control group received lidocaine aerosol 100 mg 2 minutes prior to endotracheal intubation through a spray, but the control group received no spray. While leaving the recovery room and the following day, the patients were examined in terms of sore throat, coughing, and hoarseness. No significant difference showing that local anesthesia produces mucosa in air track was observed [15]. Another research by Dingley et al. (1994) studied the occurrence and duration of sore throat following an appropriate anesthesia using three different methods to control air tract including face mask, laryngeal mask, and laryngeal mask with insertion aid. In this prospective research, 150 patients were randomly divided into three groups. The following frequencies were reported for sore throat in each case: 8% for face mask, 18% for laryngeal mask with insertion aid, and 28.5% for laryngeal mask [16]. The results of our research also show that the type of pack used in rhinoplasty can significantly reduce the level of sore throat, coughing, nausea, and anesthesia compared to oral-pharyngeal pack ($p < 0.05$). It should also be noted that users of nasopharyngeal pack experienced a better recovery state than those who had used oral-pharyngeal pack. A review of the results of this research helps us conclude that nasopharyngeal pack has a better overall performance in preventing severe pains such as nasopharynx, facilitates the process of recovery, and prevents coughs.

Competing interests

The authors declare that they have no competing interests.

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Studying the effect of guided relaxation on pain and physiological indices after coronary artery bypass grafting surgery

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Abstract

Aim: Pain and relieving it are of the major challenges of nursing in care after Coronary artery bypass graft (CABG) surgery. In this regard, the use of effective, simple, and cost-effective methods of pain relief with minimal side effects is considered. Thus, the present study has been conducted to determine the effect of guided relaxation on patients' pain after CABG surgery. Material and Method: In the present study, which is a preliminary experimental study of before and after, 90 patients undergoing CABG surgery at the educational hospital of Heshmat in Rasht with the characteristics of the units studied were randomly selected. After signing a written consent, the subjects were trained on how to implement Benson relaxation, which is a progressive relaxation, at the stage before the operation. Data collection tool in this study was a three-part questionnaire including 1) demographic data, 2) visual analog scale (VAS) of pain, and 3) sheet of recording values of physiological parameters (blood pressure, pulse, and respiration). Data were collected in the first 24 hours of the transfer of the patient from the intensive care unit (ICU) to the surgical ward two stages before intervention (with the announcement of pain by the patient) and after intervention. Data analysis was done using paired and independent t-tests and Pearson with SPSS version 12. Results: The findings related to demographic characteristics of the majority of units studied were composed of men (78.9%), in the age group 41-55 years (51.1%), with an average age of 55 years and a standard deviation of 9.56 years, with third grade guidance-school degree (37.8%), history of hospitalization (71.1%) and surgery record (50%). The findings showed a considerable reduction in pain and physiological parameters after intervention (p=0.0001). The mean and standard deviation of pain intensity before and after the intervention, and in terms of hospitalization history (p=0.04), and the mean and standard deviation of physiological parameters in terms of gender (p=0.05) and education level (p=0.36) were statistically insignificant. Discussion: The results showed that relaxation, as a complementary non-invasive therapeutic method, could cause a significant decrease in pain and physiological parameters in patients after CABG surgery.

Keywords

Coronary Artery Bypass Graft; Admitted Patients; Nursing Care; Post-Operative Pain; Relaxation

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Introduction

Surgery is a treatment for a variety of ailments. One of the major surgeries is Coronary artery bypass graft (CABG) surgery, where the nurse should try to prevent its complications with her rational considerations [1]. CABG is the most common cardiac surgery in America. Annually, per thousand people, almost one person in this country undergoes CABG surgery [2], and costly intensive care is a burden on the shoulders of funding of health services and gets about 1985 dollars per capita of health expenditure [3]. Therefore, in today's care conditions, the issue of cost is a very critical issue, and they have always sought ways in which health care and nursing of patients undergoing CABG surgery is not only safe and effective but also financially affordable [4]. Undoubtedly, cardiac surgery is one of the most vital and most sensitive operations and has exceptional circumstances compared to many other surgeries due to the need to stop the heart and establish extracorporeal circulation. There are many actual and potential side effects after heart surgery, and the patient is delivered with such conditions to nurse of intensive care unit (ICU) and then to the nurse in cardiac surgery ward [5]. Changes in physiological parameters such as tachycardia, shallow and rapid breathing, and increase in blood pressure are the common physiological protests accompanied by pain [6]. Phipps et al. (2004) stated that of the main goals of postoperative care are to improving cardiopulmonary function, adequate tissue perfusion, and stabilization of vital signs [7]. Increase in blood pressure is dangerous for patients who have had coronary surgery because it causes blood to leak from the newly transplanted site [8]. Diastolic blood pressure is also important and should be enough because myocardial muscle receives 70 percent of its blood at this stage of the heart cycle. Hypotension signs include cerebral ischemia, heart attack, shock, and kidney failure [9]. Changes in the rate after heart surgery are common that with the reduction in heart rate, cardiac output decreases and increases in heart rate, due to a decrease in fluid volume or over-stimulation of the sympathetic system, reduces stroke volume [10]. Rapid shallow breathing is of complications after heart surgery. Many of these complications can be identified and controlled by attention and interventions of nurses, and due to the side effects of medication and its high costs, it is recommended that, as far as possible, non-pharmacological methods be used [6]. Considering that in choosing a method, attention should be paid to its simplicity, low cost, and the possibility of more autonomy, the researcher has considered relaxation method and has studied its influence on the intensity of pain, physiological parameters due to pain in patients undergoing CABG surgery. Accordingly, the present study has been done to investigate the effect of guided relaxation on the severity of pain of patients after CABG surgery.

Material and Method

This study is a single-group clinical trial of before and after type, and its population is all patients undergoing CABG surgery admitted to Heart Surgery Unit of Heshmat Hospital in Rasht. The sample consisted of 90 patients who were selected randomly based on the characteristics of the subjects studied, and after written consent by convenient sampling. Data collection tool was a questionnaire with three parts: 1) demographic characteristics of the subjects (gender, age, education, history of hospitalization, surgery record, frequency of drug use in the 24 hours, and the time interval from the last painkiller used in ICU), 2) visual analog scale (VAS) of pain, and 3) values of physiological indicators due to pain (blood pressure in millimeters of mercury, pulse according to the number of per minute, respiratory rate according to the number per minute). Within the first 24 hours after the transfer of the patient from ICU to heart surgery unit and with expressions of pain by the patient, the researcher examined intensity values of pain and physiological parameters along with pain. Then relaxation tape was played for the patient using a voice recorder device and headphones, during which the patients were asked to slowly make comfortable position, slowly close their eyes, relax all muscles of the body deeply and in order from the feet until the face, maintain this relax state, then take a deep breath hold it for a few seconds, exhale it out, and take a slow and deep breath. Then the values of pain at the stage immediately after the end of intervention and physiological indicators due to pain were measured immediately, 5 minutes, and 15 minutes later and recorded on sheets.

In the end, mean values and standard deviation of pain intensity, before and after the intervention, and each of the physiological parameters before and after the intervention were measured and the results were used. Data analysis of this study was done with the help of computer software SPSS12. It should be noted that paired t-test was used to study whether there is a significant difference between the mean and standard deviation of pain before and immediately after the intervention, as well as mean and standard deviation of physiological parameters before and after (average of three stages after intervention). Evaluating the significance of the relationship between variables related to demographic characteristics and the average of the difference in intensity of pain and physiological parameters was done with t-test, ANOVA, and Pearson. To achieve the research objectives, the following hypotheses have been proposed and tested:

- Guided relaxation decreases the severity of pain of patients at the stage after CABG surgery.
- Guided relaxation affects blood pressure of patients at the stage after CABG surgery.
- Guided relaxation affects the pulse of patients at the stage after CABG surgery.
- Guided relaxation affects the respiratory rate of patients at the stage after CABG surgery.

In addition, the question of the type of the relationship between differences that exist in physiological parameters rates after CABG surgery before and after the intervention with some individual characteristics have been answered in this study.

Results

According to the findings related to demographic features, majority of the subjects were male (78.9%), in the age group 41-55 years (51.1%), with an average age of 55 years and a standard deviation of 9.56 years, with third grade guidance-school degree (37.8%), history of hospitalization (71.1%) and surgery record (50%). The majority of the subjects (84.4%) used analgesic (acetaminophen codeine) 1-2 times in the first

24 hours after being transferred from ICU to the surgery ward and the time interval between intervention with the last use of analgesic in ICU in the highest percent (37.7%) in the subjects studied was in the range of 5-8 hours.

The results of the paired t-test showed a significant difference between the pain intensity values and all physiological parameters effects due to pain at the stages before and after the intervention (p=0.0001) (Tables 1 and 2).

Table 1. Comparing means of pain intensity in subjects studied at stages before and after treatment

STAGE VARIABLE	Before intervention		After intervention		Paired t-test results
Pain	Mean	SD	Mean	SD	24.5 = T 89 = df P=0.0001
	5.7	1.3	3	1.1	

Table 2. Comparison of the means of physiological parameters before and after the intervention in the subjects units

Stage Index	Before intervention		After intervention		The average difference between before and after		Statistical test results T
	Mean	SD	Mean	SD	Mean	SD	
Systolic blood pressure	132.2	15.2	127.3	14.6	4.9	6.4	T=7.3 P=0.0001 Significant
Diastole blood pressure	81.6	10.6	78.8	8.8	2.8	4	T=73.6 P=0.0001 Significant
Heart rate	88	12.6	84.9	11.3	3.2	3.9	T=79.8 P=0.0001 Significant
Respiratory rate	19.2	1.3	18.2	0.9	0.9	0.7	T=12.2 P=0.0001 Significant

The results in Table 3 indicate that the mean and SD difference of pain intensity before and after the intervention in terms of demographic characteristics show a significant difference only in the history of hospitalization (p=0.04) (Table 2). The results of the independent t-test, Pearson, and ANOVA showed no significant difference between the mean difference in systolic blood pressure, diastolic blood pressure, and respiratory rate before and after the intervention with the demographic characteristics of the subjects. On the other hand, the results of ANOVA have shown a significant correlation between the mean difference in heart rate before and after the intervention with sex (p=0.05) and education (p=0.036).

Table 3. The relationship between the mean and the standard deviation of the difference in pain intensity and heart rate in terms of demographic characteristics

Demographic characteristics Physiological index	Gender	Education	Hospitalization record
Mean and SD of pain intensity difference	-	-	0.04=p
Mean and SD of the difference in heart rate	0.05=p	2.69=f	-

Discussion

The results of this study indicate that the intensity of pain after intervention compared to before that has significantly reduced. The results of the study by Good et al. also confirm this finding [11]. In their study, Hatan et al. (2002) found no significant differences in pain before and after relaxation [12]. According to the researcher, small sample size of relaxation in their research can be of the restrictions causing this result [9].

The systolic and diastolic blood pressures in the stage after relaxation, compared to before it, has significantly decreased, so the second hypothesis is confirmed. However, the average systolic blood pressure in the stage after the intervention, according to the classification of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure, is in pre-hypertensive range (120-139) [8]. In their investigation to determine the effect of relaxation on blood pressure, Sheila et al. (2003) found a significant difference in systolic and diastolic after and before intervention with systolic and diastolic blood pressure after it. The researchers consider this finding due to inhibition of sympathetic effect on blood vessels [13]. The important point in this study is that relaxation has not led to a severe decrease in diastolic blood pressure more than acceptable. Minimum normal diastolic blood pressure is 60 mm Hg in adults [14], and severe reduction of this pressure can disrupt the blood supply to the myocardium [3]. Therefore, the effect of this intervention has been adequate and with no special side effects.

On the other hand, results from these findings indicate that heart rate and respiratory rate after the intervention, compared to before, have significantly reduced, so the third and fourth hypotheses are recognized. In this regard, Jacobs (2001) and Benson and Clipper (2000) write that relaxation could reduce heart rate and respiratory rate by reducing sympathetic system performance [16, 17]. In their study to determine the effect of Benson relaxation therapy on hemodynamic status in patients undergoing coronary angiography, Hanifi et al. found a significant decrease in heart rate in the relaxation group compared to the control group [18].

Moreover, independent t-test revealed a significant difference (p=0.04) between the mean of pain intensity difference before and after the intervention was based on the history of hospitalization. In analyzing this, the researcher states that although hospitalization history increases pain in the subjects with this feature, this could increase the incentive to the effective relief of pain, so probably the subjects have done this intervention more accurately and as a result have experienced more pain reduction.

On the other hand, the average difference of values physiological indices of systolic and diastolic pressure and the respiratory rate had no statistically significant relationship with any of the demographic characteristics of the subjects. Peggy et al. confirmed this by evaluating and comparing two different rehabilitation programs to improve the quality of life of patients with heart disease [19].

Finally, the results of this study showed that the mean difference in heart rate before and after the intervention had a significant relationship only with gender (p=0.05) and education (p=0.036). The highest influence of relaxation was on heart rate in women and people with literacy to read and write. In their study to evaluate the effects of psychosocial factors and cardiovascular and respiratory indicators on the stress of employed men and

women, Chill et al., showed that women had more changes in heart rate than men [20]. These findings may be connected to more influence of heart rate compared to blood pressure to human states and more suggestibility of women than men may. Therefore, with knowledge of the purpose of this research and its possible impact on heart rate, women have had more control over their pulse rate than men have. More influence of relaxation on heart rate in patients with literacy to read and write is perhaps connected to the suggestibility of people with lower education levels and heart rate being influenced more compared to human states.

Thus, according to the above findings, it can be stated that all four hypotheses have been confirmed. Therefore, relaxation could be an effective non-pharmacological intervention, easy, fast, non-invasive, affordable and suitable for acceptable changes in physiological parameters and pain in patients after CABG surgery. Using this method not only reduces the consumption of drugs and their side effects in patients, but also improves good therapy relationship between hospitalized patients and nurses, and this can increase patient satisfaction with provided care and quality of care.

Competing interests

The authors declare that they have no competing interests.

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Physical exercise on the power of axial balance muscles among the patients suffering from a discopathy and a nonspecific backache

Influence of physical exercise on the power of axial balance muscles

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Abstract

Aim: Backache is one of the most common skeletal-muscular disorders experienced at least once by everyone in their life. It is the third cause of people's disablement in the range of 15 to 65 years old in Iran. One of the major causes of the backache is the lumbar disks whose chronic cases are mostly due to swelling. The present research seeks to investigate the effect of axial balance muscles power among those suffering from a discopathy and nonspecific backache. Material and Method: The population of the research included 60 people with a record of at least 4 weeks of backache resorting to the physical medicine department of Baghiyat Allah Hospital who had been advised to undergo Magnetic Resonance Imaging (MRI) based on the clinical symptoms and their status. These people were divided into the nonspecific and discopathic categories. The core muscles power was measured in both groups and compared against one another. After eight weeks of axial balance exercises, the muscular power was once again checked. The resulting data were analyzed using SPSS. Results: The initial results indicated no significant difference between the two groups in terms of factors such as gender, age, job, family background of backache, history of previous diseases, and the average age of backache. As the results indicated after eight weeks of central balancing exercises, the level of pain decreased significantly in both groups and the muscular power distribution also improved. Discussion: Eight weeks of central balancing exercises will result in the significant decrease and improvement of pain and muscular power distribution respectively.

Keywords

Exercise; Muscular Power; Backache; Discopathy; Patient.

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Introduction

Backache is one of the most common skeletal-muscular disorders experienced at least once by everyone during their life [1]. It is the third cause of people's disablement in the range of 15 to 65 years old in Iran [2]. The high cost of backache on the healthcare system has encouraged the researchers to take up new approaches to studying and diagnosing all types of backaches so that they may take the proper measure to treat them [3]. Concerning the diagnosis and treatment of backache, the Pain Association, and the Medical College of the US states that it is impossible to place all those suffering from backache in a homogeneous group, but they must be divided into subgroups so that proper treatments can be recommended for them [4].

One of the major causes of the backache is the lumbar disks whose chronic cases are on the rise. A chronic backache causes discomfort for nearly 80% of the people during their life.

Nearly 7% of the elderly resort to the general practitioners due to those pains and 32% of them are referred to a specialist [5,6].

Spinal disc bulging is one of the major causes of the backache. Due to the extraordinary movement of the lumbar region which is located adjacent to the nearly motionless region of the sacrum, this area is subject to the mechanical pressures which can damage the lower back spinal discs. Lumbar disc bulgings are usually observed between L4-L5 and L5-S1 [7]. The effectiveness of the balancing muscles in the lumbar area is defective in those suffering from disc bulging. As a protective feedback, these muscles will suffer from spasm and shortness [8,9]. Special exercises for the muscles around the spinal column which play a major role in creating dynamic balance and segmental control of the vertebrae have been taken into consideration excessively in rehabilitating those suffering from a chronic backache. This method emphasizes retraining the detailed simultaneous contraction pattern of deep muscles of the torso such as the transverse abdominal muscle and multifidus. The pain reduction mechanism of these specific exercises includes enhancing the stability of lumbar segments [10].

Considering the results of the anatomical and biomechanical investigation of this issue, it is completely accepted that those suffering from backache would experience higher levels of weakness and exhaustion in the muscles of the torso. On the other hand, reduction of the power and bearing stamina of the torso muscles is described to be a potential danger of getting afflicted with a backache. According to the researches and studies conducted in the 1990s, strength and bearing exercises (especially the bearing exercises) are considered to be one of the major principles of treating backache [11]. Spinal column balancing exercises are specific exercises for the muscles around the lumbar vertebrae whose primary role is to create dynamic balance and control the spinal column segments [12]. The primary goal of active balancing exercises for the spinal column is to create the physical capacity to preserve the neutral state of the spinal column during the daily activities of life. This is accomplished by enhancing the bearing and harmony of the balancing muscles of the spinal column [13].

The axial balance muscles are located in the body's center of gravity. If the axial balance muscles are effective enough, the paired force and normal correlation will be formed, and the body will make its moves in a normal biomechanics. If the axial balance muscles of the body are weakened for any reason, this correlation and arthro-kinematics of the joints will be disrupted, and we will observe muscular imbalance. As a result, we will experience chronic pains such as backache and non-natural movements in the spinal column. That is why the recent researches have paid a lot of attention to the role of axial balance muscles in preventing and treating the backache [14].

As a large number of the Iranian people suffer from discopathy or nonspecific backaches, we thought it was a good idea to measure the power of the balancing muscles of the axial spinal column and determine if the muscles are weak or strong. If the muscles are weak, proper exercise can be prescribed to enhance the power of axial balance muscles and improve the patients' backache and their life quality without using medical therapy. Thus, the present research seeks to investigate the power of axial balance muscles in the patients suffering from a discopathy and nonspecific backache.

Material and Method

The population of the research included 60 people with a record of at least 4 weeks of backache resorting to the physical medicine department of Baghiyat Allah Hospital who had been advised to undergo MRI based on the clinical symptoms and their status. All the participants were aged 18 to 65 years old and their formal consent was gained before participating in the research. The following exclusion criteria were also defined: any material or micro-piece in the body which made the MRI impossible, psychological disorders based on examinations, new pain or intensification of pain during the study, lack of cooperation by the patient, impossibility of stretching due to the possible skin problems during stretching, lumbar traction contradictions, cases requiring surgery, lumbar surgery history, other symptoms such as fever and notable weight, and evidences of tumor infection and trauma in discovered in MRI.

Based on the results of MRI, the participants were divided into the normal group, and those with pathology (disc bulging) and the age and gender of the two groups was matched, and the power of the core muscles was measured in both groups and compared against one another. After eight weeks of axial balancing exercise, the power of the muscles was checked again. To measure the power of muscles, the patient was placed in the supine position, and a compressive biofeedback device (Stabilizer 25) was placed under the lumbar vertebrae in the region of L4-L5. The compressive cuff was filled up to 40 mm of HG, and the patient's legs were held in the total extension state, while the pelvis was flexed in an angle. The individual was then asked to perform the drawing maneuver. He was then requested to lower his legs towards the desk while still holding his back straight. When the lumbar curve increased, the cuff pressure was reduced. This indicates a positive result for the test and a weakness for axial balance muscles. Next, the hip angle was measured using a goniometer and scored based on Kendell grading system. If the individual is unable to retain the pressure in an angle of 60° to 90°, the test will be interpreted as positive, and the balancing muscles (rectus abdominus and external oblique) are weak.

SPSS ver. 17 was utilized for data analysis. Kolmogorov-

Smirnov (KS) test was used to investigate the quantitative variables and the normal distribution of them. Based on the distribution of variables, parametric and non-parametric tests were utilized to compare the means of each group. Chi-square, T-test, and One-way ANOVA were used to study qualitative variables. In all statistical analyses, a P-value of less than 0.05 was considered to be significant.

Results

The total number of the participant in this study was 60 with an average age of 46.88 ± 7.60 including 40 male and 20 female participants. The first group (nonspecific) and the second group (discopathy) each had 30 members. The average age in the nonspecific group was 39.38 ± 3.73, while this average for those suffering from discopathy was 36.00 ± 4.63. The gender frequency in these groups was equal for both men and women with 66.6% and 33.4% respectively. No significant difference was observed between the 2 groups in terms of age and gender distribution (p>0.05). The participants were also compared against one another in terms of their jobs (employee or housewife) and family history of backache. No significant difference was observed here either (p>0.05).

Of all the participants, 23 (38.3%) had a history of diseases including 8 cases (34.8%) of blood pressure, 5 cases (21.7%) of diabetes, 4 cases (17.4%) of high blood fat, etc. (Table 1). Four people (17.4%) from the nonspecific group and 4 (17.4%) from the discopathy group had blood pressure. No significant difference was observed between the two groups in terms of the history of various diseases (p=0.81) (Table 1).

As the results indicate, the average length of the pain in the nonspecific group was 2.20 ± 1.34 years, while this value for the group not afflicted with discopathy was 0.95 ± 1.90 years. No significant difference was observed between the length of backache in both groups (p = 0.62).

The average level of backache before and after exercise in both groups can be observed in Table 2. The statistical results indicate that the difference of this variable before and after the exercise is not significant. However, the statistical analysis indicated a significant difference between the level of backache before and after exercise in both groups.

Table 3 represents the distribution of lumbar muscles power in both groups before and after exercise. As the statistical results indicate this difference before and after exercise is not significant in any of the groups. But the statistical analysis represented a significant difference between the level of backache before and after exercise in both groups.

Table 1. Distribution of people based on the history of diseases in both groups.

Groups		History of Disease								P-Value
		BP	Dia	LD	Dia and LD	HP	Dia and BP	BP and LD	Total	0.81
Nonspecific	No.	4	2	1	1	0	0	1	9	
	Percent	17.4	8.7	4.3	4.3	0.0	0.0	4.3	39.1	
Discopathy	No.	4	3	3	0	1	2	1	14	
	Percent	17.4	13.0	13.0	0.0	4.3	8.7	4.3	60.9	
Total	No.	8	5	4	1	1	2	2	23	
	Percent	34.8	21.7	17.4	4.3	4.3	8.7	8.7	100.0	

BP: Blood Pressure; Dia: Diabetes; LD: Lipid Disorder; HP: Hypothyroidism

Table 2. Comparison of backache length in both groups.

	Mean pain	Mid	Mean pain	Mid	
Nonspecific	6.97 ± 0.85	7 (5-9)	3.73 ± 1.26	3 (2-7)	<0.001
Discopathy	7.07 ± 0.83	7 (6-9)	3.57 ± 1.01	3 (2-6)	<0.001
Total	7.02 ± 0.83	7 (5-9)	3.65 ± 1.13	3 (2-7)	<0.001
P-Value	0.69		0.85		

Table 3. Comparison of the distribution of lumbar muscles power in both groups.

Groups		Before			After				P-value
		60	75	Total	30	45	60	Total	
Nonspecific	No.	10	20	30	10	17	3	30	<0.001
	Percent	16.7	33.3	50	16.7	28.3	5.9	50	
Discopathy	No.	5	25	30	5	22	3	30	<0.001
	Percent	8.3	41.7	50	8.3	36.7	5	50	
Total	No.	15	45	60	15	39	6	60	<0.001
	Percent	25	75	100	25	65	10	100	
P-Value		0.13			0.31				

Discussion

The present research seeks to study the effect of exercise on the power of axial balance muscles among patients suffering from discopathy and those suffering from a nonspecific backache. The population was composed of 60 patients composed of 2 groups with a nonspecific and discopathic backache and equal members.

The initial statistical results indicated no significant difference between the two groups in terms of age, gender, job, family history of backache, history of diseases, and the average length of backache. This implies the similarity between these groups in terms of the factors mentioned. The results point to the fact that an eight-week period of central stabilizing exercises will reduce the pain significantly in both groups and increase the muscular power distribution. These results are in line with the previous researches conducted in this field.

Javadian et al. conducted a research to study the effects of stabilizing exercise on the pain, performance disability and muscular stamina among those patients suspected of segmental instability backache. As the results indicate, stabilization exercises are more effective than regular exercise in improving the intensity, performance disability, muscular stamina, and motion domain in patients suspected of segmental instability [15]. Their results are in line with the results achieved in our research.

Momen et al. studied the therapeutic effect of exercise on pain, disability, and stamina of torso muscles among women afflicted with the chronic idiopathic backache. As the results showed, exercise therapy was capable of enhancing the stamina of muscles body in women suffering from chronic idiopathic backache. It can reduce pain and disability in the population [16]. The results of this group are also in line with the results achieved in our research. Furthermore, Lee et al. also studied the level of pain and entropy changes following an 8-week period of stabilizing exercises. In

this study, 60 patients were placed in 2 categories: those suffering from a nonspecific backache and those with discopathy. The two groups were then matched in terms of age and gender, and the CORE muscles power was measured for both groups and compared against one another. After 8 weeks of axial stabilizing exercise, the power of the muscles was studied again. After 8 weeks of intervention, the level of pain in all the participants had witnessed a significant decrease, but no difference was observed between the groups in terms of pain reduction [17].

Concerning this fact that physical exercises need to be a part of the treatment for those suffering from backache, there is a consensus. There are, however, different ideas concerning the type of the exercise, the length of the period and their effectiveness mechanism. Some researchers prescribe only those physical exercises that cover all the muscles of the spinal column so that they can control the whole motion of the spinal column. These researchers believe that the effectiveness of these exercises is due to the enhancement of the general and local muscles of the torso, higher thoracolumbar fascial tension, multifidus hypertrophy, higher local pressure, and facilitation of the simultaneous contraction of the flexors and extensors of the torso. Researchers believe that the goal of the therapeutic exercise of those suffering from backache needs to be the enhancement of the stability of spinal column rather than enhancing the power or hypertrophy of torso. Contrary to power enhancement approach, the present approach seeks to increase the stability of the spinal column, activate balancing muscles especially the multifidus and transverse abdominal muscle separated from other muscles of the spinal column during the initial phases of treatment [18].

Physical exercises and exercise therapy to treat those suffering from backache have been a subject of great attention during the past few years. The influence of balancing exercises on the nervous-muscular performance in the patients with a chronic backache has also been proved [2]. The balancing exercises are mostly focused on the small, deep and the posterior muscles of the spinal column and retain and stabilize the correct body posture through retraining and increasing the stamina of the muscles. Stabilizing the spinal column results in less pain and enhancement of the patient's performance [18]. As the previous researches indicate, stabilizing exercises reduce the pain and enhance the level of performance disability among those suffering from a chronic backache [19]. Hayden et al. conducted a random trial research and concluded that therapeutic exercise is the best type of treatment for a chronic backache which can decrease the pain and enhance the performance disability. Of course, it needs to be designed exclusively based on the individual's abilities and run under the supervision of a physiotherapist [17].

Conclusion

In this study, the stabilizing exercises were conducted under the full supervision of a physiotherapist. One of the causes of the enhancement of the performance disability of the patients in this research was probably the facilitation of the motion sense and reduction of backache. We may also conclude that the stabilizing exercises in our study reinforce the transverse abdominal muscle and prevent belly drooping and result in the greater stability of the spinal column in the lumbar region. As a matter of fact, the transverse abdominal muscle acts like a balloon and press the abdominal organs to the spinal column. This will all result in greater stability of this region in daily activities.

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None

Conflict of Interest Statement

We declare that we have no conflict of interest.

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Ethical Standards

All authors obey the rules of Helsinki Declaration, and no ethic problem exists in the manuscript.

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Molecular identification of types TEM, SHV and CTX extended-spectrum-β-lactamase of escherichia coli, edwardsiell and erwinia spp. Isolated from feces of carriers

Molecular Identification

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Abstract

Aim: Healthy ESBL carrier patients are the major challenge in control of infections produced by members of Enterobacteriaceae. The aims of the present study were to investigate the isolation of TEM, SHV, and CTX type ESβLs producing E. coli, Edwardsiella, and Erwinia spp. from feces of carriers.Material and Method: Two hundred fresh stool samples collected from non-hospitalized and hospitalized patients were cultured on MacConkey agar supplemented with 2 mg/L cefotaxime. After 24 hr. Incubation at 37°C the E. coli, Erwinia and Edwardsiella spp were identified by routine biochemical tests. Combined tests were carried out to select ESBLs producing bacteria and susceptibility of isolates was determined by disc diffusion method. Multiplex-PCR was used to identify TEM, SHV and CTX type ESβLs producing isolates. Results: Of the 34.5% bacteria resistant to cefotaxime, 81.63% and 55% ESBL producing organisms were recovered from inpatients and outpatients respectively. E. coli was the predominant ESBL-producing organism; One Erwinia and three Edwardsiella producing ESBL were detected. Overall, carbapenems including imipenem and meropenem and amikacin were the antibiotics most active against the ESBL-producing organisms. The overall prevalence of these ESBL genes was 73.92%, including the blaTEM and blaSHV genes alone in 27.45% and 5.88% respectively; blaCTX-M were not distinguished alone in any of the isolates. Discussion: More than one ESBL was produced by most isolates carried by patients and Carbapenems, imipenem and meropenem continue to show good in vitro activity against the isolates. Patients can act as a source of ESBL producing bacteria in hospitals.

Keywords

Healthy Carrier; ESBL; E. Coli; Erwinia; Edwardsiella

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Aim

Some genera among *Enterobacteriaceae* family carrying extended-spectrum β-lactamases (ESBLs) have emerged as significant pathogens. Infections due to such strains of these genera are associated with extended hospital stays, increased healthcare costs and, in the setting of bloodstream involvement, development of mortality if proper therapy is delayed. [1]

The most important species of genus *Edwardsiella*, that 2is, *E. tarda, E. ictaluri* and *E. hoshinae* have a wide environmental distribution. Of these, *E. tarda* has been shown to be pathogenic in humans.[2]Most members of this genus characteristically produce diseases of plants, vegetables, and fruits.[3]Reports of *Erwinia* isolates as human pathogens are limited, but the phytopathogen *E. persicina[4]* has been isolated from human urinary tract infections.[5] *Escherichia coli* are the common opportunistic pathogen, isolated from different infections of humans and have demonstrated an increasing antimicrobial resistance to most antibiotics.[6] In the past 2 decades, antibiotic-resistant strains have emerged among the *Enterobacteriaceae* members by a production of extended-spectrum β-lactamases (ESBLs). [7] Recently, a group of ESBLs that hydrolyze cefotaxime (CTX), the CTX-M β-lactamase, has been detected and reported with increasing frequency.[8] Several papers have recently reported the distribution of ESBLs in the community, mainly in patients with chronic conditions.[9-11] The increase of drug resistance among these organisms has made therapy of different infections difficult and has led to greater use of expensive broad-spectrum antibiotics such as the third generation of cephalosporin. Hence, regular monitoring of such resistance at local, national and international levels is necessary as control plan by most national and international organizations.[12,13] ESBLs are frequently plasmid-mediated and can hydrolyze penicillins, third-generation cephalosporins, and monobactams.[14] Distribution of human clinical isolates and capacity to produce ESBLs has been found out among inpatients, as well as among those in the community.[15] we know carriers of ESBL producing organisms exist, but in general practice, this condition has rarely been reported. Until now, more than 600 ESBL variants have been reported. Among them, CTX-M, SHV, and TEM enzymes so far considered to be important in *Enterobacteriaceae.[16]* This is nearly known that resistance caused by ESBLs is often associated with resistance to some other antibiotics such as fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole.[17,18] In the recent few years, there has been an increase in the finding of ESBL-producing strains in the general community[19] but few studies have been published about ESBL dissemination in healthy humans, explaining prevalence between 6 and 7%.[20,21] Percentage of the carriage in the stool is changeable and is found to be higher in rural than the urban population.[2] Recently, ESBL producers have also been reported increasingly among infection-associated members of *Enterobacteriaceae* family in France[22,23], Italy[24], the Czech Republic[25], and Austria.[24] These studies were the reason to look for ESBL producers among healthy carriers.[27]This study was carried out to determine rates of ESBL mediated resistance in fecal isolates of *E. coli*, *Erwinia and Edwardsiella spp.* in hospitalized and outpatients without suffering from diarrhea.

Material and Method

Specimen collection and Screening for and confirming the presence of ESBLs

Two hundred fresh stool samples were collected from non-hospitalized (n=100) and hospitalized patients after 48 hours admission (n=100) in Shahid Madani training and treatment center from November 2014 to February 2015. Those with gastrointestinal illness and diarrhea were excluded from the study. Stool samples were cultured on MacConkey agar supplemented with 2 mg/L cefotaxime ('CTX-MacConkey') and incubated at 37C for 24 h. The isolated bacteria were identified by routine biochemical tests and *E. coli*, *Erwinia and Edwardsiella spp.* stored at -20°C in trypticase soy broth containing 12% glycerol. This study was approved by the ethical committee of regional Medical Research of the Tabriz University of Medical Science, and all patients provided written informed consent for this research (TBZMED.REC.1394.352). ESBL expression was confirmed by the disc diffusion method on Mueller–Hinton agar using cefotaxime (30μg) or ceftazidime (30 μg) with and without clavulanic acid (10 μg), as recommended by the CLSI, and each set of samples was tested with CLSI quality control strains *E. coli* ATCC 25922.[28]

Antimicrobial susceptibility testing

All ESBL-producing *E. coli*, *Erwinia and Edwardsiella* isolates were tested for susceptibility to imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, and tetracycline by the disc diffusion method using Mast Discs (Mast Ltd, UK) according to the CLSI and manufacturer's instructions.[28]

blaTEM, SHV, CTX genes identification

The *bla*TEM, SHV, CTX genes were identified by Multiplex- PCR using DNA extracted by boiling suspensions of isolates. DNA samples at a concentration of 1 μL were used as PCR templates, and the genes were amplified using the primers (Cinnagen Co, Tehran, Iran) as described previously.[29,30]

SHV	ATGCGTTATATTCGCCTGTG	(747 bp)
SHV	TGCTTTGTTATTCGGGCCAA	
TEM	TCGCCGCATACACTATTCTCAGAATGA	(445 bp)
TEM	ACGCTCCCGGCTCCAGATTTAT	
CTX	ATGTGCAGYACCAGTAARGTKATGGC	(593 bp)
CTX	TGGGTRAARTARGTSACCAGAAYCAGCGG	

A loopful of bacteria colonies harvested from a blood agar plate was suspended in 0.5 ml of sterile water and heated at 95°C for 10 min. After centrifugation at 5,000 rpm for 5 min at 4°C, the DNA-containing supernatant was used as the source of template for further amplification.[31] PCR reactions were performed with an automated thermal cycler (Eppendorf mastercycler gradient, Germany) with the PCR cycling conditions of initial cycle at 94ºC for 10 min, 35 cycles of denaturation at 94ºC for 30 s, annealing at 60 ºC for 30 s, extension at 72 ºC for 1 min, and final cycle extension at 72 ºC for 10 min. Gel electrophoresis was performed for 60-120 min in a 1.2% agarose gel at 75 V. DNA profiles were visualized by ultraviolet (UV) light after ethidium bromide staining on a UV transilluminator. The gels were photographed using a gel documentation system

(UVP, USA) for the analysis of bands. Molecular marker (Fermentase; 100 bp DNA ladder) was used to assess PCR product size. Multiplex PCR reactions were carried out in a final 25 µL volume containing 2.5 µL of 10X PCR reaction buffer, 1 µL DNA solution, 0.5 µL MgCl2 (50 mM), 0.5 µL of each gene-specific primer (10 pmoL), 0.5 µL (3 U/mL) Hot Star Taq Mastermix DNA polymerase (Qiagen) and 0.5 µL deoxynucleoside triphosphates mix (dNTPs, 10 mM).

Results

Bacterial isolates other than *E. coli, Erwinia and Edwardsiella spp.* That grew on the MacConkey agar were disregarded. Of the 200 stool samples tested, 69 (34.5%) bacteria resistant to cefotaxime and ceftazidime, were isolated. Out of the 49% and 20% resistant isolates to cefotaxime and ceftazidime, 40 (81.63%) and 11 (55%) ESBL producing organisms were recovered from inpatients and outpatients respectively (Table 1, Fig 1). *E. coli* was the predominant ESBL-producing organism; it was recovered from 38 (95%) of inpatients and 9 (81.81%) of outpatients. One *Erwinia* and three *Edwardsiella* producing ESBL were detected. Overall, carbapenems including imipenem and meropenem and amikacin were the antibiotics most active against the ESBL producing organisms. The susceptibility data for the isolates are shown in Table 2. The overall prevalence of these ESBL genes among inpatients and outpatients was 73.92% (51/69). The PCR assay detected the results for each of the resistance genes as follows: the *bla*TEM and *bla*SHV genes alone in 27.45% (14/69) and 5.88% (3/69) respectively; *bla*TEM and *bla*SHV identified in 13.72% (7/69); *bla*TEM and *bla*CTX-M recognized in 13.72% (7/69); *bla*SHV and *bla*CTX-M detected in %7.84 (4/69) and *bla*TEM, *bla*SHV and *bla*CTX-M were distinguished in 31.37% (16/69) of the isolates (Fig. 2).

Table 1. Distribution of Extended-Spectrum β-lactamase (ESBL)- Producing Fecal Isolates of Escherichia coli, Erwinia and Edwardsiella spp.

		No. (%) of isolates		
Study group	No. of individuals	Caz-Ctx* resistant	ESBL producing carrier	Non-ESBL Producing carrier
Inpatients	100	49 (49)	40(40)	60(60)
Outpatients	100	20(20)	11(11)	89(89)
All	200	69(34.5)	51(25.5)	149(74.5)

*Note. Caz, ceftazidime; Ctx, cefotaxime.



Fig1. A positively combined disc (CD) using ceftazidime (CAZ 30 µg), ceftazidime /clavulanic acid (30µg/10µg) discs. A representative of E. coli isolates showing a ≥ 5 mm zone size enhancement in the CD test indicating inhibition of ESBL production.

Table 2. Antimicrobial Susceptibility Profiles of Extended-Spectrum β-lactamase–Producing Fecal Isolates of Escherichia coli, Erwinia and Edwardsiella spp.

Study group	No. of isolates	No. (%) of isolates susceptible, by agents					
		Cfep	Cip	Gm	Pip-Taz	Ak	Car*
Inpatients	40	3 (7.5)	9 (22.5)	19 (47.5)	23 (57.5)	32 (80)	40 (100)
Outpatients	11	0 (0)	5 (45.45)	7 (63.63)	8(72.72)	10 (90.90)	11 (100)
All	51	3 (5.88)	14 (27.45)	26 (50.98)	31(60.78)	42 (82.35)	51(100)

Note. Ak, amikacin; Car, carbapenem; Cfep, cefepime; Cip, ciprofloxacin; Gm, gentamicin; Pip-Taz, piperacillin- tazobactam.
* Imipenem and/or meropenem.

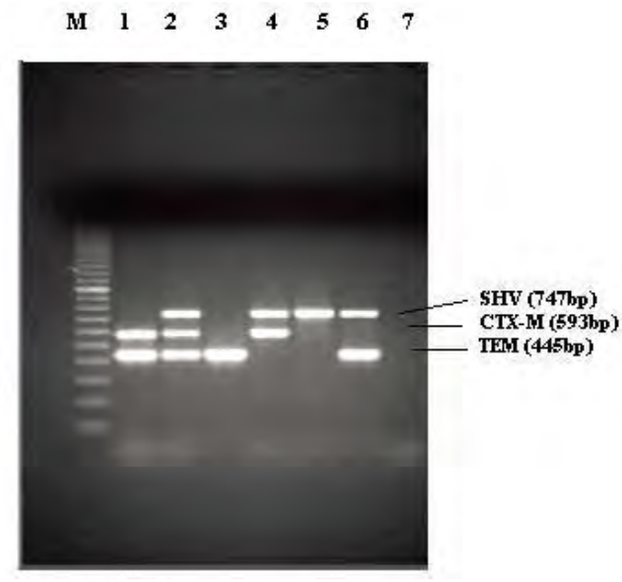


Fig 2. Multiplex PCR detection of SHV, CTX-M and TEM β-lactamase genes in E. coli (EC), Erwinia and Edwardsiella isolates. Lanes M, 100bp ladder molecular size marker; Lanes 1, 2, 4, 6, EC isolates; Lane 3, Edwardsiella, Lane 5, Erwinia; and Lane 7, No template (water)

Discussion

Although *E. coli, Erwinia and Edwardsiella spp,* normally live harmlessly in the gut, they can cause various types of infection, most commonly urinary tract infection.2,5-6 Study of susceptibility patterns for 2,302 gram-negative pathogens obtained from urine samples in Saudi Arabia found that 10.2% of the isolates were ESBL-producing *E. coli*.[32] In another study, the rate of fecal carriage of ESBL-producing organisms among inpatients (26.1%) was higher than that among outpatients (15.4%).[33] In a study done in Lebanon, the rate of fecal carriage for ESBL-producing *E. coli* in inpatients was reported to be 80.5%.[34] These correspond nearly with our result obtained for inpatients (40%) that is much higher than the results of outpatients (11%). In our hospital, most of the inpatients before surgery and also in surgery process receive prior therapy with third-generation cephalosporins and/or fluoroquinolones

as prophylactic. The routine consumption of these antimicrobial agents could clarify the higher spread of fecal carriage of ESBL-producing bacteria in the hospital, a contrast to the rate in the community. The same reason could cause the greater resistance of amikacin, piperacillin-tazobactam, and ciprofloxacin in the ESBL-producing isolates obtained from inpatients, compared with those obtained from outpatients.

The spread of ESBL-producing organisms to the community could be the result of previous hospital infection, as some inpatients maintain to carry ESBL-producing bacteria over prolonged periods, and such carriage may contribute to their propagation outside the hospital.[35] In the present study, none of the outpatients or inpatients had any acute gastroenteritis problem, and there was no evidence of any recent hospitalization. In our study, the fluoroquinolone resistance rate was high both in isolates recovered from inpatients (31 of 40, 77.5%) and in those recovered from outpatients (5 of 11, 54.54%). Although we could not obtain enough information about recent exposure to antibiotics among the outpatients, the unlimited sale of antibiotics in developing countries is probably the most important reason for the creation of resistant organisms in the population. Some antibiotics such as amoxicillin-clavulanate, and fluoroquinolones are often purchased and used without prescriptions. Therefore, it can be deduced that even if clinical laboratories to attempt to detect ESBL-producing bacteria in individuals with community-onset infection, the exact prevalence rate of ESBL producing organisms will not be determined in the community, and asymptomatic carriers may remain unnoticed for long periods. The presence of ESBL producing bacteria in the gut will cause problems because the intestinal colonization for the majority of infections caused by ESBL-producing bacteria is essential.[36] Monstein et al in Sweden by multiplex-PCR method detected the presence of genes in K. pneumoniae as follows: blaSHV in 8% (3/37), blaSHV and blaTEM in 2.7% (1/37), and blaTEM, blaSHV and blaCTX-M in 8% (3/37) of isolates.29 The ESBL prevalence in our study showed a higher prevalence compared with the Sweden results. The variation in the prevalence of ESBL producing isolates in our results could be due to poor infection control, distribution of hospital-acquired ESBLs into the community and vice versa. Therefore, epidemiologists and clinical microbiologists to control the prevalence of ESBL-producing organisms need sufficient knowledge about the status of these bacteria not only in the hospital environment but also in the community. The restricted availability of treatment choices for infections caused by ESBL-producing organisms requires prevention of these infections by limiting the use of antibiotics, along with the performance of prompt infection control actions. To control or reduce the high rate of carriage for these organisms, helpful measures should be taken to forbid the sale of antibiotics without a prescription and to increase knowledge of the hazards of taking antibiotics without medical consultation among the population.

Conclusion

Most commonly one or more than one ESBL was produced by many strains, and this was correlated with increased resistance levels. Carbapenems, imipenem, and meropenem continue to show good *in vitro* activity against isolates. Patients as healthy carrier can act as a source of ESBL producing bacteria to influx resistant bacteria to hospitals and vice versa. The necessity of antimicrobial resistance surveillance is warranted in light of these findings.

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Effect of Web-based education on knowledge and preventive behaviors of Iron Deficiency Anemia among high school girls

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Abstract

Aim: Iron deficiency anemia is one of the largest public health problems in the world, especially in developing countries. Adolescent girls are among high-risk groups so that 25% of students suffer from iron deficiency anemia. The objective of this study was to evaluate the impact of web-based education on the knowledge and preventive behaviors on iron deficiency anemia among high school girls. Material and Method: The present study was an interventional study conducted on the 104 high school girl students, who randomly placed in two control and experimental groups (52 people in each group) in 2016. The experimental group received a Web-based education. Data were collected through a questionnaire and conducting Hemoglobin (Hb) and Serum Ferritin(SF) experiments before and 4 months after the intervention. The results were analyzed using the statistical Chi-square, paired t-test independent t-test through SPSS-19. Results: Before the educational intervention, the mean score of knowledge and preventive behaviors of iron deficiency anemia in both groups was not significantly different (P>0.05). However, a significant increase was observed in the experimental group compared to the control group after education (P<0.001). The rate of ferritin and hemoglobin in the experimental group increased compared to before the study (P<0.001), while the significant increase was not seen in the control group (P>0.05). Discussion: The results of this study showed that Web-based education program improves awareness and preventive behaviors of iron deficiency anemia if girl adolescents. In addition, it had a positive impact on improving the rate of Hb and serum ferritin in them.

Keywords

Educational Intervention; Girls; Iron Deficiency Anemia; Iran.

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Introduction

Iron Deficiency Anemia (IDA) is one of the most important and widespread public health issues in the world that has a negative impact on the health of many children and women in developing countries [1]. Iron deficiency plays a major role in the occurrence of anemia so that iron deficiency accounts for approximately 75% of anemia [2]. Studies in Iran show that the prevalence of iron deficiency in different regions of the country is between 2.4% to 36.5% [3]. The World Health Organization (WHO) defined iron deficiency as a nutritional disorder that affects about 80% of people in the world [4]. Also, according to the WHO, 25% of students in developing countries are suffering from iron deficiency anemia [5]. In Iran, several studies have reported that the prevalence of anemia among female high school is between 30-55% [6]. Iron deficiency anemia is associated with complications such as increased risk of maternal mortality, preterm delivery, low birth weight [7-8]. In addition, it disrupts the attention of teenage girls and decreases educational opportunity, work efficiency, and physical strength as well as increases the risk of infection [9]. Since the main cause of iron deficiency anemia in developing countries is getting low iron from food sources, and the low content and bioavailability of iron [10], nutritional education is one of the most important measures for prevention of IDA [11]. Therefore, the promotion of nutritional knowledge in the community through education in reducing malnutrition and improvement and reduced complications are considered a necessity for the developing world and our country [12]. The aim of this study was to evaluate the effectiveness of web-based training in iron deficiency anemia among female high school.

Materials and methods

This study used an interventional design which was carried out on 104 female high school students aged 16-17 years old in two experimental (n=52) and control groups (n=52) in 2016 in Andimeshk. The sample size was determined with a 95% confidence level and power of 80%. This study used a multistage random sampling method. For this purpose, a list of high schools in Andimeshk was firstly prepared, and two high schools were chosen randomly. 52 students from the first school and 52 students from the second school were enrolled as test and control groups, respectively. Inclusion criteria were: onset of menstruation, lack of hereditary anemia, lack of acute infection during the sampling, providing an address and phone number for the follow-up call, access, and ability to use the Internet. Exclusion criteria were: unwillingness to participate in the study. Data collection was carried out via Hemoglobin (Hb) and Serum Ferritin (SF) tests and completing the questionnaire, which took place before and 4 months after the intervention. A 2 cc of blood in the brachial artery in the non-fasting state was taken from each of the subjects by laboratory expert. A 1 cc of the blood was transferred to a CBC tube (Cell Blood Count) containing anticoagulant solution with EDTA (Ethylene Diamine Tetra Acetic Acid) and 1 cc of blood also was transferred to the tubes for evaluating serum ferritin. Blood samples were sent to the laboratory immediately. Hemoglobin tests were carried out using Cyanmethemoglobin method by cell counter KX-21N Sysmex (Japan) using Pars Azmoon kit (Iran). Serum ferritin was measured by ELISA method (Mindray, MR96A, South Korea) and using Padtan Elm Company (Iran). According to the WHO, anemia is defined as levels of Hb<12 g /dL and iron deficiency is defined as a level of SF<12 µg/L and those with both anemia and iron deficiency were defined as iron deficiency anemia. The questionnaire was composed of two sections. The first section is included demographic questions and the second section included knowledge questions (24 items) which were scored with options (Yes=1), (No and I Do not know=0) in a range of (0-24; preventive behaviors (12 items) were scored for 4 Likert scale (always=3, often=2, sometimes=1, never=0). The scores ranged from 0-36. The validity was confirmed by obtaining the opinions of experts and specialists and re-test was used to determine the reliability (Cronbach's alpha=0.74). For implementing an educational intervention, a website was set up for this study. During a briefing session, how to use the website and educational contents were trained for the experimental group, and an exclusive username and password were given to them. Username and password were found invalid for students after 4 weeks, and the course was ended. Students contacted the researcher via email and asked their questions during this period. The educational program was included the definition and importance of iron deficiency anemia, symptoms, risk factors, diagnosis, complications, prevention, food sources of iron and the role of nutrition in prevention and treatment. 4 months after the intervention in both experimental and control groups, questionnaires and blood tests were performed again. Data were collected and analyzed using statistical tests of Chi-Square, Paired T-test, Independent T-test software SPSS19.

Results

In this study, 104 female high school students aged 16-17 years old were included in two experimental (n=52) and control groups (n=52). The results of this study showed that there was no statistically significant difference between the two groups in terms of job and education (Table 1). The results also that the

Table 1. Characteristics demographic of the Intervention and Control Groups

Variables		Intervention group n (%)	Control group n (%)	P value
Father's education	Lower than diploma	16(30.8)	17(32.7)	0.162
	Diploma and Upper than diploma	36(69.2)	35(67.3)	
Mather's education	Lower than diploma	13(25)	22(42.3)	0.064
	Diploma and Upper than diploma	39(75)	30(57.7)	
Father's job	Employed	50(96)	49(94.2)	0.675
	Not employed	2(4)	3(5.8)	
Mather's job	Employed	2(4)	0(0)	0.361
	Not employed	50(96)	52(100)	

two groups had no significant difference in the mean scores of knowledge before intervention (p>0.05). However, the scores of the experimental group were increased compared with the control group 4 months after the intervention (p>0.05). After the intervention, the experimental group had a significant increase in the mean score of knowledge than before the intervention, while no significant difference was observed in the control

group before and after training (p<0.05). The findings revealed that after the training, the average score in preventive behaviors of iron deficiency anemia had a statistically significant increase in the experimental group compared with the group before training and also compared to the control group after the intervention (p<0.001) (Table 2). Before and after the training,

Table 2. Comparison of the mean scores of knowledge and preventive behaviors before and after the intervention between two groups

Variables	Research time	Experimental group Mean (SD)	Control group Mean (SD)	p-value*
Knowledge	Before Intervention	12.04±2.25	12.86±2.87	0.088
	After Intervention	18.66±3.09	13.42±2.21	0.043
	p-value**	0.000	0.112	
Preventive behaviors	Before Intervention	12.06±3.76	11.17±3.06	0.060
	After Intervention	24.38±2.73	10.80±3.06	<0.001
	p-value**	0.000	0.335	

* Independent T-test ** Paired T-test

comparing the mean serum ferritin in the experimental group showed that the mean ferritin level was obtained 44.88 in the experimental group and 45.42 in the control group before the intervention, respectively. Independent t-test showed no significant difference between the two groups before the intervention (p=0.911). The results indicated that after the intervention, the mean serum ferritin for the experimental group and the control group was obtained 57.80 and 47.23, respectively. After the intervention, the independent t-test showed a significant difference between the two groups (p=0.045). Before the educational intervention, the mean hemoglobin was not significantly different between the two groups (p=0.986), but the average level of hemoglobin in the experimental group was significantly higher than the control group after training (p=0.024). Furthermore, no significant difference was observed in the mean in the control group before and after the intervention (p=0.178), while the mean was found to be significantly increased in the experimental group after the intervention (p<0.001) (Table 3).

Table 3. Comparison of mean score of Hemoglobin and Serum Ferritin between groups before and after the intervention

Variables	Research time	Experimental group Mean (SD)	Control group Mean (SD)	p-value*
Hemoglobin	Before Intervention	12.66±0.97	12.67±0.86	0.986
	After Intervention	13.02±0.82	12.64±0.86	0.024
	p-value**	0.0001	0.178	
Serum Ferritin	Before Intervention	44.88±15.45	45.42±13.65	0.911
	After Intervention	57.80±13.25	47.23±19.54	0.045
	p-value**	0.0001	0.508	

* Independent T-test ** Paired T-test

Discussion

Today Iron deficiency anemia is one of the most common public health problems in developed and developing countries [13]. Teenage girls are identified as a group at risk of iron deficiency and the prevalence of the disease in the group will increase after puberty due to the onset of menstruation [14]. On the other hand, the lack of prevention and control of iron deficiency can have an adverse effect on the health of girls and women, followed by serious economic and social damages [15]. So, training and improving knowledge of the target group as one of the strategies recommended in order to deal and prevent iron deficiency, are of particular significance in this respect. Therefore, this study was designed to determine the effect of the educational intervention based on knowledge and preventive behavior of iron-deficiency anemia among female high school in Andimeshk city.

Several studies have shown that increasing the level of knowledge is one of the first steps to move towards behavior change; therefore, having sufficient knowledge about nutrition can be the basic foundation for healthy eating behaviors [16-17]. In contrast, the low awareness level is a risk factor of malnutrition and anemia [18]. In general, every effort which will be made to establish a health behavior requires having sufficient knowledge as the first key element [19]. Based on the results obtained, the mean score of knowledge has increased significantly after the intervention compared with the control group, which is a positive effect of educational program on improving the knowledge and behavior of students in the experimental group. The findings of the study were consistent with the results of the study by Mehrabian et al., regarding the raising awareness of female high school students and reported successful training in promoting awareness about iron deficiency [1]. The findings of the study by Fathizadeh et al. are also consistent with the results of this study, demonstrating the effectiveness of education in raising awareness of female students [2]. Also, the findings of the study by Fallahi [11] are in agreement with our findings indicating the effectiveness of educational interventions in increasing the knowledge regarding the iron deficiency anemia. Additionally, in the study by Ivan Bagha et al. among female students in the secondary school in Khalkhal, it was suggested that educational interventions did not significantly increase the level of awareness [13], which could be due to different target groups in the study. Kanal et al., have also shown in their study that the educational program improves and increases awareness of female students concerning the causes, consequences, and ways to prevent anemia, which is in line with the results of our study [20].The findings of our study have shown that web-based training led to increased levels of preventive behaviors of iron deficiency anemia among female high school and the performance of the experimental group was improved compared to the control group after the intervention and significant difference was observed between the mean performance score in two groups. Fathizadeh observations [2] demonstrated that the behavior of girls in the experimental group regarding the prevention of iron deficiency anemia has improved and there was a significant difference between their behavior before and after the intervention. The results of the study by Mehrabian [1] also revealed that using of training programs improved eating behaviors among female high school with regard to the iron deficiency anemia. Moreover, the study by Sadeghifar [14] and Shakoori [21] has confirmed that an educational program could improve and promote preventive behavior of iron-deficiency anemia. Bandura contends that behavior is the strongest source of information adequacy because it is directly inferred by subtle experiences. By implementing these practices, people will develop and refine the skills that are important in the continued

fulfillment of behavior [22]. The studies conducted by Hosseini [23], Fallahi [11] and Rao [24] confirmed the above findings and verified the effectiveness of educational interventions on modifying nutritional behavior. The results of this study indicate the positive impact of education on improving blood iron indicators. Four months after the intervention, a significant increase was observed in ferritin and hemoglobin levels in the experimental group, but no significant change was found in the control group. The results of the study by Mehrabian et al., also showed increased ferritin levels among female high school [1]. In a study conducted by Halimatou Alaofe and colleagues on teenage girls in Benin, the results showed that after the implementation of the educational program, hemoglobin and serum ferritin levels in the intervention group were increased significantly [25]. The results of the study by Hafzan et al., on Malaysian adolescents showed that a significant improvement has been observed in hemoglobin and ferritin levels in teens 3 months after the training which confirms our findings [26]. Similar results can be observed in the studies by Fallahi [11] and Duncan [27] showing that training and change in eating habits can be the perfect solution for the promoting blood indices and reducing iron deficiency anemia. A follow-up study 4 months after the intervention was the strength of this study. The limitations of the present study were that no similar study has the in Khuzestan and Andimeshk cities in this respect. Another limitation of the study was completion of self-report questionnaires by students. Overall this study has shown that the implementing of educational program has promoted the level of awareness and prevention of iron deficiency and also improved blood indices in the studied girls. Girls are the future mothers of our society, and nutritional education has a direct and positive impact on their health. Students are supposed to learn best and in comparison, with other activities in the field of health, educational activities are less expensive. With regard to the consequences of iron deficiency especially in girls, providing persistent training and using modern techniques such as web-based approach can have an important role in the prevention and disease.

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Competing interests

Authors have declared that no competing interests exist.

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Adaptation in metal-ceramic and all-ceramic restorations

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Abstract

Aim: Lack of good marginal adaptation in dental restorations over time tends to dissolve the cement in oral cavity, which leads to the accumulation of plaque, tooth decay, pulp contention, gingivitis and periodontal diseases and ultimately treatment failure. The aim of this study is to evaluate and compare the internal and marginal adaptation in metal-ceramic and all-ceramic restorations made by traditional and CAD/CAM methods. Material and Method: 1. Preparation of working cast and die 2. Preparation of restorations: In this study the samples were divided into 6 groups of 10, which are as follow: Group A: metal-ceramic restorations without collar made by manual method (traditional and conventional). Group B: metal-ceramic restorations without metal collar, in which the wax coping was made of special blanks by CAD/CAM method and the rest of process is manual. Group C: metal-ceramic restorations without metal collar, in which their frame was made by using dry milling method and Sintron technology and the rest of process was done manually. Group D: E.max-Press all-ceramic restorations (lithium disilicate). Group E: All-ceramic restoration with Core Zirconia prepared by CAD/CAM method and porcelain layering. Group F: Trans-Lucent zirconia (solid) all-ceramic restorations as full-contour by CAM/COD method. 3. Measuring the amount of the gap: Replica technique was used for this purpose. Results: The lowest mean gap in marginal and internal restorations was in group B and the highest amount was in Group C and D, respectively, and altogether there was a significant difference between 6 study groups (P<0.001). The mean marginal gap in all groups (except group B) was more than 120 microns, which is not clinically acceptable. The best marginal and internal adaptation was observed in Group A and B. Discussion: Based on the findings of this study, traditional spruing technique, invesment, wax removing and alloy injection still provide the best marginal adaptation and in general comparison, metal-ceramic restorations are preferred over all-ceramic restorations.

Keywords

Marginal; Internal; Restoration; Metal-Ceramic; All-Ceramic

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Introduction

The milling of abutment teeth is one of the main steps of crown fabrication. milled parts should be covered completely and accurately to prevent onset or recurrence of tooth decay. This is only possible by good adaptation of crown edges with finishing line of teeth milling. Lack of good marginal adaptation in crowns over the time tends to dissolve the cement in oral cavity and provide a way for penetration of micro-organisms and toxins caused from their activities, it also leads to plaque accumulation, recurrent caries, pulp contention, and onset of inflammation in periodontal tissue around the finishing line of teeth milling and ultimately restoration failure. [9, 10, 11]

Restorations are divided into two categories: **1-** metal-ceramic and **2-** all-ceramic. Metal-ceramics melt at relatively low temperature (800 C). Today, with the changes that have been done on metal frame, there has been an attempt to restore the beauty and natural property of metal-ceramics by using investment techniques and very thin coping (2.0 to 3.0 mm) [7]. In a classification system by America Dental Association (ADA) metals used in metal-ceramics are divided into 3 categories: **1-** High noble metals, having more than 60% noble metal (like gold–palladium). **2-**

Noble alloys (35% to 45%) with a small amount of gallium. **3-** Alloys that generally have less than 25% noble metal. Selecting a suitable alloy depends on the factors such as price and stiffness, pouring capability, easy finishing and palishing, resistance to corrosion and compatibility with porcelain. Suitable compounds include gold (44% to 55%) and palladium (35 to 45%) with a small amount of gallium [7]. Metal-ceramic restorations still are the gold standard in fixed denture [16, 17].

All-ceramic restorations (without metal) are increasingly being prescribed to patients, which due to the high aesthetic functionality and histocompatibility features they are great. In order to improve the usability as dental material and to improve the strength and stiffness properties, from 1980 up to now, various ceramic materials and manufacturing techniques were introduced, which lithium disilicate, alumina and zirconia can be named [9, 10, 11]. The method used to build an all-ceramic crown is actually simple, but to create a beautiful, harmonious and functional structure, great skill is required. Of all the all-ceramic systems, Inceram in the best way has all of these factors. This material has the best mechanical properties (almost three times more flexural strength compared to other systems, except Porcera system), Spinell core, which is composed of MgAl2O3, has natural teeth translucency. Inceram margins fit well (marginal gap depth of 10-40 mm), core transparency is able to cover the undesirable reflection in oral cavity. The problem of using these system is that they require special equipment [6].

Possible errors during the construction of the restorations by CAD/CAM, including process of scanning, designing by software, milling by machine and contraction during sintering, affect the amount of marginal integrity [12-15]. New technology of using designing technology and computer-aided manufacturing (CAD/CAM) for making crowns, laminates and 3-unit anterior fixed partial dentures require precise teeth preparation and molding, in order to be used as a prosthetic repair with margins. This technology often allows us to complete various cases, even single tooth restoration, in collaboration with numerous specialist, without the need for direct contact with patient and though electronic communication and memory structures. 4.0 and 6.0 mm coping with different crowning ability and two different materials (zirconia and alumina) and multiple liners can be outlined as features of all-ceramic CAD/CAM crown [8].

The marginal adaptation is one of the essential factors to achieve long-term success for each restoration. As there is not always a precise definition for marginal adaptation, it can be said that the best way to check it is by measuring non-adaptation of different areas of prepared teeth to edge of the crown [1-5]. Lack of marginal adaptation can be due to inaccuracies in the fabrication of crown, lack of full sitting during cementation of it or a combination of both. The aim of this study is to evaluate and compare the marginal and internal adaptation in metal-ceramic and manual all– ceramic (conventional) and CAD/CAM restorations.

In a study by A.M. Fahmy et al. (2012) on marginal adaptation of metal-ceramic restorations without metal collar and IPS Empress CAD/CAM restorations, it was revealed that metal-ceramic restorations without metal collar have the best adaptation and they are recommended in important areas in terms of beauty without worrying about the marginal gap [18]. Tamac et al. (2014) in a comparative study for comparing marginal fit of metal-ceramic restorations made with three methods of CAD/CAM, Laser Sinter and conventional casting suggested that each of 3 methods have a similar marginal fit, which are in the range of clinical standard [19]. According to a study by Zhuoli Huang et al. (2015), metal-ceramic crowns made with CAD/CAM technique, Laser-Sinter (chrome – cobalt) and gold–platinum casting had similar margin fitting and chrome–cobalt casting crowns had the least marginal adaptation [20]. Nejatidanesh et al. (2016) examined the marginal and internal adaption of implant-supported restoration made with 2 different methods of CAD/CAM and 2 different traditional methods and from this study concluded that CAD/CAM technology provides better marginal fit.

Material and Method

In this experimental study to prepare the cast and die, first two maxillary dental arches were selected and first molar tooth above it was prepare for similarity with clinical conditions with a shoulder milling with a depth of approximately 1 mm for full crowning and the tooth was examined with surveyor to ensure that there is no undercut. Then template was prepared from the maxillary and mandibular arches by two perforated metal trays and additive silicone impression material (BONASIL,DMP,Greece) and working cast was obtained by stone gypsum (dentona,dentona AG,Germany) and under vacuum, in which the die was prepared after trimming and sawing (cutting) steps. The above steps were repeated for the preparation of each restoration. 6 groups of 10 and a total of 60 restorations (crowns) were created, in which the restorations of groups A, B and C were metal-ceramics and the restorations of D, E and F were all-ceramics. It should be noted that Group A is the conventionally, manually and controlled group in the study. In order to provide restoration of Group A, after preparing the die, the two layers of Die spacer (mega-Stumpflack,megadental GmbH,Germany) were placed on it, thickness of each layer is 15 microns and is extended up to 1 mm of margin. Cement space for all the samples whether manual or CAD/CAM was considered as 30 microns. Then the wax-up coping was done and the labial margin wax was removed. After completing the

waxing-up, spruing and investing, cylinder was filled with Investment gypsum (CODENT/PODENT,Dandiran,Iran) and cylinders were placed inside the removing wax furnace (SUNNYTHERM-1,KFP,Iran). Then the inductive centrifuge machine (DUCATRON,KFP,Iran) was used for melting and casting of molten chrome-cobalt alloy (NEW CAST,YAMAHACHI DENTAL MFG,Japan) into the productive space and then it was allowed to become cool. Clean investment gypsum and sandblasting were used for the final cleanup. feldspathic porcelain layering (Super porcelain EX-3,NORITAKE CO,Japan) was done according to its routine. Placing of opaque layer, shoulder porcelain (initial,GC,E.U) with Direct Lift technique (direct removal of restorations from top of die and direct placement of shoulder porcelain), dentin and enamel and finally firing the porcelain in the special furnace (Programat P500,IVOCLAR VIVADENT, Liechtenstein) were completed and then contacts and occlusions were set according to the opposite arc and adjacent teeth. Wax copings from special wax blanks for milling with COD/CAM (Ceramill wax,Amann) were used to prepare the restorations of the Group B. Casts were scanned with Scanner (Ceramill map400, Amann Girrbach , Austria) and processes of CAD/CAM designing were done in computer software. After preparation of wax copings of CAD/CAM milling (imes-icore GmbH,Germany imes-icore 550 i,) the rest of process was similar to group A. Sintron technology was used to prepare the restorations of group C. First the casts were scanned by a scanner. Coping were milled by CAD/CAM machine from soft blanks and gypsum such as chrome-cobalt alloy (Ceramill Sintron,Amann Girrbach , Austria) and then were placed inside of sinter furnace to sinter and they were put under argon gas pressure (Ceramill Argotherm, Amann Girrbach , Austria) and they have strength comparable to manual and conventional types. It should be noted that the CAD/CAM milling used in study groups was from soft milling zirconia types (dry milling). To prepare the restorations of group D which are E.max-Press (lithium disilicate or glass-ceramic), a full wax-up was done on samples of this group and then they were placed in wax removal furnace to achieve the productive space. Then Ingots for E.max (IPS e.max, ,IVOCLAR VIVADENT, Liechtenstein) in furnace for Press (Programat EP 3000, ,IVOCLAR VIVADENT, Liechtenstein) were casted into the productive space by special plunger, after cleaning the plaster Investments, an all-ceramic full-contour restoration was obtained. The restorations of group E are Zircon. To prepare the samples of this group, first scanning of casts and processes of CAD/CAM designing were carried out. Then a core zirconia was milled by CAD/CAM from blanks for zirconia (Ceramill Zi,Amann Girrbach, Austria). Binder was put on it and then special porcelain layering was carried out and porcelain shoulder specific for zirconia was placed in the area of buccal margin and zirconia was put inside of sintering furnace. To prepare the restoration samples of group F, first scanning of casts and processes of CAD/CAM designing were carried out. Name of the restorations of this group is Zolid, which is a translucent zirconia and it was obtained as full-contour from Zolid soft blanks (Ceramill Zolid,Amann Girrbach,Austria) by CAD/CAM milling and then was put in the furnace for sintering the zirconia. The replica technique was used for measuring the internal and marginal gap. This means that the restoration was filled with additive silicon with light body consolidation (BONASIL,DMP,Greece) and was put on the respective die. Immediately and with caution additions of impression material was cleaned and the restoration was held for 2 minutes with finger pressure (for similarity with clinical conditions). After setting of the impression materials, restoration was removed from the respective die. Thin layer of light body silicon is attached to the inner surface of the restoration, which is actually indicative of the gap in different parts of restoration and in order to strength it and make it examinable, we fill the inside of restoration with Injectable additive silicone with medium or heavy consolidation (BONASIL,DMP,Greece) and let it be set. Then we remove the silicone from inside of restoration and saw whether the light body silicone layer is attached to amplifier silicone, now according to figure this silicone block is milled with a milling razor. 8 cuts are used to examine the points and middle area does not use. Marginal gap is measured at 8 points and internal gap measured at 4 points (cervical, middle of axial level, axial occluso line angle and center of occlusal surface). Light body silicone layer thickness, which is actually equal to amount of the existing gap, is photographed by stereomicroscope (Dino-Lite,Taiwan) with a magnification of 60 times and then it was calculated and declared using Dino Capture 2.0 software. Tables and appropriate statistical charts were used for describing the data and one-factor variance analysis test or its non-parametric equivalent was used for data analysis. The sample size for two independent groups was determined based on the study by Kim Ki-Baek et al. (2014) with 85% power and 10 samples in each group [22].

Results

In this study, three variables of internal, marginal and buccal marginal adaptations were examined between six groups as well as between metal-ceramic and all-ceramic restorations. The normality of the data was evaluated using the Shapiro-Wilk test and it was determined that the data for some variables and some groups are not normally distributed. The results showed that for the internal adaptation, range of data changes of group 4 is much greater than the other groups. The lowest value observed belongs to group 6 and the highest values belongs to group 4. The lowest mean belongs to group 2 and the highest mean belongs to group 4, the lowest mean value belongs to group 1 and the highest mean value belongs to group 3. In total, the distributions among 6 groups are significantly different with each other (P<0.001), which in pairwise comparison of groups with each other, it was determined that groups 1, 2 and 3 were significantly lower than groups 3 and 4. Group 6 was significantly lower than group 4, group 3 was also significantly lower than group 4. There was no significant difference between the other groups (Table 1).

Table 1. The mean, standard deviation, minimum, maximum and median of data for internal adaptation in study groups and statistical test result

Group	Numbers	Mean	Standard deviation	Lowest	Highest	Median	Kruskal-Wallis test result
1	320	113.77	52.44	30.61	329.63	98.21	
2	320	112.40	53.44	43.44	336.71	99.23	
3	320	149.85	99.66	43.44	792.80	159.18	X2=153.04 P<0.001
4	320	172.25	115.76	54.30	1650.76	139.26	
5	320	117.80	46.84	46.07	314.92	127.29	
6	320	120.72	53.39	26.02	292.40	131.21	

Based on the results of marginal adaptation data, range of data changes in group 3 is greater than other groups. The lowest value observed belongs to group 2 and the highest belongs to group 3. The lowest mean belongs to group 2 and the highest belongs to group 3, the lowest median belongs to group 2 and the highest belongs to group 5. In total, the distributions among 6 groups are significantly different with each other (P <0.001), which in pairwise comparison of groups with each other, it was determined that group 2 is significantly lower than other groups. Group 1 was significantly lower than group 3, 5 and 6. There was no significant difference between the other groups (Table 2).

Table 2. The mean, standard deviation, minimum, maximum and median of data for marginal adaptation of the study groups and the statistical test result

Group	Numbers	Mean	Standard deviation	Lowest	Highest	Median	Kruskal-Wallis test result
1	80	135.42	69.34	49.79	372.33	106.91	
2	80	92.49	54.80	39.15	369.38	72.85	
3	80	195.17	123.33	54.30	680.33	152.41	X2=122.36 P<0.001
4	80	155.92	73.70	69.53	607.05	136.71	
5	80	181.05	85.55	65.16	602.08	179.86	
6	80	168.72	54.11	87.56	347.67	165.04	

The box chart below shows the distribution of data for internal and marginal adaptation with separation of study groups. As it can be seen, there is a large distribution in groups of 1, 3 and 4, and there are large outlier values in the data for marginal adaptation of groups 3 and 5 (chart 1).

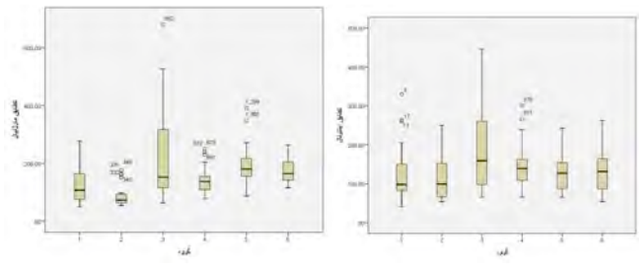


Chart 1. The distribution of Internal and marginal adaptation, with separation of study groups

The range of data changes in buccal marginal adaptation data for groups 5 is higher than other groups. The lowest value belongs to group 2 and the highest belongs to group 5. The lowest mean belongs to group 2 and the highest belongs to group 5, the lowest median value belongs to group 2 and the highest belongs to group 3. In total, the distribution among 6 groups are significantly different with each other (P <0.001), which in pairwise coparison of groups with each other, it was determined that group 2 is significantly lower than other groups. There was no significant difference between the other groups (Table 3).
The box chart below shows the distribution of data for buccal marginal adaptation with separation of study groups. As it can be seen, there are large outlier values (chart 2).

Table 3. The mean, standard deviation, minimum, maximum and median in the study groups and the statistical test result

Group	Numbers	Mean	Standard deviation	Lowest	Highest	Median	Kruskal-Wallis test result
1	30	155.21	81.45	61.21	372.33	121.48	
2	30	96.22	58.97	39.15	342.18	82.31	
3	30	174.43	87.98	54.30	414.65	169.11	
4	30	144.42	51.42	69.53	262.65	148.48	
5	30	183.21	118.36	65.16	602.08	152.99	X2=33.37 P<0.001
6	30	158.62	34.37	87.56	222.81	159.03	

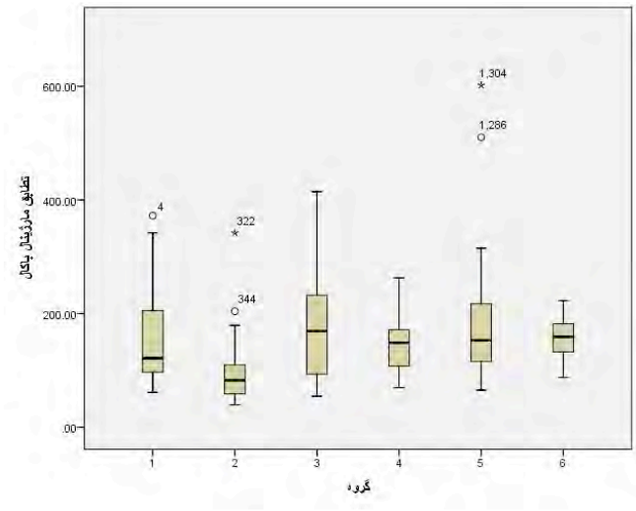


Chart 2. The distribution of data for buccal marginal adaptation with separation of study groups.

The results of the marginal adaptation data indicated that range of data changes in all-ceramic group is lower than metal-ceramic group. The lowest and the highest value observed belongs to metal-ceramic group. The lower mean and median belongs to metal-ceramic group and the higher mean belongs to all-ceramic group. The difference between the two groups was statistically significant (P <0.001) (Table 4).

Table 4. The mean, standard deviation, highest, lowest and median of marginal adaptation data in metal-ceramic and all-ceramic groups and statistical test result.

Group	Numbers	Mean	Standard deviation	Lowest	Highest	Median	Mann-Whitney test result
Metal-ceramic	240	141.03	96.90	39.15	680.33	105.92	Z=6.93 P<0.001
All-ceramic	240	168.57	70.66	65.16	607.05	155.49	

As shown in Table 5, range of data changes in all-ceramic group is higher than metal-ceramic group. The lowest and highest value observed belongs to all-ceramic group. The lower mean and median belongs to metal-ceramic group and higher mean belongs to all-ceramic group. The difference between the two groups is statistically significant (P <0.001).

Table 5. The mean, standard deviation, highest, lowest and median of internal adaptation data in metal-ceramic and all-ceramic groups and statistical test result.

Group	Numbers	Mean	Standard deviation	Lowest	Highest	Median	Mann-Whitney test result
Metal-ceramic	960	125.34	73.96	30.61	792.80	106.93	Z=5.28 P<0.001
All-ceramic	960	136.92	82.23	26.02	1650.76	121.41	

The box chart below shows the distribution of data for internal and marginal adaptation with separation of all-ceramic and metal-ceramic groups (chart 3).

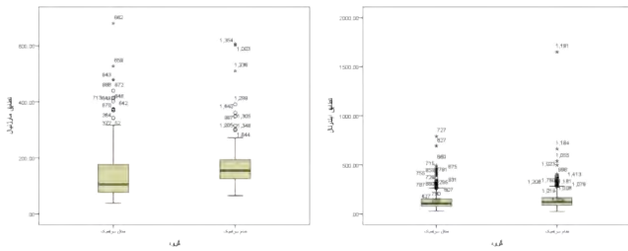


Chart 3. The distribution of data for internal and marginal adaptation with separation of all-ceramic and metal-ceramic groups

Discussion and Conclusion

Marginal adaptation is one of the key criteria in successful clinical restorations [4-1). After clinical examination of over a thousand metal-ceramic crowns, Mclean & Von Fraunhofer reported that marginal gap of up to a maximum of 120 mμ is acceptable. Other clinicians stated the maximum value as 100 mμ [8]. All-ceramic restorations (without metal) are increasingly being prescribed to patients, which is due to their high aesthetic capability and their excellent histocompatibility properties [9, 10, 11]. Possible errors during the construction of the restorations with CAD/CAM, including process scanning, designing by software, milling by machine and contraction during sintering, affect the amount of marginal adaptation [12 – 15].

The aim of this study was to evaluate and compare the marginal adaptation in metal-ceramic and all-ceramic CAD/CAM restorations. Therefore, in this study, a total of 60 dies created from milled molar teeth were prepared on the arch and dies were divided to 6 groups of 10, in which metal-ceramic restorations for 3 groups and all-ceramic restorations were made in the following order: in group A, all-ceramic restorations were made in the traditional way and this group considered as control group. In group B, wax copings were made from millable wax blocks by CAD/CAM machine and after making of metal coping, porcelain was done by conventional method. In group C, Sintron technology was used, in which metal copings are prepared from chrome-cobalt alloys milled by CAM/CAD machine. In group D, E.max press restorations were used. Zircon restorations were made for group E and Zolid restorations were made for group F and for all of the samples of study, the internal, marginal and buccal marginal adaptations were measured using gap measuring by Replica technique. The results showed that the best internal, marginal and buccal marginal were observed in groups 1 and 2. This finding suggests that using traditional techniques of sprue-ing, investment, wax elimination and alloy casting provide the best marginal adaptation. Vojdani et al. (2013) examined the internal and marginal adaptations in metal-ceramic restorations which are made by traditional method by using CAD/CAM. They prepared 12 copings by CAD/CAM method and 12 copings by traditional method and measured the internal and marginal adaptations in 15 points. In this study, they concluded that the internal and marginal adaptation in metal-ceramic made by traditional method is significantly better than the internal and marginal adaptation in metal-ceramic made by CAD/CAM [23]. The mean internal, marginal and buccal marginal adaptations for teeth in group C were 148.9, 195.17 and 174.4, respectively, which in overall these amounts are indicative of lesser adaptation of restorations made by Sintron technology compare to other restorations. Also, the lowest internal adaptation was related to group D with the mean of 172.2, which shows that glass-ceramic restorations that are made by lithium disilicate casting into mold space have lesser internal adaptation compare to all-ceramic restorations made by CAD/CAM method. But marginal adaptations in E.max restorations were lesser than restorations made by CAD/CAM. From these findings, we cannot make judgment about advantage of all-ceramic restorations made by CAD/CAM method over E.max restorations. Among the metal-ceramic restorations, restorations made by Sintron technology had the worst adaptation. But in comparison with restorations of A and B, internal adaptation in these two groups were the same, but marginal gap in group B, in which wax blocks were made by CAD/CAM technology, was significantly lesser than restorations made by traditional method. These finding could be indicative of priority of metal-copings that their wax pattern is made by CAD/CAM method. Since there is a general agreement among researchers about clinically acceptable gap of less than 120 μm [8 ,29], based on the findings of our study, only the adaptations in group B are acceptable. Several studies have examined the different methods of preparing all-ceramic restorations made by CAD/CAM method in terms of marginal adaptation. According to the findings of the study by Paolo Vigolo, Seven Reich and Beuer, different methods of preparing all-ceramic restorations by CAD/CAM have no significant difference in terms of marginal adaptation and in all of these study, marginal gap was clinically acceptable at the end [24, 25, 26]. In the study by kohorstp et al. (2009), in which they examine the marginal precision of 4-unit zirconia restorations made by different CAM/CAD methods (Digident, Inlab, Everest, Cercon) before and after sintering, it was determined that the marginal adaptation of zirconia is highly dependent on used CAM/CAD system and restorations prior to sintering have better marginal adaptation [27]. Kianoosh Torabi et al. (2011) examined the zirconia copings made by CAD/CAM and Slip–Cast in terms of marginal adaptation and suggested that CAD/CAM is competitive with conventional methods and clinically and in vitro has acceptable marginal adaptation [28]. In comparison of marginal adaptation of 3-unit restorations with two methods of Laser sintering and Lost Wax which was conduced by Ki-Baek Kim (2013), It was determined that the marginal adaptation of conventional method (Lost Wax) is significantly better and marginal adaptation of Laser sintering method is not clinically acceptable [29]. On the study by Zhuoli Huang et al. (2014), it was determined that Laser–sinter metal-ceramic restorations have better marginal adaptation compare to CAM/CAD method (both zirconia and disilicate system) [20].

In this study, results showed that there is no difference between two methods of preparing all-ceramic restorations by CAD/CAM machine. But in all 3 groups of all-ceramic restorations, the mean of internal and marginal gap was more than 120 µm, which according to many researchers is not clinically acceptable. Perhaps we could associate the difference between this finding of our study and some studies [14, 30, 31, 32] with difference in preparing restorations, as in these studies measuring the gap on restorations were preformed prior to sintering, while in our study, all-ceramic restorations after preparation undergone sintering again. According to the findings of study by Vigolo, restorations prepared by CAD/CAM technique, prior to sintering have better adaptation compare to restorations post sintering. General comparison of metal-ceramic and all-ceramic restorations was also indicative of priority of internal and marginal adaptation of metal-ceramic restorations over all-ceramic restorations. The findings of this study, regarding better internal and marginal adaptation of metal-ceramic restorations compare to all-ceramic restorations, were similar to other studies [26, 27, 33, 34].

Comparing the results of different studies conducted on marginal adaptation of restorations is difficult, because these studies have significant differences, for example, some studies have been conducted in vitro, some on clinical samples, some on single-unit restorations and some other on multi-unit restorations. There are considerable differences in the details of laboratory procedures and materials used in these studies, in addition, different methods of measuring the marginal gap of restoration, itself can be a source of difference between results of different studies.

Competing interests

The authors declare that they have no competing interests.

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Anxiety and general health of spinal-cord-injury (Sci) patients

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Abstract

Aim: The aim of this study was to compare the effectiveness of group physiotherapy and individual physiotherapy in reducing anxiety and increasing general health in patients with Spinal-Cord-Injury (SCI). Material and Method: This study is an experimental study conducted on 40 SCI patients. We assigned patients randomly to two groups: group physiotherapy (n=20) and individual physiotherapy (n=20), then conducted group physiotherapy for one group and individual physiotherapy for the other. Pre- and post-physiotherapy tests were conducted for both groups. We used Zung Self-Rating Anxiety Scale (SAS) and General Health Questionnaire as a measurement tool, and to extract the results, we used multivariate analysis of variance. Results: Comparison of the means of the two groups at the end of the study showed that group physiotherapy is significantly better in reducing anxiety in SCI patients ($P<0.01$). However, individual physiotherapy has increased anxiety in these patients. In contrast, individual physiotherapy has been more effective than group physiotherapy in increasing general health of SCI patients. Discussion: Group physiotherapy, compared with individual physiotherapy, reduces the anxiety of patients but individual physiotherapy is more effective in increasing general health compared with group physiotherapy.

Keywords

Anxiety; General Health; Group Physiotherapy; Individual Physiotherapy; Spinal Cord Injury

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Introduction

According to the UN Assembly resolution in December 1993, SCI is a type of disability [1]. A disabled person with SCI refers a person whose spinal cord is injured from the area below the medulla oblongata to the end of cauda equina, protected by the spine. Moreover, its injuries vary from incomplete damage to complete cessation or crash resulting in a motor, sensory, and/or autonomic effects in one or more limbs and/or the whole body [2].

If the damage happens in a thoracic vertebra and lower, the person suffers paralysis of the lower limbs (paraplegia). If it happens in the cervical spinal cord, it leads to paralysis in all four limbs (tetraplegia or quadriplegia). In fact, as the injury area is closer to the brain, the SCI severity increases [3].

Road accidents, occupational accidents, natural disasters, and social conflicts such as war are among the factors that can lead to transient or permanent disability [4]. The average global prevalence of SCI is 20-50 per one million people. However, in Iran, according to the report by Center for Research on SCI, the number of SCI patients is 1400-2800 cases in a year. As mentioned, SCI can occur for many different reasons. Whatever the reason is, it will leave deep and wide impacts on physical and mental health and lifestyle [6].

These patients have many physical, emotional, and self-esteem restrictions along with restrictions on the ability to perform daily activities. These restrictions greatly affect the quality of life of patients and their families [7]. Stresses created after SCI can make the person isolate and withdraw from the community and activities, and cause a lot of mental and mood disorders, including depression. Depression is a state associated with lower self-esteem, feelings of inadequacy, incompetence, poor perceptions of oneself, and anxiety. It is an agonizing feeling associated with a current situation or an expectation of risk with a unknown origin [8].

Among the main problems that patients with SCI suffer are anxiety and reduction of general health, which may be caused by social isolation. People with physical disabilities have less social contact and are more susceptible for social isolation than ordinary people [9]. This social isolation might be because compatibility with SCI, compared with physical condition, needs more effort in psychological terms. This is especially because disability in patients with SCI occurs suddenly, and these patients need more time for adaptation to the conditions created [10]. Special conditions in patients with SCI have a great impact on psychological state and familial and social relationships of these individuals, and this physical disability affects socio-psychological adjustment and mental health of the person [11]. However, individual features before the injuries are effective in psychological complications and different people react in different ways to these psychological pressures. Some people are better than others in dealing with these stimulants and stresses, whereas much more are quite prone to stresses and have no resistance because of personality aspects [12]. There is a significant relationship between socio-psychological adjustment and negative emotional responses, such as depression, anxiety and stress management techniques, and there is also a significant relationship between intensity of disability and lower levels of adjustment [13].

In comparison to non-disabled people, research suggests that people with disabilities are socially isolated, depressed, and have fewer intimate relationships [14]. In 30% of patients with SCI, the experience of depression and anxiety continues two years after the injury [15]. Psychological effects of SCI reach their maximum value in the first five years after the injury [16].

In connection with treatment, although patients with SCI cannot be completely cured, they should receive psychological support and rehabilitation services [1]. Rehabilitation services offered to people with SCI include different fields. Physiotherapy, speech therapy, occupational therapy, orthopedics, psychology, and nursing are some of these services. One of the most important services of rehabilitation is physiotherapy. Since physiotherapists perform physiotherapy mostly individually, the disabled individuals have no communications with other disabled people, so they are in an isolation state and lack social connection. This social isolation and withdrawal, in return, may increase anxiety and destroy general health [9].

Group physiotherapy may have some effects on social interactions of people with disabilities. Group physiotherapy provides a kind of social support. Social support is considered as a factor preventing stress against losses from internal and external pressure factors [17]. Studies show that people with more social protection have more resistance in the face of stressful events and show fewer signs of anxiety and confusion [18], so that the person gets away from social isolation and communicates with other people with SCI through group participation. One may reduce anxiety and promote general health by group physiotherapy. This partnership may affect the effectiveness of physiotherapy. This study specifically looks for an answer to the following question: What effects does group physiotherapy have on anxiety and general health of patients with SCI compared with individual physiotherapy?

Material and Method

This study was performed as an experimental therapeutic intervention study. The population of this study is patients with SCI covered by Kahrizak Charity Foundation (KCF) of Tehran. We selected 40 patients using random sampling and randomly assigned 20 patients to the experimental group and 20 patients to the control group. The experimental group was the one receiving group physiotherapy, and the control group received routine individual physiotherapy. Moreover, through the interviews, we ensured that the participants received no other training at the same time. According to research design (pretest and posttest with the control group), after random placement of samples in the experimental and control groups, both groups completed Zung SAS and general health questionnaire (GHQ).

Zung SAS is a 20-question scale. Diagnostic criteria of the questionnaire are 15 physical signs for anxiety and five emotional signs. While scoring, considering the type of question, if it is positive, “never” receives 1 and “always” receives 4, but if the question is negative, “always” or “almost always” receives 1 and “never” receives 4. The validity of this scale was 0.71 using the correlation of Hamilton Anxiety Scale. The reliability of this scale showed a coefficient equal to 84% using consistency coefficient.

Goldberg and Hiller have presented GHQ with 28 questions. Scoring the questionnaire is as follows: "never" gets 0, "at usual level" receives 1, "more than usual" gets 2, and "much more than usual" gets 3. The validity of the questionnaire is 0.55 using concurrent validity. Reliability is 0.90 according to Cronbach's alpha. After the pre-test, the experimental group underwent ten sessions of group physiotherapy, and the control group underwent ten sessions of individual physiotherapy. After the intervention, both groups completed the questionnaire again.

Informed consent was obtained from patients while explaining how to complete the questionnaire, no personal data were collected to adhere to ethical considerations. We used multivariate analysis of variance (MANOVA) for data analysis.

Results

Contents in Table 1 show indices of dispersion among the variables studied.

Table 1. Descriptive statistics

Variable	n	Mean	Standard deviation	Variance
Pre-test of GHQ	40	72.07	14.6	2.3
Post-test of GHQ	40	78.2	14.4	2.2
Pre-test of anxiety	40	48.8	8	1.2
Post-test of anxiety	40	53.1	9.4	1.4

Table 2 (M Box test) is for homogeneity of covariance matrices. Contents of Table 2 show that the correlation of the variables in the studied groups is homogeneous because F calculated is not significant at P<0.05.

Table 2. M Box test

F	Degrees of freedom 1	Degrees of freedom 2	Sig.
½	3	25	0.09

Bartlett Test is used to study the presumption of canonical correlation between variables. Contents of Table 3 show that the precondition of canonical correlation of variables is established because Chi-square value calculated is significant at P<0.01.

Table 3. Bartlett Test

Sig.	Degrees of freedom	Chi-square
0.01	2	19.4

As the presumptions of MANOVA are realized, we use MANOVA to show the effects of different treatment methods. Contents of Table 4 show that all MANOVA tests are significant. In other words, therapeutic methods used (group and individual physiotherapy) have different effects on anxiety and general health in patients with SCI. In other words, there is a difference between treatment methods used in this research in reducing anxiety and increasing general health in patients with SCI. Thus, we compare the means of groups to determine this difference.

Contents of Table 5 show that group physiotherapy is more effective in reducing anxiety in patients compared to individual therapy. This is because the mean of pre-test of anxiety is 48.8 and this value has dropped after group physiotherapy, but individual physiotherapy increases the anxiety.

Table 4. MANOVA

	Value	F	Assumed degree of freedom	Error	Sig.	Test power
Pylayy effect	0.72	47.1	2	35	0.01	1
Wilks Lambda test	0.27	47.1	2	35	0.01	1
Hotelling's T	2.6	47.1	2	35	0.01	1
The highest root	2.6	47.1	2	35	0.01	1

Thus, group physiotherapy is recommended to reduce anxiety. Moreover, individual physiotherapy is more effective than group physiotherapy in improving the general health of SCI patient. This is because the mean of pre-test of general health has been 72.07 increasing to 84.8 after individual physiotherapy, which proves to be more effective than group physiotherapy.

Table 5. Table of means

Dependent variable Intervention	Mean	Sig.
Anxiety Group physiotherapy Individual Physiotherapy	46.8	0.05
	59.4	0.01
General health Group physiotherapy Individual Physiotherapy	71.7	0.05
	84.8	0.01

Discussion

The results showed that group physiotherapy is more effective in reducing anxiety than individual physiotherapy. It seems that group physiotherapy has reduced feelings of loneliness and isolation. This feeling of loneliness is understood as real or mental. In mental loneliness, the person thinks that no one understands him and he does not receive enough emotions. This feeling of loneliness may even cause frustration and lead the person towards depression [19]. These findings are consistent with the results of Nosek MA et al. They have shown that SCI patients' lack of social capital and good social relations has led to an exacerbation of their mental problems [20]. Moreover, these patients try to create a sense of loss and then interpret it for themselves concerning how and why this incident occurred to me [21].

Furthermore, the results of this study are in line with the results of Frank. R. G et al. They concluded that social support has the role of neutralizing the stressors of SCI. Patients with SCI have a low quality of life compared with healty individuals. However, it is not the case for those who have good and broad social relations [22]. As B.j Kemp et al. showed in their study, having social relations and family relations as well as membership in an association of SCI is a predictor of quality of life for these patients more than the other factors [23]. Another result of this study indicates that although group physiotherapy, compared with individual physiotherapy, has reduced the anxiety of these individuals, it is individual physiotherapy that improves general health. These findings according to the above results represents the fact that group physiotherapy reduces problems related to social relations, and it does not seem to be more effective in problems associated with physical health, compared with individual physiotherapy.

Conclusion

The findings suggest that group physiotherapy reduces anxiety more than individual physiotherapy. Thus, we recommend that efforts should be made to create opportunities to strengthen social relations (group physiotherapy) in these patients to reduce anxiety, enhance the quality of life, and reduce depression and negative emotions such as despair and loneliness. As these patients' distance from society, they will feel isolated, which in turn will exacerbate the problems of these people in the form of a vicious cycle. Thus, group situations such as group physiotherapy have a special status. However, to reduce problems related to physical health such as bedsores or general health, individual therapy is more effective.

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Original Research
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A study of the effects of three gloves donning techniques on the contamination

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Abstract

Aim: hospital personnel's hands are considered as the most important way of transmission of pathogens such as methicillin-resistant Staphylococcus aureus and spore bacteria such as Clostridium. Wearing gloves correctly and in a standard way is an essential principle to prevent the surgical site infections. The present study aimed to investigate the effects of three gloves donning techniques on the contamination of operating room personnel's sterile gloves and gown. Material and Method: this research was a field trial study. 96 pairs of gloves were randomly and equally divided between three groups and three ways were determined to wear the gloves: open, closed-gloving techniques and open staff-assisted. After obtaining informed consents, three operating room personnel were selected according to the research objective and they were placed in the three groups. They were taught how to wear gloves and they were controlled in terms of wearing gloves standardly and correctly. After washing hands standardly and glitterbug powder was applied to them and the gown was worn, one of the three mentioned techniques was selected to wear the gloves by random allocation. Each techniques was repeated 32 times. One hour after surgery, the gloves and gown were taken off and contamination of them was checked by irradiation of UV and it was recorded in a related list. The data was analyzed using SPSS V.23 and performing analytical and descriptive statistical tests. Results: in the closed-gloving techniques, the mean contamination of gloves was statistically less compared to two other techniques. The mean contamination in open staff-assisted was less compared to open-gloving technique (p-value < 0.05) (open-gloving technique: 157.34±64.15 VS closed-glovingtechnique: 58.02±34.34 and open staff-assisted: 86.22±45.48). Also, total mean contamination of gown (glitterbug powder) in open-gloving technique was significantly greater than closed-gloving technique and open staff-assisted (p-value < 0.05) (open-gloving technique: 221.92±104.08 VS closed-gloving technique: 121.14±133.21 and open staff-assisted technique: 72.72139.03). Discussion: according to the results, it is recommended that the policy and protocol of wearing gloves with open staff-assisted technique and closed-gloving technique are emphasized in order to reduce contamination more by operating room personnel. Also, more research is needed in this area.

Keywords

Surgical Gloves; Contamination; Operating Room; Gown; Gloves Donningtechnique

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Introduction

Nosocomial infections are a major problem for the health care system. According to the World Health Organization, nosocomial infections are those infections which are created within 48 hours after admission to the hospital or staying in health care centers and at the time of admission, the patient did not have it and were not even in the incubation period [1]. The prevalence of nosocomial infections is estimated from 5 to 30 percent in different countries and its rate in developing countries such as Iran, has been reported %25 [2, 3, 4]. According to the Center for Disease Control and Prevention, nearly 2 million Americans suffer from this type of infection and cost of more than $ 11 billion is imposed to the hospitals in the country and in %16 of them, resistance to antibiotics used to treat them, has been reported [5].

The contamination existing in the equipment, environment and personnel of operating room are the factors causing nosocomial infections in the patients [1]. The studied performed show the rate of microbial contamination in operating rooms from %2.5 to more than 50 percent [6, 7]. So the operating room can be a great source of nosocomial infection [8].

Surgical site infections are the most common nosocomial infection that are included as %31 of nosocomial infections in the hospitalized patients [9]. The mortality rate associated with surgical site infection is 3% and 3/4 of this amount is directly caused by the surgical site infection itself [10].

The principles of prevention of surgical site infections are defined in three before, during and after surgery. Appropriate attire for patients and staff, cutting the hair of surgical site, bowel preparation, the use of two pairs of gloves and antibiotic prophylaxis can be noted as the cases before surgery [8, 11]. In addition to them, scrubbing hands is an integral part of disinfection process but it is necessary to know that the bacteria tend to remain on the hands as much as possible even after scrubbing [12]. Hospital personnel's hands are considered as the most important way of transmission of pathogens such as methicillin-resistant Staphylococcus aureus and spore bacteria such as Clostridium difficile. Washing hands plays a key role in preventing infections. In addition to disinfecting hands, wearing gloves is an important and essential part of a multi-barrier strategy for hand hygiene [13]. Gloves act as a mechanical barrier and prevent the transmission of infection from patients to operating room personnel and vice versa, when contacting with blood, body fluids, secretions, wounds, mucous membranes, chemicals and dangerous drugs [14]. There are various techniques of wearing gloves in the operating room: open- and closed-gloving technique and open-gloving technique with assistance of scrub staff [15]. Closed-gloving technique is theoretically a gold standard of wearing gloves [16]. There are a few studies performed to compare gloves donningtechniques but in all of them two techniques (closed-gloving technique and open-gloving technique, closed staff-assisted and open staff-assisted) were compared [12, 16 and 17] and no study has been performed to compare the three techniques with each other. Nowadays, two open-gloving technique and open staff-assisted technique are used more. In the open technique, there is the possibility of contamination and non-sterilization of surgical equipment and field during surgery due to randomly return of gloves cuff to back, causing contamination of equipment [12]. Surgical gown is worn on operating room clothing as a personal protective equipment to participate in the sterile surgical field. The purposes of wearing a surgical gown are to prevent transmission of contamination between operating room clothing and sterile field and to distinct sterile individuals from non-sterile ones. Gloves donning technique affects the contamination of gown [15]. The results of previous studies can be affected by individuals' skill and performance or environmental conditions and not doing some of them in the operating room (done in vitro). Control of the above was considered in the present study. The presents study has been conducted to compare the effects of three gloves donning techniques (open, closed-gloving techniques and open staff-assisted technique) on the contamination of operating room personnel's sterile gloves and gown.

Material and Method

This research was a field trial study. The objective of it was to compare the effects of three gloves donning techniques on the contamination of operating room personnel's sterile gloves and gown at Al-Zahra Hospital affiliated to Isfahan University of Medical Sciences. The samples were 96 pairs of gloves which were equally and randomly divided into three open, closed-gloving techniques and open staff-assisted. Closed-gloving technique was considered as control group because it is an approved method in the literature. Inclusion criteria were sterile surgical gloves, the scrub staff should have no sensitivity to gloves without powder and glitterbug powder. Exclusion criteria were the existence of holes in the gloves and the time of surgery was less than an hour. After obtaining informed consents, three operating room personnel were selected with the criterion of having work experience of 5 years and having the knowledge of wearing gloves standardly and they were placed in the three open-, closed-gloving and open staff-assisted. They were taught how to glove and also, they were controlled in terms of gloving correctly and standardly.

A pair of Ansell Gammex pf latex gloves without power was used for each test. Glitterbug powder was used as material revealing Ultraviolet (UV) and UVA light with a long wavelength (Glow bar) was used to display powder revealing UV. The sterile fabric gowns routinely provided at hospitals, were used.

Glitterbug powder revealing UV was sterilized by the plasma device. The personnel were taught how to apply powder to their hands. After washing hands standardly, a personnel gets glitterbug powder from a third party who also wear sterile gloves and applies it to his hands (palms and backs of hands and between fingers) from the fingertips to the metacarpal surface and then he wears the gown. After wearing gown, one of open-, closed-gloving and open staff- assisted was selected by random allocation. Each technique was repeated 32 times. In open-gloving technique, the scrub staff wears the gown and then brings out his hands from the cuff and gloves but in the closed-gloving technique, the hands are kept in the gown's cuff and the gloves are worn. In the open staff-assisted, scrub staff opens the package of gloves and helps team members in gloving. An hour after surgery, the personnel's gloves and gown were taken off by a third party who wore disposable gloves (he changed them for each time), and this was similar for all the samples (in all

samples, the gloves was firstly taken off from right hand and then left hand) so that he got the edge of gloves and shoulder of gown and took off them from the personnel's hands carefully and slowly. Immediately researcher used UV lamp in a relatively dark place and put it under gloves and opposite of gown to detect contamination (glitterbug powder) on the gloves and different areas of gown (contaminated areas of gloves and gown become white after shining UV light to them). The areas of contaminated areas of gloves and gown were measured in cm (because the areas of contaminated areas were great) by ruler and recoded in check list. The data was recoded and analyzed by a person who didn't know how the personnel worn the gloves (in a blind way) in (Figure 1).

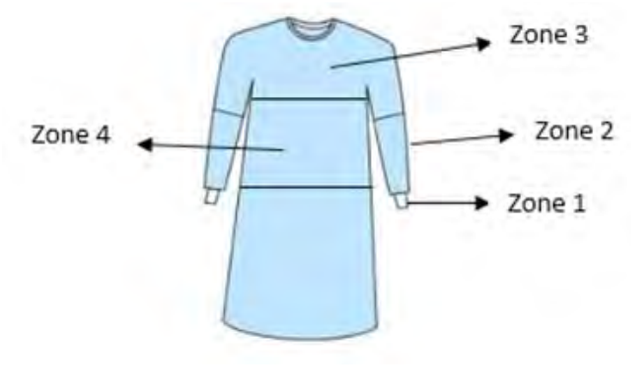


Figure 1: Different zones of gown

In order to determine the content validity of check list, 10 faculty members of operating room and nursing department, Nursing and Midwifery school, Isfahan University of Medical Sciences, were asked to comment on its items and then it was corrected so that its content validity would be approved. In order to estimate reliability of research tools, test-retest method was used so that in 5 cases of applying powder to hands, the number of contaminated areas was counted in the same conditions by several persons. In order to estimate the reliability of the UV lamp, glitterbug powder was applied to a 1*1 (cm^2) (cm^2) area and UVA lamp was shined on it and the area of contaminated zone was measured. After 15 minutes, UVA lamp was shined again and the area of contaminated zone was measured. According to Pearson's coefficient, its reliability was estimated 0.98, confirming high reliability. The data was analyzed using SPSS V.23 and performing analytical and descriptive statistical tests, including One-Way ANOVA, Tukey, Chi-square test, paired t-test and non-parametric Kruskal-Wallis tests.

Results

In the present study (field trial), 96 pairs of gloves used by three elective operating room personnel at the Al-Zahra Hospital in 2016, were used in order to compare the effects of three gloves donning techniques (open-, closed-gloving and open staff- assisted) on the contamination of operating room personnel's gloves and sterile gown. They were divided into three groups (in each group, n=32). Frequency distributions of participants' demographic characteristics were listed in table 1-1. It is noteworthy that all the studied personnel were female. According to **(table 1)**, no significant differences were observed between the groups in demographic characteristics of age, work experience, education and type of employment (p-value> 0.05).

Averagely, in open-gloving group, 2.31±0.138 persons were scrubbed and 2.06±0.118 and 2.16±0.120 persons were scrubbed in closed-gloving and open staff-assisted groups, respectively. No significant difference was observed between the groups in average number of persons scrubbed during surgery (p-value = 0.292 > 0.05). It can be said that averagely, 2 persons were scrubbed during surgery.

Table 1. Frequency distributions of demographic characteristics of operating room personnel of each group who scrubbed during surgery

		Technique			Total	P-value
		Open	Close	Open with Scrub		
Age(Year)	20-30	11	12	7	30	
		36.7%	40.0%	23.3%	100.0%	
	30-40	16	14	13	43	0.243
		37.2%	32.6%	30.2%	100.0%	
	40-50	5	6	12	23	
		21.7%	26.1%	52.2%	100.0%	
Total		32	32	32	96	
		33.3%	33.3%	33.3%	100.0%	
Work Experience (Year)	5-10	15	13	13	41	
		36.6%	31.7%	31.7%	100.0%	
	10-15	5	12	8	25	0.336
		20.0%	48.0%	32.0%	100.0%	
	15-20	12	7	11	30	
		40.0%	23.3%	36.7%	100.0%	
Total		32	32	32	96	
		33.3%	33.3%	33.3%	100.0%	
Education	Associate Degree	15	8	18	41	
		36.6%	19.5%	43.9%	100.0%	
	Bachelor Degree	17	23	14	54	0.085
		31.5%	42.6%	25.9%	100.0%	
	Master Degree	0	1	0	1	
		0.0%	100.0%	0.0%	100.0%	
Total		32	32	32	96	
		33.3%	33.3%	33.3%	100.0%	
		33.3%	33.3%	33.3%	100.0%	

The results showed that there were significant differences between the groups in average total distance of contamination of gloves (p-value < 0.05). According to the results of Post Hoc test (P-value), in open-gloving technique, average total distance of contamination was greater compared to the closed-gloving and open staff-assisted(p-value < 0.05) (open-gloving technique: 157.34±64.15 VS closed-gloving technique: 58.02±34.34 and open staff-assisted: 86.22±45.48). Also, average total distance of contamination in closed-gloving technique was significantly less compared to open staff-assisted (p-value < 0.05) (closed-gloving technique: 58.02±34.34 VS open staff-assisted: 86.22±45.48) (Figure 1).

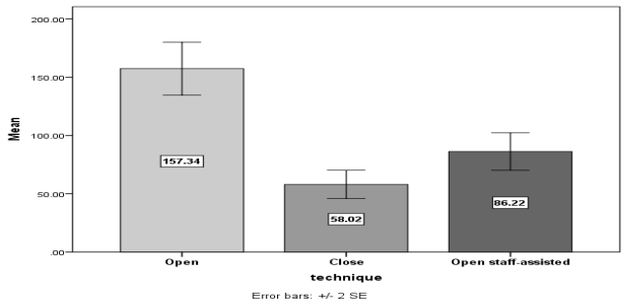


Figure 1. The total average distance of contamination of gloves in the three studied techniques

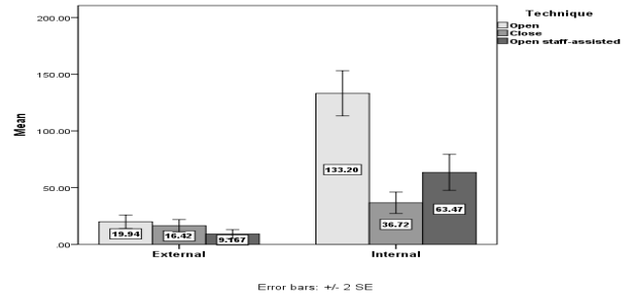


Figure 3. The average distance of contamination of the beginning and end of cuff in terms of internal and external parts of cuff in the three studied techniques

Also, the results showed that there were significant differences between the three groups in contamination between the beginning and end of the cuff (p-value = 0.003 <0.05) so that average contamination in the closed-gloving technique was less than two other techniques (p-value <0.05) (open-gloving technique: 153.14±61.36 VS closed-gloving technique: 53.14±33.57 and open-gloving with assistance of scrub staff technique: 53.14±33.57). Average contamination in open staff-assisted-was significantly less compared to open-gloving technique (p-value=0.024 < 0.05) (open-gloving technique: 80.61±45.77 VS open staff-assisted technique: 153.14±61.36) (Figure 2).There were significant differences between the three groups in average contamination between the internal and external parts of the cuff (p-value <0.05) so that according to the results of Post Hoc test (*P-value), in the internal part of glove cuff, average contamination between the beginning and end of cuff in the open-gloving technique was significantly greater than two other techniques (p-value <0.05) (open-gloving technique: 133.20±56.07 VS closed-gloving technique: 36.72±26.62 and open staff-assisted technique: 70.81±43.09). Also, average contamination in open staff-assisted was significantly greater compared to closed-gloving technique (p-value < 0.05) (closed-gloving technique: 36.72±26.62 VS open staff-assisted technique: 70.81±43.09). About external part of cuff, there was significant difference only between open-gloving and open staff- assisted and it was less in open-gloving technique (p-value < 0.05) (open-gloving technique: 19.94±16.67 VS open staff-assisted technique: 9.80±10.85((Figure 3).

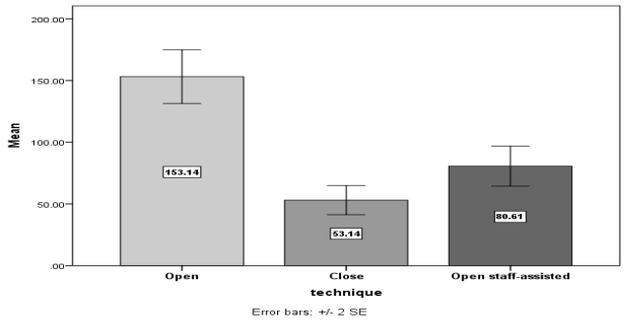


Figure 2. The total average contamination of the beginning and end of cuff in the three studied techniques

It was observed that there were significant differences between the three groups in the contamination rate in zone 1 of the gown (p-value <0.05) so that according to the results of Post Hoc test (P-value), average contamination rate (glitterbug powder) in zone 1 in closed-gloving techniques was significantly less than two other techniques (p-value <0.05) (open-gloving technique: 115.81±60.74 VS closed-gloving technique: 51.98±62.24 and open staff-assisted technique: 99.09±53.9) (Figure 4).

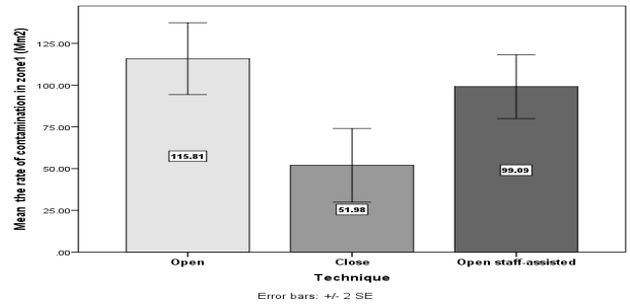


Figure 4. The average of contamination rate in zone 1 in the three studied techniques

It was observed that there were significant differences between the three groups in the contamination rate in zone 2 of the gown (p-value <0.05) so that according to the results of Post Hoc test (P-value), average contamination rate (glitterbug powder) in zone 2 in open staff- assisted was significantly less compared to open-gloving technique (p-value <0.05) (open-gloving technique: 69.28±46.02 VS closed-gloving technique: 54.31±69.23 and open staff-assisted technique: 33.39±21.41) (Figure 5).

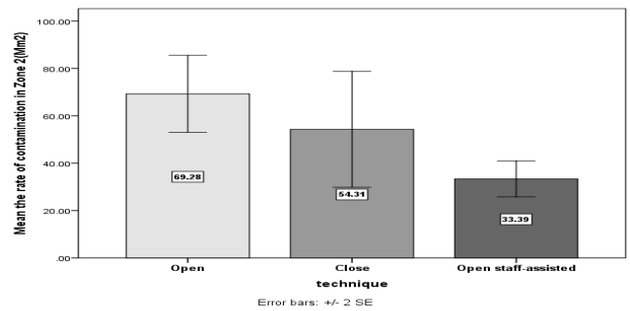


Figure 5. Bar chart of average contamination rate in zone 2 in the three studied techniques

It was observed that there were significant differences between the three groups in the contamination rate in zone 3 of the gown (p-value <0.05) so that according to the results of Post Hoc test (P-value), average contamination rate (glitterbug powder) in zone 3 in open staff- assisted was significantly less compared to two other techniques (p-value <0.05) (open-gloving technique: 28.42±23.93 VS closed-gloving technique: 12.09±16.95 and open staff-assisted technique: 4.55±9.11). Also, in closed-govening techniques, it was less compared to open-gloving technique (p-value <0.05) (open-gloving technique: 28.42±23.93 VS closed-gloving technique: 12.09±16.95) (Figure 6).

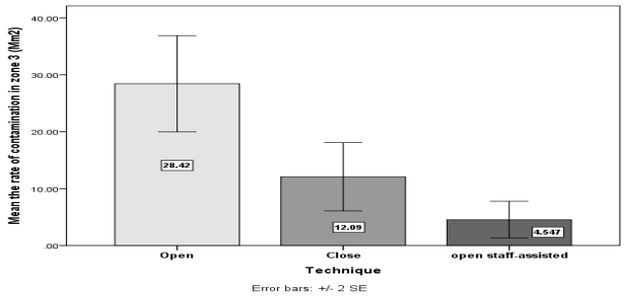


Figure 6. The average of contamination rate in zone 3 in the three studied techniques

It was observed that there were significant differences between the three groups in the contamination rate in zone 4 of the gown (p-value <0.05) so that according to the results of Post Hoc test (*P-value), average contamination rate (glitterbug powder) in zone 3 in open-gloving was significantly greater compared to two other techniques (p-value <0.05) (open-gloving technique: 8.41±11.04 VS closed-gloving technique: 2.75±4.96 and open staff-assisted technique: 2.00±4.83) (Figure 7).

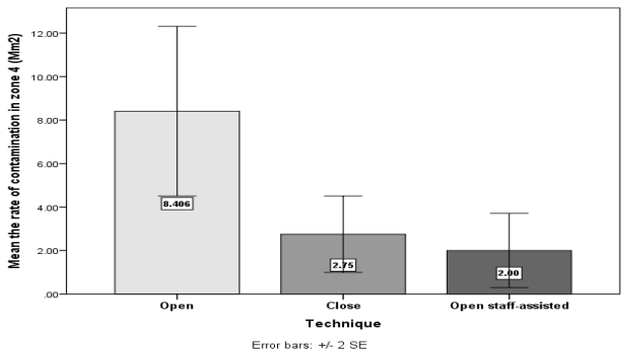


Figure 7. The average of contamination rate in zone 4 in the three studied techniques

It was observed that there were significant differences between the three groups in the total contamination rate in zones 1 to 4 (p-value <0.05) so that according to the results of Post Hoc test (P-value), average total contamination rate (glitterbug powder) in open-gloving technique was significantly greater compared to two other techniques (p-value <0.05) (Table 2).

Table 2. Average total contamination in the four zones in the three studied techniques

	Technique	N	Mean	Std. Error	P-value
Contamination in Total Zone	Open	32	221.92	18.40	0.001*
	Close	32	121.14	23.55	
	Open staff-assisted	32	139.03	12.85	
	Total	96	160.70	11.64	

Discussion

The present study aimed to compare the effects of three gloves donning techniques on the contamination of operating room personnel's sterile gloves and gown. Despite efforts to reduce bacterial contamination, such as the use of ultra-clean air and good ventilation systems, there is a need to seek other solutions. Transmission of microorganism through the hands can be considered as an important factor. Since hospital personnel's hands are considered as the most important way of transmission of pathogens such as methicillin-resistant Staphylococcus aureus and spore bacteria such as Clostridium and the bacteria tend to remain on the hands as much as possible even after scrubbing, a standard gloving technique should be selected to reduce the transmission of contamination to surgical field and surgical wounds [16].

The present study showed that gloving techniques are not similar and the rate of contamination indirectly transmitted from operating room personnel's hand skin to the gloves and gown and consequently surgical wound can be different.

The results of the present study showed that there were significant differences between the three studied groups in terms of average total distance of contamination (p-value < 0.05) so that according to the results of Post Hoc test (*P-value), in open-gloving technique, average total distance of contamination was greater compared to the closed-gloving and open staff-assisted (p-value < 0.05) (open-gloving technique: 157.34±64.15 VS closed-gloving technique: 58.02±34.34 and open staff-assisted technique: 86.22±45.48). The results of a microbiological study performed by Newsom et al. (1988) (open- and closed gloving techniques in 50 cases) showed that in closed-gloving technique, less contamination was transmitted compared to open-gloving technique (2 cases vs. 13 cases). This result is consistent with the results of the present study. It can be due to that in closed-gloving technique, the scrub staff's hands are kept in gown but in open-gloving technique, the fingers touch the glove cuff and during the return of glove cuff to back (Unintentionally), it can contaminate other parts of the glove and the surgical field.

Also, it was observed that, there were significant differences between the three groups in the total contamination rate in zones 1 to 4 (p-value <0.05) so that according to the results of Post Hoc test (P-value), average total contamination rate (glitterbug powder) in open-gloving technique was significantly greater compared to two other techniques (p-value <0.05). The results of a study by Newman et al. showed that the rate of contamination in open-gloving method was greater compared to closed-gloving and open gloving with assistance of scrub

staff techniques (8 parts vs. 4parts) and it is consistent with the result of the present study. But in their study, it was noted that in closed-gloving with assistance of scrub staff technique, there was no contamination and contamination rate in it was less compared to closed-gloving technique (0 part vs. 4 part). This result is inconsistent with the result of the present study. It can be due to the use of closed-gloving with assistance of scrub staff technique instead of open-gloving with assistance of scrub staff technique.

Jones et al. reported that closed-gloving with assistance of scrub staff technique is more preferable than open staff-assisted (12) and in the present study, closed-gloving with assistance of scrub staff technique was not studied and there are a little research on it and it is recommended to study on it.

Existence of a few studies on this topic and limited number of samples can be noted as the limitation of present study, leading to caution in generalizing the results.

Conclusion

Since not gloving correctly and standardly can lead to transmission of infection to the patient, increased cost of treatment, complications and increased mortality, it is recommended that the policy and protocol of wearing gloves with open staff-assisted and closed-gloving technique are emphasized in order to reduce contamination more by operating room personnel. Also, more research is needed in this area.

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Competing interests

The authors declare that they have no competing interests.

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A review: ultrasonography for nasal bone fractures

Nazal kemik kırıklarında ultrasonografi

Ultrasonography and nasal bone fractures

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Özet

Nazal kemik kırıkları acil servis başvurularının önemli bir kısmını oluşturmaktadır. Radyografi ve bilgisayarlı tomografi (BT) genellikle burun muayenesinden sonra istenir. Ultrasonografi (US), noninvaziv, ucuz bir teknik olup yüz, burun, ekstremite kırıklarını göstermede kullanılmıştır. Acil serviste avantajlarından (hızlı, ucuz, radyasyonsuz) US nun faydaları bilinmektedir. Fakat acil serviste nazal kemik kırıklarının tanısı ve yönetiminde kullanımı konusu net olarak tanımlanmamıştır.

Anahtar Kelimeler

Nazal Kemik Kırıkları; Ultrasonografi; Bilgisayarlı Tomografi

Abstract

Nasal bone fractures are one of the most common reasons for emergency service admissions. Radiography and computed tomography (CT) examinations are usually performed following rhinologic examination. Ultrasonography (US) is a non-invasive, inexpensive technique that has been shown to reveal fractures of different areas of the face, such as the nasal bone and other extremity bone fractures. The advantages of US (fast, unexpensive, radiation-free) are well known in the emergency department (ED), but it's use for the diagnosis and management of nasal bone fractures in the ED are not as well-established.

Keywords

Nasal Bone Fractures; Ultrasonography; Computed Tomography

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Introduction

The nose is the most prominent part of the facial structure, and the nasal bone is the most common facial fracture [1-4]. The nasal pyramid consists of two nasal bones and the two frontal processes of the maxillary bone. All parts of the nasal region may be involved in a trauma although the lateral nasal walls, the nasal dorsum and the nasal septum usually require the most attention [5].

A careful clinical examination is the first step in the diagnosis of nasal fractures, but haematoma and oedema of soft tissues can make it difficult to diagnose. Radiography and other imaging procedures in midface traumas are also required for forensic reasons [6]. It may be a problem to determine which side is fractured using conventional radiographs [7, 8]. Computed tomography (CT) has been known as the gold standard in the diagnosis of midfacial fractures including nasal bone fractures [9-11].

CT imaging is expensive, not always readily available and causes high exposure dose. Because of cancer risk it's use is limited. Also, patients who are pregnant, uncooperative or suffering cervical trauma and needing coronal sections are not appropriate for CT examination [12, 13].

These difficulties made it necessary to find easier and safe techniques for nasal fractures. Ultrasonography (US) is a non-invasive, inexpensive technique and many studies have reported that it can detect fascial bone fractures, such as the nasal bone, orbital floor, anterior wall of the frontal sinus, and zygomatic fractures [5, 6, 9, 10, 14-16].

In the literature, the first use of US for nasal fracture was reported in 1996 by Danter et al. They used 20 MHz B-scan US for patients with clinical and/or radiological evidence for fracture and demonstrated that in certain cases ultrasonography is correlated with nasal fracture detection [17]. The increasing prevalence of such injuries emphasizes the need for adequate imaging of nasal fractures depending on the etiology of the fracture [6]. US is a common and easy method that does not use radiation. Use of US for other bone fractures such as the scaphoid and ribs has been shown in various studies [18, 19].

In a small patient population study, Ardeshirpour et al. determined the appearance of nasal fractures on US. They used US to image 12 patients with a clinical or radiologic (CT or x-ray) diagnosis of nasal fracture. All patients presented within two weeks of their injuries. The researchers found that they could easily diagnose nasal bone fractures on lateral-view US. They suggested that lateral US could be used to detect nasal fractures in adults [20, 21].

If US is used in the first evaluation of nasal bone fracture by an experienced operator, radiation exposure can be prevented, but when complicated fractures are suspected, a plain radiography or a CT scan will be required [9].

Hong et al. described the sonographic findings of nasal fracture in children, and they compared US and CT with the patients' clinical findings to find the first step diagnostic value of US for nasal bone fractures. US was found to be beneficial for the first radiologic evaluation but the autors similarly found that it should be supported by CT in complicated cases of nasal bone fractures in children [6].

Nasal Us For Estimating the Time of Occurrence of Nasal Trauma

Clinicians should always be careful in medico-legal issues. A recent nasal bone fracture should be differentiated from an old one, especially in emergency clinics. In one study, US was reported as a reliable diagnostic tool for estimating the time of a nasal bone fracture. Forty-five patients with nasal bone fractures were followed for six months. They underwent US evaluation regularly: in the first 5 days and the 3rd, 6th, 12th and 24th weeks after the trauma. The thickness of the subperiosteal hematoma was measured with US on those dates. Subperiosteal hematoma with a mean thickness of 1.14 mm (0.79-1.31 mm) was highly sensitive (100 %) for the diagnosis of nasal bone fracture during the first few days after the trauma, and disappeared in all patients by the 24th week, with a mean thickness of 0.47 mm [22]. So, the results of this study were important for emergency clinicians to estimate the time of nasal bone fractures.

Intraoperative Nasal Us

US is not just important for the diagnosis of nasal bone fractures, but it has also been used for intraoperatively assessing surgical outcomes [23-25]. The use of US findings before and after a closed reduction was compared to the use of visual inspection and palpation. One study has suggested that visual inspection and palpation are as reliable as US for intraoperatively evaluating the outcomes of surgery for acute nasal fractures [23].

In a patient satisfaction study, the benefits of intraoperative ultrasonic guidance in the management of isolated nasal bone fractures were evaluated. In this study, sixty-eight patients who had isolated fracture nose were treated by either a simple closed reduction or by ultrasound-guided reduction (34 patients each) with a follow up for an average of 4.5 and 5.5 months, respectively. They evaluated the nasal profile and also asked patient groups whether they were satisfied with the appearance of profile of their noses. Patients who had undergone USguided nasal bone reduction had significantly better nasal profile scores than patients who underwent simple closed reduction, however the patient satisfaction scores had no significant difference between the groups. These results indicated treating nasal bone fractures with the assistance of intraoperative US resulted in a significantly better nasal profile appearance than by treating it by simple closed reduction, but the the patient satisfaction was the same in both groups [24].

In a similar study, the nasal profile was considered via CT and photograph one year after USguided surgery. Park et al. classified patients according to their CT score. In almost all patients, postoperative external photographs showed a symmetrical nasal dorsum without external deformity, and postoperative CT showed stabilization of bony fragments and good alignment of the nasal bone. Postoperatively, the CT score was 3 (excellent) in 25 patients, 2 (good) in 5 patients, and 1 (fair) in 2 patients. They suggested that ultrasonography is very useful for evaluating intraoperative repositioning of nasal bone fractures [25].

Kishibe et al. used US intraoperatively to confirm adequate bone restoration. US findings and the CT scan of the nasal bone were almost the same, indicating that ultrasonography may be suitable and sufficient for the diagnosis of nasal fractures and that objective intraoperative evaluations can be performed by only using ultrasonography. US is a useful tool for the diagnosis of nasal fractures and also for the evaluation of medical treatment [26].

Ct/Us/Radiography Sensitivity Specificity

US was compared with CT and plain radiography for nasal fracture diagnosis in various studies [5, 27-34]. Lee et al. compared the diagnostic efficacy of US with radiography and multi-detector CT for the detection of nasal bone fractures. They included 41 patients who had a nasal bone fracture who underwent prospective US examinations. Plain radiographs and CT images were obtained on the day of trauma. In their study the radiologist used a linear array transducer (L17-5 MHz) in 24 patients and hockey-stick probe (L15-7 MHz) in 17 patients. The bony component of the nose was divided into three parts (right and left lateral nasal walls, and midline of nasal bone). Fracture detection by three modalities was subjected to analysis. They compared results with intraoperative findings. Their findings suggested that CT had greater sensitivity and specificity than US or radiography, and better intraoperative findings for the right and left lateral nasal walls. On the other hand, US had higher specificity, positive predictive value (PPV), and negative predictive value (NPV) than CT for midline fractures of the nasal bone. Two different US probe evaluations showed good agreement at all three sites, US findings obtained by the hockey-stick probe showed closer agreement with intraoperative findings for both the lateral nasal wall and midline of nasal bone. These results showed that US may be helpful for evaluating the midline of nasal bone and a smaller probe and a higher frequency US may be required for the nasal bone evaluation [27].

In another study 128 patients with suspected nasal bone fracture were enrolled and the diagnostic values of US and radiography were compared with clinical examinations. Radiography and a 10-MHz US were performed on all patients. Their findings: US sensitivity was 84%, specificity 75%, accuracy 82%, PPV 91%, and NPV 61%. Lateral-view radiography, sensitivity was 50%, specificity 72%, accuracy 55%, PPV 84% and NPV 32%. Waters view radiography, sensitivity was 53%, specificity 65%, accuracy 56%, PPV 82%, and NPV 31%. Lateral-Waters view radiography, sensitivity was 64%, specificity 58%, accuracy 62%, PPV 82% and NPV 34%. They suggested that when compared with radiography, fracture diagnosis by ultrasound was significantly better [28].

According to a study published in 2013, US examination of nasal bones is a more accurate method for diagnosis of fractures than x-ray examination [29]. The diagnostic sensitivity and utility of high-resolution ultrasonography (HRUS) were compared with CT in 87 patients with nasal trauma. Ultrasonograms were obtained with a high frequency linear transducer (10 MHz). In that study, results of the sensitivity and specificity of HRUS, CT, and conventional radiography (CR) compared with clinical exam in the diagnosis of nasal bone fracture were: HRUS 97%, exam 100%; CT 86%, exam 87%; CR 72% and exam 73%. The sensitivity and specificity of HRUS and CR in detecting fracture line in comparison with CT were HRUS 100%, CT 91% and CR 79%, CT 95% [30]. In another study, the sensitivity and specificity of US in assessing nasal bone fracture in comparison with CT was 94.9% and 100%, respectively. The PPV and the NPV of US evaluation of the nasal bone fractures were 100% and 95.3%, respectively [31].

Lee et al. suggested that the accuracy rates for detecting nasal fractures by HRUS, CT, and conventional radiography were 100%, 92.1%, and 78.6%, respectively. Compared with HRUS, CT revealed only 196 of 233 lateral nasal bone fractures; its accuracy was 80%. In high-grade fractures, the accuracy of CT was 87%, but it decreased to 68% in low-grade fractures. Compared with HRUS, CT had lower accuracy, especially in low-grade nasal fractures [32]. To detect fractures of the nasal dorsum, both modalities had high sensitivity (US 98, x-ray 88%) and specificity (95% for both US and x-ray). In lateral nasal wall fractures, specificity was higher for x-ray (US 75%, x-ray 94%). Sensitivity was significantly higher for the US examination (US 98%, x-ray 28%) [33].

In conclusion, US is a reliable method for the diagnosis and management of nasal bone fractures. There are advantages of using US (fast, inexpensive, radiation free) and emergency clinicians easily can use US for diagnosis and in treatment of nasal fractures. Further studies of their use in emergency departments with enrolment of large patient groups are needed.

Competing interests

The authors declare that they have no competing interests.

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Review
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Evaluation expression icaabcd biofilm formation genes in staphylococcus aureus by real-time PCR

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Abstract

Staphylococcus aureus is one of the most significant pathogens that cause several nosocomial and community infections. Adhesion to surfaces and biofilm formation is considered the main step in staphylococcal infection. This study aimed to investigate the expression of ica(intercellular adhesion) genes in clinical isolates of S.aureus. Material and Method: A total of 93 clinical S. aureus isolates were collected from hospitals in Tehran. Quantitative biofilm formation was determined by using Congo red agar (CRA). Out of 93 isolates, only 18 (19.35%) isolates had positive biofilm formation, and they were examined for expression the icaABCD genes by Real-time PCR method. Results: The Congo red agar assay results showed that attachment abilities in 4 (4.3%) strains were strong and in 14 (15.05%) strains were moderate. All isolates were positive for icaABCD genes expression. The average gene expression for 18 strains was as follows for icaA (9.332), icaB (1.485), icaC (17.612) and icaD (3.390), respectively. Discussion: The data obtained suggest that clinical S. aureus isolated from the evaluated patients has a potential for biofilm formation. S. aureus clinical strains have different capacity to produce biofilm. This may be caused by a difference in the expression of biofilm genes and heterogeneity in genetic origins.

Keywords

Staphylococcus aureus; Biofilm; icaABCD Genes Expression

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Aim

The collection of microbial cells that are connected tightly to the surface with a polysaccharide matrix being microbial originally is called Biofilm. Biofilms can consist of one species or a mixture of several species, being formed in different places possessing losses and benefits [1]. Biofilms were explained regarding bacteria in 1978 by Custer ton. The stressed situation causes the bacteria to connect to different surfaces. Generally, the microorganisms live by the side of solid surfaces, in nature. The connection with solid surfaces brings about the biofilm formation [2]. The bacteria's through biofilm forming causes resistance against antimicrobial agents, resistance against the host immune system and maintenance of physical and chemical conditions suitable for growth; so it induces resistance of biofilms in unfavorable conditions. Also, the synergistic and helping relations among bacteria or biofilm influences their resistance against unfavorable conditions [3]. Staphylococcus aureus is an optional anaerobic gram-positive coccus, considered to be the most important species in Staphylococcus genus medically. The so mentioned bacteria causes a wide range of infections, including simple skin infections (like acne, pimples, anthracoid, sties and abscess) and life-threatening diseases (like pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome, and septicemia) [4, 5]. The bacteria contains genes, coding pathogenic factors, some of them are located on chromosome and some are moving as genetic elements. The pathogenic factors being coded, induce bacterial colonization in the host, influx to damaged mucus and skin, spreading through the body and invade from host defense mechanisms. Some of the factors include:

Peptidoglycan, lipoteichoic acid, protein, hemolysin, enterotoxin, clamp factor, and biofilm formation. The above – mentioned bacteria can produce polysaccharide and protein factors connected to the surface, through this production process, the bacteria is effective in biofilm production [6, 7]. In fact, a Staphylococcus biofilm is a group of microorganisms related to a network of internal canals in glycoprotein and extracellular polysaccharide matrix named extracellular polymeric substance. The Extracellular polymeric substance is composed of polysaccharide, protein, phospholipid, teichoic acid, and other hydrate and polymeric materials containing water of 85 to 95 %, making it able to adhere to pathogenic agents on the internal surface of carriers and food industry equipment surface, the process causes different pathogenic microbes to be transferred. Locus ica (intercellular adhesion) is composed of genes ica A, ica B, ica C, ica D, in which PIA is synthesized by synthesis mediated protein. The genes ica A and ica D are the most effective form among locus ica in the formation of biofilm in Staphylococcus Aureus and Epidermis. The gene ica A encodes N-acetyl glucosaminyl transferees, that is the involved enzyme in the synthesis of N- acetylglucosamine PCR oligo [5, 8]. It is reported that ica D has a vital role in expressing the maximum N- acetyl glucosaminyl transferees and it makes the phenotypic expression of capsular polysaccharide possible [5,9]. The study aimed to examine the expression of biofilm formation genes in clinical isolates of Staphylococcus Aureus isolated from clinical samples of Shariati Hospital in Tehran using the method Real-time PCR.

Material and Method

Sample collection and evaluation of biofilm formation by phenotypic methods:

In a cross-sectional study, 93 isolates of Staphylococcus Aureus were collected separated from patients referring to Hospital in (year). All the isolated had been proved using biochemical tests including catalase, coagulase, oxidase, fermenting the sugar mannitol, DNase, and sensitivity to novobiocin. The number of 18 isolates from whole were able to produce biofilm. The phenotypic formation of biofilm was studied in Staphylococcus Aureus using the medium of CRA (Merck, Germany) containing 36 gr sucrose (sigma, USA) to evaluate its formation. The isolates have been incubated at 37°C for 24 hours and room temperature for a night after culturing. The black colonies in isolates were identified as biofilm forming strains, Red almost black colonies as weak strains of biofilm formation and the bright red colonies as strains unable to produce biofilm [10].

Draining expression of ica ABCD by Real-time PCR:

Real-time PCR was used to quantitatively analysis of ica ABCD and 16 sr RNA (as an internal controlling gene) individually, by the use of ferment as a kit and the presented primers in table 1. For this purpose, RNA was extracted using micro kit RNeasy (Ki agene). Reverse transcription reaction was done for cDNA synthesis using Hexamer primers produced by Ki agene company. According to protocol, Master mix including synthesized cDNA and primers (PCR mixture: 0.3 ⊠M each primer, 0.2 ⊠M each d NTP, 1.5 ⊠M Mgcl2, 1x PCR buffer, 1.5 Utaq polymerase) were mixed in an appropriate volume, and the reaction was done by Bio-Rad Real-time PCR device. The reaction volume was 25 ⊠L and included CDNA, sweep primer, master mix, and double distilled sterile water. Temperature cycling included initial denaturing in 95°C for 5 minutes, followed by 40 cycles in 95°C for 20 Seconds, 60°C for 20 seconds and 72°C for 20 seconds, and a final cycle of 72°C for 5 minutes. The expression of ica ABCD was compared with expression of 16sr RNA as housekeeping gene. The reaction was done 3 times for each sample, and the average resulted was considered to be the expression quantity of the sample. The relative reference formula of expression (was used to determine the target gene expression. is obtained through subtraction of of the clinical sample from of the standard sample of Staphylococcus Aureus ATCC 25923.

Table 1. Primer sequences used for icaABCD genes for Real-Time-PCR (8)

primer sequence	Gene	Gene size
5-GAGGTAAAGCCAACGCACTC-3 5-CCTGTAACCGCACCAAGTTT-3	icaA	188
5-ATACCGGCGACTGGGTTTAT-3 5-TTGCAAATCGTGGGTATGTGT-3	icaB	190
5-CTTGGGTATTTGCACGCATT-3 5-GCAATATCATGCCGACACCT-3	icaC	192
5-ACCCAACGCTAAAATCATCG-3 5-GCGAAAATGCCCATAGTTTC-3	icaD	198

Results

Biofilm formation using the medium CRA showed that 18 isolates (19.3570) were able to form biofilm in which the black colonies (strong biofilm) were numbered as 4 strains (4.3 %) (Figure 1) and the black and Red ones (moderate biofilm) as 14 strains (15.05) (Figure 2). 16sr RNA gene showed positive results in all strains as the internal controlling gene and housekeeping one, suggesting accuracy in PCR reaction individually. In examining the presence or absence of ica ABCD in 18 strains under the study, in this essay, it was shown that all the strains possessed it. Also, the results from Real-time PCR using cDNA suggested that all the clinical strains expressed ica ABCD (fig-

ure 3). The results from analysis of ica ABCD expression using qRT- PCR for standard strains and 18 clinical isolates is shown in table 2. The curve of melting point for ica ABCD is demonstrated in figure 3. The average of gene expression for 18 isolates of ica A was obtained as (9.332), and for ica B as (1.485), for ica C as (17.612) and for ica D as (3.390). The graph 1 shows expression amount of the 4 genes in 18 isolates of staphylococcus aureus.



Figure 1. Biofilm formation on Congo red agar medium (strongly)

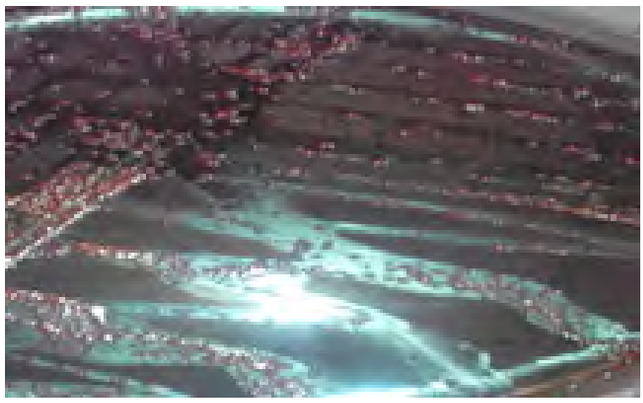


Figure 2. Biofilm formation on Congo red agar medium (on average)

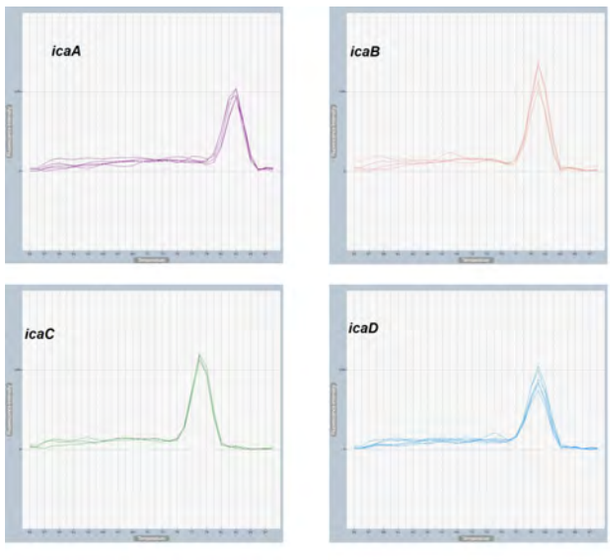


Figure 3. The melting curve for genes icaABCD
Chart 1. IcaABCD gene expression in 18 clinical S. aureus isolates

Table 2. IcaABCD analysis of gene expression in biofilm-producing S. aureus 18 strains

Name samples	icaA	icaB	icaC	icaD
N	1	1	1	1
U1	6597/0	0196/0	521/0	806/0
U2	556/10	5368/1	1/77	735/5
U3	8898/0	1445/0	099/0	339/0
u4	832/13	2116/0	979/0	515/1
W1	556/10	5800/1	0055/0	747/0
W2	765/18	0178/0	223/16	550/0
W3	81712/12	5315/0	285/0	0656/0
W4	426417/5	856/4	78/40	273/30
W5	784/22	1698/4	62/85	563/4
W6	010/4	004/1	051/2	005/1
T1	502/5	705/1	111/0	8969/9
T2	221/14	829/0	182/3	705/1
T3	282/8	7526/0	784/22	5987/0
W7	784/13	169/2	627/58	563/2
W8	010/4	0428/1	0518/2	005/1
T4	502/3	705/2	012 /1	989/1
Abse	382/10	515/0	404/2	569/3

Discussion

Biofilm matrix includes exopolysaccharides, protein, lipid, and nucleic acids. The matrix has known structural role in defense and protection, and causes new genetic features and provides food and combined metabolic activity. The most important microorganisms that are effective in polymicrobial biofilm formation contain Staphylococcus aureus, Pseudomonas aeruginosa, Staphylococcus epidermidis, some members of Enterobacteriaceae family, and the yeast Candida albicans. The first step in infectivity of S. aureus is its adhesion to surfaces such as medical devices, host tissues and so on; that is attributed to a combination of extracellular factors like the ability to connect or to form biofilm [11]. This step is mediated by cell–adhesive polysaccharides or PIA in which protein in intracellular adhesion agents ica A, ica B, ica C and ica D are involved in its production. The collection is set on an operon [12, 8]. This polysaccharide is synthesized following the expression of related enzymes by ica A. Ica participation with locus increases synthesis in polysaccharide and induces capsule phenotype. Role of ica B is to De–acetyle polysaccharide before adhesion to the cell membrane and ica C genes encode a membrane protein helping in elongation and transudation of polysaccharide from the coll. The expression and operon ica ABCD increase by regulatory systems like sar A and sigma B. On the other hand, ica R as a strong negative controller can decrease expression of genes in the operon through adhesion to promoter area [13]. Therefore, the amount of ica ABCD genes is obvious according to their direct effect on biofilm formation and pathogenicity of Staphylococcus aureus mac than before, to achieve a solution to combat this phenomenon. The paper is aimed to study the expression of operon ica ABCD in Staphylococcus aureus strains that form the biofilm. The previous studies suggested an important relation between biofilm formation and presence of ica ADBC among S. aureus clinical isolates [14 -16]. Although less attention was paid to the expression of these genes and fewer studies reported the ability of S. aureus clinical isolates in the expression of ica [3, 8]. Park et al. observed no difference in studying the presence

of operon ica and the relation with biofilm formation on those S. aureus ones, isolated from clinical samples and saprophytic strains; all possessing this gene [17]. However, none of the strains produced biofilm, and it seems similar to the present study in this regard. Atshan et al. suggested in a study on S. aureus in 2013 that expression of operon induces production of PIA and leads intracellular adhesion, some S. aureus strains were also observed not producing biofilm, but possessing ica [8]. It is found out in this paper that biofilm formation occurs just when ica D and ica A are expressed simultaneously. It was observed that ica C average along with ica A expression were more influential in forming the biofilm in this respect, it was inconsistent with the results of the study of Atshan [8]. This difference and inconsistency of expression under study may lie on other factors including bacteria's physiological conditions and on the difference in bacteria's genetic origin. Identifying possible sources and ways of infection may be effective in prevention from the initial biofilm formation, due to the significance of S. aureus in medical departments and its ability in creating multiple infections.

Conclusion

Clinical isolates of Staphylococcus aureus were able to form biofilms, and the expression of all four ica genes in these isolates were high and therefore, and a significant relation was observed between biofilm formation and presence of ica ADBC.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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