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ORIGINAL ARTICLE

A controlled trial of erythromycin and UDCA in premature infants during parenteral nutrition in minimizing feeding intolerance and liver function abnormalities

T Gokmen, SS Oguz, S Bozdag, O Erdeve, N Uras and U Dilmen

Neonatal Intensive Care Unit, Zekai Tahir Burak Maternity and Teaching Hospital, Ankara, Turkey

Objective: To compare the effectiveness of oral erythromycin versus ursodeoxycholic acid (UDCA) treatment in preventing feeding intolerance and liver function abnormalities.

Study Design: A prospective, double blind, randomized, controlled trial in which three groups of preterm infants (birth weight <1500 g) were randomized to erythromycin (12.5 mg kg^{-1} per day), UDCA (5 mg kg^{-1} every 6 h) or placebo treatment. During the period 352 infants were admitted to our unit of which 75 infants whose parents accepted participation were enrolled in the study. Full enteral feeding or intestinal failure-associated liver disease was considered as the primary outcome measures.

Results: Time to achieve full feeding after beginning the treatment was significantly shorter in the erythromycin group ($P = 0.014$). γ-Glutamyl transpeptidase levels in the placebo group were significantly higher than in the intervention groups ($P = 0.001$). GTT level was slightly lower in UDCA groups than erythromycin.

Conclusion: Oral erythromycin was most effective in facilitating enteral feeding and UDCA was most effective in preventing cholestasis in very low birth weight infants. Prophylactic usage of UDCA could be considered in infants with prolonged parenteral nutrition.
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Keywords: preterm; feeding intolerance; erythromycin; ursodeoxycholic acid; cholestasis

Introduction

Feeding intolerance is a common problem in preterm, very low birth weight (VLBW) infants.[1] It usually manifests as residual food in the stomach, intermittent regurgitation or vomiting. In some cases, abdominal distension, bile-stained aspirates or lack of stooling can be seen. The clinical entity results from ineffective, infrequent, uncoordinated bowel activity secondary to immaturity of the gastrointestinal tract.[1,2] Preterm infants lack migrating motor complexes (MMCs). Physiological studies have shown a lack of the propagative phase III of the MMC in the duodenum of preterm infants <32 weeks gestational age.[3] As motor patterns mature in the preterm neonate, feeding tolerance improves.

In adults, the initiation and propagation of MMC phase III is partially under hormonal modulation by motilin.[4,5] The macrolide antibiotic erythromycin increases overall motor activity in the stomach and intestine by competitive binding to the motilin receptor.[6] Because of the immaturity of the gastrointestinal tract in VLBW infants, slow advancement of enteral feeding is seen in intensive care units. This often leads to prolonged use of parenteral nutrition (PN), which predisposes the infants to nosocomial infections, intestinal failure-associated liver disease (IFALD) and prolonged hospitalization.[1,2]

IFALD usually resolves once intravenous alimentation is discontinued. In some patients, hepatic recovery may take several months, and a few may develop permanent liver injury. Prokinetic agents such as erythromycin enhance gastrointestinal motility and may be beneficial in VLBW infants by reducing the duration of PN. Ursodeoxycholic acid (UDCA) is a hydrophilic dihydroxylated bile acid that decreases secretion of cholesterol from the liver and its intestinal absorption. UDCA has been used widely in IFALD.[7–9] In VLBW infants, the most susceptible group, the clinical data for UDCA use are limited.[10,11]

Our aim in this study was to compare the effect of UDCA, erythromycin or placebo in minimizing IFALD and feeding intolerance in VLBW infants.

Methods

The study was conducted in the Neonatal Intensive Care Unit (NICU) of Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey between August 2008 and September 2009. Patients were eligible for this prospective study if they fulfilled the following inclusion criteria: birth weight <1500 g and <32 weeks gestation, who received <75 ml kg^{-1} per day of milk feeds by the fourteenth

Correspondence: Dr T Gokmen, Zekai Tahir Burak Maternity and Teaching Hospital, Talat Pasa Bulvari, Ankara 06330, Turkey.
E-mail: drtuling@yahoo.com.tr
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day of life and who received total parenteral nutrition at least 12 days. Infants with other causes of cholestasis or who had severe congenital anomalies, and patients who had received abdominal surgery or who had suspected or proven necrotizing enterocolitis during or before therapy were excluded. Informed consent was obtained from the parents for their child's participation in this research trial. The study was approved by the Clinical Research Ethics Committee of the Zekai Burak Hospital.

Using computer-generated randomization, the drugs were assigned to the infants to form three groups in a 1:1:1 ratio. Oral erythromycin, UDCA and placebo were commenced on day 14 of life. Per previous reports the erythromycin dose was 12.5 mg kg^{-1}.[12–14] UDCA was given at a dose of 5 mg kg^{-1} every 6 h. Placebo solution was given as an equivalent volume of normal saline.

Erythromycin is a white liquid suspension, therefore, all the medications were mixed thoroughly into milk feeds to mask their appearance. The drug was identified only by a code number to ensure effective blinding. Medicine or placebo addition to the milk was performed by a dietician, so that, the neonatal nurses were blind to the particular intervention in each infant. All infants received 14 days treatment.

Feeding regimen and outcomes

In our institution, all premature infants were started on PN within the first 48 h using solutions that contained 6% amino-acid solution, 20% lipid solution, trace elements, and minerals and vitamins. Dextrose infusion was started after birth with an optimal glucose infusion rate of 6 to 8 mg kg^{-1} min^{-1}, and adjusted according to blood sugar level and clinical conditions. Amino acids were used at 3 g kg^{-1} per day, and lipids were used according to bilirubin level at up to 3 g kg^{-1} per day.

Enteral feeding with breast milk or special care formula for premature infants was begun through a gastric feeding tube. Breast milk was fortified with human milk fortifier, (Eoprotin, Milupa, Fulda, Germany) when the feeding volume reached 90 ml kg^{-1} per day. PN was discontinued when enteral feeding volume reached 120 ml kg^{-1} per day.

Full enteral feeding (FEF) was considered as the primary outcome measure. Secondary outcomes were liver function abnormality, number of episodes of gastric residuals, duration of total parenteral nutrition and days of hospitalization. FEF was defined as the time when enteral feeding reached 150 ml kg^{-1} per day. Feeding intolerance was defined either as increased residuals if on gastric aspiration >50% of previous feed or >30% of two previous feeds was noted, or presence of abdominal distension or bloody stools in the absence of culture-positive sepsis or radiographic evidence of necrotizing enterocolitis. If oral feeding had to be discontinued after starting the study, all oral medications were also discontinued. The study solutions were restarted only after the enteral nutrition was restarted. Administration of other prokinetic agents was not allowed during the study period.

Electrocardiography was performed before drug treatment began and after the first and second week of treatment to assess the QTc intervals. Abdominal ultrasonography was performed before and after drug treatment to evaluate infantile hypertrophic pyloric stenosis.

Statistical analysis

Demographic variables are expressed as frequency counts and percentages. χ^2 tests were used to compare ratios. The Kruskal–Wallis test and analysis of variance were used to compare the groups, Conover and Bonferonni multiple comparisons were used after these tests, respectively. Repeated-measures analysis of variance used to evaluate difference between before and after measurement of groups and because of the differences in gestational age among the three groups, this variable used as a covariate in the analysis. Also, we used analysis of covariance for testing the difference between groups according to FEF, again gestational age used as covariate. $P<0.05$ was considered to be statistically significant. Statistical analyses were performed with SPSS 16.0 program for Windows (SPSS, Chicago, IL, USA).

Results

During the study period, 352 VLBW preterm infants of gestational age <32 weeks were admitted to our NICU. Enteral feedings began on the first or second day of life according to condition of the infant, and increased the amount 10 to 20 ml kg^{-1} per day. In all, 81 VLBW infants who did not succeed reaching half of the required enteral feeding by the fourteenth day of life qualified for the trial. Of these, 75 patients were enrolled in this study following informed consent of the parents. Subsequently, four infants were excluded during the study. In the placebo group, one infant died at the beginning of the study and one had missing laboratory data. Two infants' parents, one of whom was in the UDCA and the other was in the erythromycin group, refused to continue the participation.

The clinical characteristics of the groups are summarized in Table 1. All clinical features except birth weight and gestational age were comparable among the three groups. Erythromycin- and UDCA-treated infants had higher gestational age and birth weight than the placebo group. The 5-min Apgar scores were higher in the erythromycin group than in the UDCA and placebo groups. The γ-glutamyl transpeptidase (GGT) levels just before treatment were similar among the three groups. After treatment the lowest GGT levels were found in UDCA group (Table 2). At the end of treatment, the incidence of IFALD according to the elevation of GGT (difference in GGT before and after treatment) in the placebo group was significantly higher than in the UDCA group. When further evaluation was made according to gestational age, the results did not change. When we examined the elevation of GGT, we found the greatest difference in the placebo group ($P = 0.0001$), and no significant difference was found between the

Table 1 Comparison of the clinical characteristics of the infants receiving oral erythromycin, ursodeoxycholic acid (UDCA) and placebo

Clinical features	*Erythromycin* (n = *24*)	*UDCA* (n = *24*)	*Placebo* (n = *23*)	P *value*
Gestational age (weeks)[a]	28.5 (26–32)	28 (24–32)	27 (25–30)	0.006
Birth weight (g)[b]	1152 (±182)	1038 (±221)	975 (±200)	0.011
Gender (female/male)[c]	11 (45.8)/13 (54.2)	16 (66.7)/8 (33.3)	10 (43.5)/13 (56.5)	0.212
Antenatal bethamethasone	13 (54%)	11 (45.8%)	14 (60.8%)	0.252
Mode of delivery Vaginal	4 (16.7%)	8 (33.3%)	7 (30.4%)	0.380
Caesarean[c]	20 (83.3)	16 (66.7)	16 (69.6)	
Apgar scores				
1 min	5 (2–7)	6 (2–7)	5 (1–7)	0.24
5 min[a]	8 (3–9)	7 (3–10)	7 (3–9)	0.032
Respiratory distress syndrome[c]	17 (70.8)	10 (41.7)	14 (60.9)	0.11

[a]The values are given as median.
[b]The values are given as mean.
[c]The values are given as number (%).

Table 2 Liver function tests (difference in GGT levels)

	Erythromycin (n = *24*)	*UDCA* (n = *24*)	*Placebo* (n = *23*)	P *value*
Pretreatment GGT[a]	85.65 (23.8–333)	59 (12.9–313)	62 (12–135)	0.44
Post-treatment GGT[a]	97.75 (31.0–287.0)	72 (12.9–222)	121 (12–521)	0.002
GGT (>120 IU/l)[b]	10 (41.7)	5 (20.8)	13 (56.5)	0.04

Abbreviations: GGT, γ-glutamyl transpeptidase; UDCA, ursodeoxycholic acid.
[a]The values are given as mean ± s.d.
[b]The values are given as number (%).

UDCA and erythromycin groups. The maximum serum total bilirubin and conjugated bilirubin levels, serum alanine aminotransferase and aspartate aminotransferase levels did not differ significantly among the three groups. The time to achieve full feeding after beginning the treatment was significantly shorter in the erythromycin than placebo group (Table 3). When comparisons were further evaluated by analysis of covariance with covariate including gestational age, similar results were found ($P = 0.014$). The median PN duration in the erythromycin-treated infants was shorter than that in the placebo group (Table 3). After analyses were conducted according to gestational age, the results were similar ($P = 0.029$). No significant difference was observed between the UDCA and placebo or between the erythromycin and UDCA group in PN duration. No significant difference was found among the groups in reaching half enteral time ($<75\,ml\,kg^{-1}$ per day).

Postnatal clinical features were compared among the groups (Table 4). A significant lower rate of grade 3 to 4 intraventricular hemorrhage was found between the erythromycin and the other groups. This may have been related to the gestational age of that group. The duration of hospitalization was significantly longer in the placebo group than in the other groups. However, when further evaluation was made according to gestational age, no significant differences were found among the groups. Bronchopulmonary dysplasia, necrotizing enterocolitis and retinopathy of prematurity did not differ among the groups and no adverse effects associated with oral erythromycin treatment were observed.

The number of times that feeding was withheld more than 48 h was significantly higher in the placebo group than in the erythromycin or UDCA group, but no significant difference was found between the two drug-treatment groups (Table 3). When corrected for gestational age, the number of withheld feeds in the erythromycin was also significantly lower than in the placebo group ($P<0.001$). Furthermore, the number of withheld feeds was lower in the UDCA than in the placebo ($P = 0.03$) group. The number of feeds withheld because of gastric residuals (>50% feeding volume) was significantly lower in the erythromycin group than in the placebo group and lower in the UDCA group than in the placebo group even when corrected for gestational age.

After the end of the treatment, one infant in the placebo group died. Necrotizing enterocolitis developed in two infants, one each in

Table 3 Outcomes of enteral feeding in the three groups

Outcomes	*Erythromycin* (n = *24*)	*UDCA* (n = *24*)	*Placebo* (n = *23*)	P *value*
Time to achieve half enteral feeding (days)[a]	11.58 ± 2.5	11.71 ± 2.8	12.39 ± 3.2	0.58
Time to achieve full enteral feeding (days)[a]	22.46 ± 3.4	24.08 ± 3.05	27.00 ± 5.8	0.004
Type of milk feeds[b]				
Breast	16 (66.7)	14 (58.3)	18 (78.3)	0.34
Formula	8 (33.3)	10 (41.7)	5 (21.7)	
Numbers of feeds withheld due to gastric residuals[a]	1 (0–3)	2 (1–3)	3 (1–5)	<0.001
Numbers of feeds withheld due to feeding intolerance[a]	1 (0–3)	1 (0–3)	2 (1–7)	<0.001
Duration of PN (days)[a]	17.5 (15–27)	19 (12–28)	22 (12–23)	0.007

Abbreviations: PN, parenteral nutrition; UDCA, ursodeoxycholic acid.
[a]The values are given as median.
[b]The values are given as number (%).

Table 4 Outcomes of other clinical features in the three groups

Outcomes	*Erythromycin* (n = *24*)	*UDCA* (n = *24*)	*Placebo* (n = *23*)	P *value*
IVH grade 3–4 (*n* (%))	1 (4.2)	8 (33.3)	6 (26.1)	0.036
Bronchopulmoner displasia- (*n* (%))	3 (12.5)	3 (12.5)	8 (34.8)	0.088
Duration of hospitalization (days)	46 (28–90)	48.5 (28–99)	70 (29–130)	0.006
Number of infants septisemia (*n* (%))	15 (62.5)	15 (62.5)	18 (78)	0.158
Presence of patent ductus arteriosus (*n* (%))	9 (37.5)	9 (37.5)	12 (52.2)	0.504

Abbreviations: IVH, intraventricular hemorrhage; UDCA, ursodeoxycholic acid.

the erythromycin and UDCA groups. The number of infants with septicemia was similar among the three groups.

Discussion

Feeding intolerance is a common problem for preterm infants, and it sometimes results in cholestatic liver disease because of prolonged PN. The majority of infants with PN-associated hepatobiliary injury respond very well to PN withdrawal and FEF.[15,16] However, some do not recover. It has been shown that UDCA treatment minimizes IFALD and leads to an improvement in bile flow. UDCA causes the exchange of hydrophobic for hydrophilic bile acids.[17] A study by Lindor *et al*. suggested that UDCA can improve IFALD in preterm infants.[18] Similar results have been confirmed in pediatric studies.[10,11,19] In addition, UDCA therapy was associated with a significant reduction in serum direct bilirubin, total bilirubin and aspartate aminotransferase.[20]

Recently, it has been shown that UDCA treatment can prevent IFALD in VLBW infants.[21] In that study, treatment began on day 3 of life, and a significant decline in GGT activity was seen in the UDCA-treated patients. Also, aspartate aminotransferase and alanine aminotransferase activities declined. In our study, aspartate aminotransferase and alanine aminotransferase levels did not differ among the three groups. However, in the UDCA group, the GGT level at the end of the treatment was lower than that in the placebo group. Also, in the placebo group, the elevation in GGT level was significantly higher than that in the UDCA group. GGT is a microsomal enzyme, widely distributed in human tissues, particularly in the bile canaliculi. GGT activity has become a widely used parameter in detecting parenteral nutrition-associated cholestasis and assessing the efficacy of UDCA treatment, because it is the earliest sensitive marker of cholestasis. Its increase occurs earlier to those for other enzymes (ALP, 5′-nucleotidase, aminotransferases) and persists longer.[22]

In one study, in which patients in the placebo group took a longer time to establish full feeds and thus received PN longer, IFALD was found to be significantly less (49%) frequent in the erythromycin group as compared with the placebo group.[14] Significantly fewer erythromycin-treated patients had abnormally raised serum alanine aminotransferase.[14] In our study, when we examined GGT elevation before and after treatment, the increase was found to be higher than in the placebo group. For that reason, it can be concluded that in the prevention of IFALD, erythromycin is more effective than is placebo. Although it should be noted that in some studies, no significant difference was found between the placebo and erythromycin groups.[23–25]

When we compared GGT level between the UDCA and erythromycin groups after treatment, GGT level was found to be

significantly higher in the erythromycin group. Our findings suggest that UDCA was the most effective agent for preventing cholestasis. UDCA being one of the secondary bile acids and it can assist in the digestion of fats. During feeding, the fat content of the duodenum is one of the major determinants of the gastric emptying. In the study of Arslanoglu *et al*.,[21] fat absorption was improved with UDCA treatment, but the difference was not significant. Time to achieve FEF was also not significantly different from that in the placebo group.[21] In our study, we could not evaluate fat absorption, and no significant difference in time to achieve FEF was found between the placebo and UDCA groups. Our results indicate that VLBW infants with feeding intolerance caused by non-anatomically obstructive gastrointestinal dysmotility achieved FEF significantly earlier after treatments.

None of our patients in the erythromycin group developed septicemia from antibiotic-resistant organisms. Infantile hypertrophic pyloric stenosis and life-threatening cardiac dysrhythmia have not been reported in previous clinical trials,[14,24,25] and we did not observe these in our patients. Our study demonstrated that erythromycin-treated infants had significantly fewer episodes of large residual gastric aspirates and were able to attain FEF more quickly, as noted in other.[24,26] Thus, we suggest that the use of an intermediate dose of oral erythromycin could significantly reduce the number of withheld feeds and the time of FEF.[23]

The main limitation of our study was that it was underpowered. Although there was no sample size calculation, we computed the observed power for repeated-measures analysis of variance with gestational age as covariate. The observed power values were 0.76, 0.92 and 0.69 for repeated factor (before–after treatment measurements), for interaction between repeated factor and group, interaction between repeated factor and covariate, respectively. The second limitation of our study was the unexpected heterogeneity in demographic characteristics of our groups in terms of gestational age and birth weight.

Conclusion

The present data suggest that oral erythromycin is the most effective treatment for facilitating enteral feeding, and UDCA is the most effective for preventing cholestasis in VLBW infants. We suggest that prophylactic UDCA treatment in infants who receive prolonged total parenteral nutrition could prevent IFALD.

Conflict of interest

The authors declare no conflict of interest.

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