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The effect of preoperative digitalis and atenolol combination on postoperative atrial fibrillation incidence

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Abstract

Purpose: The most frequent arrhythmia after coronary artery bypass surgery is atrial fibrillation (AF). The prevention and treatment of this type of arrhythmia is subobtimal. Digitalis, β-blockers, diltiazem and amiodarone are the preferred drugs for the treatment. This study was designed to compare the effects of preoperatively started digitalis and atenolol in combination and separately, on the incidence of AF that occurs within 7 days following the operation. **Materials and method**: One-hundred and sixty patients who had similar demographic properties were randomly grouped as group I, that preoperatively received combined drug therapy ($n = 40$), group II preoperatively used digitalis ($n = 40$), group III atenolol ($n = 40$), and group IV was the control group ($n = 40$). **Results**: Postoperative AF incidence was 25, 15,4, and 17,9% in groups IV, III, and II, respectively, whereas it was 5% in group I which was lower than all other groups, but the difference was only significant between groups I and IV ($P = 0.012$). **Conclusion**: The combined use of atenolol and digitalis preoperatively was considered as an efficient treatment for lowering the incidence of AF following coronary artery bypass surgery. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Coronary artery bypass grafting; Atrial fibrillation; β-Blockers; Digitalis

1. Introduction

Atrial fibrillation (AF) is one of the frequent complications of coronary artery bypass surgery (CABG). In various studies, the incidence of postoperative AF has been shown as 15–40% [1,2]. The possibility of AF increases in advanced age group. Higher ratios were noted in the studies performed by holter monitoring [3].

Age, sex, hypertension, recent myocardial infarction (MI), β-blocker withdrawal, cardiopulmonary bypass, insufficient myocardial preservation, over manipulation of the right atrium, hematoma, electrolyte imbalance and respiratory problems are the main risk factors that increase the AF incidence after coronary bypass grafting. All these factors increase the dispersion of atrial refractoriness, which is the most important cause of reentry, and is believed to be the main mechanism of postoperative AF.

AF is most frequently seen in cases when β-blockers are withdrawn preoperatively. This is known as 'β-blocker withdrawal syndrome', which is related to increased release of catecholamines postoperatively [4].

Most of the postoperative AF cases are temporary, and they may return to normal sinus rhythm spontaneously, in which the morbidity is lower. However, AF should be properly treated because high ventricular response can cause decrease in cardiac output, hypotension, congestive heart failure, and thrombo-embolism due to loss of atrial contractions. Beside this, if evaluated cumulatively, it is a major factor that increases the hospital charges [1–6].

Although electrical cardioversion is the most effective method in the treatment of postoperative AF, the medical cardioversion methods are performed primarily because of their lower risks and easier performance. Currently, β-blockers, digitalis, diltiazem and amiodarone are the most commonly used drugs for AF following CABG [1,7].

There are many studies that reported the results of β-blockers, diltiazem, amiodarone and digoxin usage in AF [2,4,7–12]. But there are very few studies which compare the effectiveness of β-blockers and digoxin usage in combination [13].

The aim of this study is to compare the effectiveness of preoperative atenolol and digitalis given alone or in combination for the prophylaxis of postoperative AF.

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Table 1
General data

	Group I	Group II	Group III	Group IV
Male/female	31/9	34/6	32/8	30/10
Age	58.1 ± 9.4	56.7 ± 7.8	57.1 ± 7.3	55.3 ± 8.1
Hypertension	9	11	12	9
Recent MI	3	4	4	5
Mean EF (%)	54 ± 4.8	49 ± 5.3	52 ± 6.1	50 ± 5.7
Mean cross clamp time (min)	59.4 ± 13.4	55.1 ± 14.7	57.7 ± 14.0	60.2 ± 12.7
Mean number of anastomoses	2.4 ± 1.1	2.3 ± 0.9	2.7 ± 1.0	2.8 ± 1.2
Mean cardiopulmonary bypass (CPB) time (min)	88.8 ± 14.3	84.9 ± 13.5	91.1 ± 12.9	87.6 ± 14.1
Mean operation time (min)	183 ± 38	177 ± 32	189 ± 40	180 ± 35
Time of extubation (h)	4.3 ± 1.5	4.5 ± 1.4	4.1 ± 1.3	4.4 ± 1.4
Duration of intensive care unit care (h)	31.3 ± 4.4	29.6 ± 4.1	32.9 ± 3.9	31.7 ± 4.2

2. Materials and methods

One hundred and sixty patients, who had undergone elective CABG operation in the Department of Cardiovascular Surgery, Ankara University Medical School, during the period between March and December, 1999, were included in this study. Patients who underwent re-operation, concomitant valve surgery, ventricular aneurysm resection or other major cardiac procedures were excluded from the study. Also, patients who had second to third degree atrioventricular (AV) block, bradicardy, asthma necessitating bronchodilator therapy and chronic obstructive pulmonary disease (COPD), history of preoperative AF and AF episodes, diabetes mellitus, renal failure, left ventricular aneurysm, left ventricular ejection fraction below 30% or who needed inotropic support preoperatively were excluded. Informed consent was taken from all participating patients, and was approved by the Ethics Committee of Ankara University Faculty of Medicine, Turkey.

All the patients were in normal sinus rhythm and none of them had cardiac failure preoperatively. In the study group, the youngest patient was 36-year-old male and the oldest one was 78-year-old female and the average age was 56.8 ± 7.3 years. One hundred and twenty-five patients were males and 35 were females. Male/female ratio was 3.57/1.

Four study groups (40 patients in each group) were formed by randomizing the patients.

In group I, atenolol and digoxin combination were given to patients 3 days before the operation. In order to reach the optimal blood levels, digoxin was started 1 mg orally for 2 days and maintained with 0.25 mg orally before and on the following days after the operation. Atenolol 50 mg single dose per day orally was started 3 days before the operation and maintained with the same dose following the operation.

In group II, digoxin was given to patients with the same doses as in group I. In group III, single dose of 50 mg oral atenolol was started 3 days before the operation. Group IV was the control group and received placebo. The demographic data of the four groups were similar and are summarized in Table 1.

Anesthesia induction was done with fentanyl, midozolam, etomidate and vecuronium in all patients. After median sternotomy and systemic heparinization, arterial canullation to the ascending aorta and venous canullation, with a two-stage canulla, to the right atrium was done and all the operations were performed by using moderate hypothermic cardiopulmonary bypass with membrane oxygenators. Multidose antegrade cold blood cardioplegia and topical hypothermia were used for myocardial preservation. All distal coronary anastomoses were performed during the single aortic cross-clamp period. Proximal anastomoses were done with partial aortic occlusion. Internal mammarian artery (IMA) was used as in-situ arterial graft in 155 patients, and as a free graft in three patients. IMA could not be used in two patients because of arterial dissection.

Patients were ventilated with volume-controlled mechanical ventilation for about 4–12 h postoperatively and were extubated afterward, none of them needed re-entubation.

For all the patients, ECG, blood pressure, pulmonary arterial pressure, urine output and mediastinal drainage were monitored for the first two days following the operation in the intensive care unit. They were monitored continuously by telemetric ECG while they were in the ward and 12 leads ECG was recorded daily and whenever arrhythmias occurred.

The results were compared for all the groups simutaneously.

2.1. Statistical analysis

Chi-square and Fisher's exact test were used to analyze the AF incidences between groups. Heart rate analysis was done with one-way analysisof variance (ANOVA). And Tuckey test was used to determine which group(s) differ(s) from other(s).

All the data were shown as ±standard deviation. $P < 0.05$ was found to be statistically significant.

3. Results

There were two deaths in four groups (1.25%). The mean cross-clamp times were 59.4 ± 13.4, 55.1 ± 14.7,

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57.7 ± 14.0 and 60.2 ± 12.7 in groups I, II, III, and IV, respectively. There were no significant differences in operative and postoperative data of the patients in four groups (Table 1).

One of the deaths was in group II because of early postoperative myocardial infarction, whereas the second one in group III was because of stroke. These two patients were excluded from the study.

Postoperative AF was seen in seven patients in group II (17.9%), six patients in group III (15.4%), while no statistically significant difference was found between groups II and III ($P > 0.05$). In group I, only two patients had AF (5%) which was lower than all other groups, but the difference between groups I and II/III was not significant (P value for the difference between groups I and II was 0.087, whereas it was 0.154 between groups I and III). However, the AF incidence was significantly lower than control group ($P = 0.012$). In the control group, AF was seen in ten patients (25%). AF incidence was increased in placebo group compared with other three groups who were receiving one of the two drugs or both, but the difference was not significant (P value for the difference between groups IV and I + II + III was 0.066).

In group II (digoxin group), AF was observed in three patients on the day of operation, and in one patient on the first postoperative day. Two patients on the second and one on the fourth postoperative day were recorded as having AF. In this group, mean heart rate for the patients with AF was 114 ± 15 beat/min.

In group III (atenolol group), AF was observed in two patients on the first, in three patients on the second, and in one patient on the fourth postoperative days. The mean heart rate of the patients who had AF was 103 ± 8 beat/min and this was not significantly different from group II.

In group I (combination group), AF was observed in two patients on the first and second days and the mean heart rate was measured as 85 ± 6 beat/min and this was significantly low compared to the former two groups ($P < 0.05$).

In group IV (control group) ten patients had AF. Of those, three had on the day of operation, three on the 1st, two on the 3rd and also 1 on the 4th, and 6th postoperative days, respectively. In this group the mean heart rate who had AF was 126 ± 15 beat/min and this rate was significantly high comparing to the other groups ($P < 0.05$).

In group I, two patients returned to sinus rhythm spontaneously without any additional medication within the 24 h.

In group II, two of the seven patients returned to normal sinus rhythm (NSR) spontaneously in a short time. The other four patients returned to NSR after amiodarone administration within 48 h, but the last one who did not respond, needed electrical cardioversion, which was successful.

In group III, one patient spontaneously, and the others with amiodarone administration returned to sinus rhythm.

In group IV, two spontaneously and six with amiodarone infusion returned to NSR, while two needed cardioversion but one did not respond and discharged with AF.

All these data are summarized in Table 2.

Amiodarone was started as 150 mg loading dose, maintained as 60 mg/h for the first 6 h and 30 mg/h for the last 18 h and continued as 200 mg/day orally.

In the study groups, when the mean heart rates of the patients who were in sinus rhythm were compared, it was lowest in groups I and III.

No serious side effects were observed due to medication in any of the study groups. All the patients were discharged with the drug(s) of their group. In 12 patients to whom atenolol was administered, bradycardia was observed. The dosage of atenolol was halved in eight of them, but in none of the patients the drug was discontinued. The hypotension was also noticed in nine of the 12 patients but it also recovered.

In seven of the digoxin-using patients, the drug dosage was halved due to increased serum digoxin levels (the mean digoxin level was 2.06 ± 1.4 ng/dL). In these patients, although the serum digoxin levels were high, none of the intoxication symptoms were observed. All the patients, except one, were discharged in sinus rhythm between seventh and eleventh postoperative days without complications. Group I patients were medicated with ASA, atenolol and digoxin. The other patients who experienced AF were medicated with oral amiadarone for 15 days after the discharge. All the patients were in sinus rhythm and were asymptomatic 45 days after discharge.

4. Discussion

The incidence of acute AF has been observed between 15 and 40% [1,2], and usually appears within 4 days after the

Table 2
The AF incidences between the four groups and the recovery in these groups after the treatment

Groups ($n = 40$ in each group)	Treatment	No. of patients who developed AF	Spontaneous recovery	Medical recovery	Recovery after cardioversion	Discharged in AF	Heart rate
I	Atenolol (50 mg/day) and digoxin (0.25 mg/day)	2 (5%)	2	–	–	–	85 ± 6
II	Digoxin (0.25 mg/day)	7 (17.9%)	2	4	1	–	114 ± 15
III	Atenolol (50 mg/day)	6 (15.4%)	1	5	–	–	103 ± 8
IV	Placebo	10 (25%)	2	6	1	1	126 ± 15

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operation. This type of arrhythmia rarely causes mortality, but can increase postoperative morbidity. Particularly, in the ischemic-natured heart patients, the alterations in the cardiac output and the increase in the working of heart due to high ventricular rates and lack of atrial contractions are the unfavorable effects [1,6].

Aranki et al. [5] have shown in their study that although AF is not the 'most expensive' complication following CABG, it is the most frequent complication and its cumulative cost will be over all other complications.

Multi-factorial precipitating mechanisms are responsible for these postoperative AF cases. Structural changes due to factors like age and hypertension, the effects of cardiopulmonary bypass and cardioplegia, postoperative electrolyte imbalance, hypoxia, hypovolemia, and sepsis are important factors [1,5,8,9,14,]. In patients whose atria have inhomogeneous refractory period locations, it was shown that intraoperative atrial ischemic injury would increase the incidence of AF [15].

Digoxin, diltiazem, amiodarone and β-blockers are the most commonly used drugs for AF [10]. Although electrical cardioversion is more effective, it is used less commonly because it is more risky especially in the earlier periods after cardiopulmonary bypass due to the increased susceptibility of myocardium to electrical stimuli. Also, it is usually painful to perform cardioversion on awake patients.

Digitalis was first used in the postoperative arrhythmia prophylaxis following pulmonary resection. Parker et al. have shown in their studies that the use of preoperative and postoperative digitalis lowered the incidence of postoperative supraventricular arrhythmias following CABG [16].

Digoxin has no antifibrillatory effect. It helps to keep the heart rate under control and improve the hemodynamics in patients with depressive myocardium. Selzer et al. contradict the routine use of digitalis in the patients undergoing CABG because of the increased myocardial susceptibility and risk of toxicity [17]. In various studies, it is shown that preoperative use of digoxin significantly decreases the AF incidence following CABG. However, Kowey et al. have observed that digoxin increases the atrial arrhythmias from 11 to 28%. In their study, it was also shown that digitalis when used alone was ineffective in postoperative arrhythmias [7].

β-Blockers were shown to be effective in majority of the patients who were under the dominant effects of catecholamines preoperatively. It was shown that the combination of the β-blockers and digitalis has the optimal effect and they were in synergism unless the vagomimetic effects of digitalis were masked by the catecholamines [15].

β-Blockers are used for lowering the supraventricular arrhythmias and for their beneficial effects in coronary artery patients [16]. The preoperative withdrawal of these drugs increases the risk of myocardial ischemia and tachyarrythmias. Many centers continue to use these drugs even preoperatively. Stephanson et al. have shown that while the arrhythmia incidence is 10% in the patients who use propranolol postoperatively, it is 23% in non-users [18].

Oka et al. have recorded a high incidence of supraventricular tachyarrhythmia (sinus tachycardia and paroxysmal atrial tachyarrhythmias) in 94% of patients in whom propronolol treatment was discontinued 48 h before the operation, but in the cases where the drug is continued both until and after the operation, they found the result to be 26% [19]. These studies concluded that the withdrawal of β-blockers increases the susceptibility to adrenergic stimuli and increased arrhythmia incidences.

Roffman and Fieldman have shown that postoperative use of digoxin and propranolol lowers the AF incidence from 29 to 2% [11].

Due to its relatively lower affinity to β2 receptors, atenolol can be used in more patients than the other β-blockers. It is less risky for patients who have respiratory problems, diabetes mellitus, or peripherial arterial disease compared to the non-selective β-blockers [4]. The reasons why we chose atenolol as a β-blocker are: longer plasma half lifetime, the advantage of single dose use, and its lower affinity to β2 receptors. So it can be used safely in diabetic and peripheral arterial disease patients.

Liprandi et al. [12] have shown that atenolol started 24 h after the operation lowers the supraventricular arrhythmia incidence from 30 to 10%. Lamb et al. [4] have shown that atenolol started 72 h before the operation lowers the supraventricular arrhythmia incidence, which is 37% in the control group, to 3%.

In our study, it was shown that the combination of atenolol and digoxin administered preoperatively lowers the postoperative AF incidence. Although the difference is significant between combination-treatment group and the control group, it is not significant between combination-treatment group and other two groups.

In light of this and similar studies, we concluded that preoperative digoxin and atenolol combination can be safely used in our patient population. Most of them are of advanced age and hypertensive and are therefore present with increased risk for AF. This combination could be used to decrease their hospital stay and lower hospital costs because AF was shown as an independent factor that prolonged hospital stay following CABG [20].

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