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Original Article

The Efficacy of Oral Erythromycin in Enhancement of Milk Tolerance in Premature Infants: A Randomized Clinical Trial

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Abstract

Background: A great number of premature neonates do not tolerate sufficient milk during the early neonatal period.

Objective: To evaluate the effect of oral erythromycin on enhancement of feeding tolerance in preterm newborns.

Methods: Sixty preterm neonates intolerant to milk of >75 ml/kg/day during 5 days after the start of feedings, were randomized into a treatment and a control groups. Oral erythromycin (12.5 mg/kg/dose) was given to the treatment group for a maximum of 10 days, or until full enteral feeding (150 ml/kg/day) was tolerated.

Results: Oral erythromycin enhanced feeding tolerance in premature neonates of ≥32 wks of gestation ($p<0.032$) with no adverse effects and led to a shorter hospital stay ($p<0.003$) as compared to the control group.

Conclusion: Oral erythromycin is an effective drug for alleviating feeding intolerance in preterms.
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Keywords • Prematurity • feeding intolerance • erythromycin

Introduction:

Gastric intolerance for the needed amount of milk is one of the most important problems involving premature infants. This causes insufficient weight gain, longer hospital stay, and increasing chance of developing infections with nosocomial resistant organisms. Low motility due to incomplete function of gastrointestinal (GI) system is a known reason for milk intolerance in preterm age group. Drugs such as metoclopramide and cisapride which are commonly used for better milk tolerance in premature infants are known for their serious side effects such as extrapyramidal reaction, lethargy and longer QT interval.[1-4]

Based on the fact that motilin increases the constriction activity of GI tract, and considering that erythromycin is a prokinetic agent and a motilin agonist,[5] this study was performed to evaluate the efficacy as well as the potential side effects of oral erythromycin on enhancement of milk tolerance in premature infants.

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Table 1: Protocol used for advancement of feeding

Body Weight (g)	Amount of breast milk or Perinan® given (ml)			
	Initiating dose	1st day, q3h	2nd day, q3h	3rd day onward
<1250	0.5	0.25–0.5	0.5–1.0	As tolerated or 1–2 ml, q3h
≥1250	0.5	0.5–1.0	1.0–2.0	As tolerated or 1–2 ml, q3h

Patients and Methods

A randomized controlled clinical trial was performed on premature newborns admitted to the newborn intensive care units of Nemazee and Hafez Hospitals of Shiraz. After approval of the study design by the Board of Pediatrics Department and the Faculty Committee of the Research Proposals, informed written consent was obtained from the parents. Initially, all premature infants born before 36 weeks of gestation considered for the study. Those with asphyxia, cyanotic heart diseases, previous GI surgery, intestinal atresia or other congenital GI anomalies were excluded from the study. During the first five days of life, feeding began for all prematures. Five days after initiating the milk, those <36 wks of gestation who could not tolerate half the amount of enteral feeding (75 ml/kg/day) were included in the study. Sixty premature infants were enrolled and randomized equally into treatment and control groups. For the treatment group, 12.5 mg/kg erythromycin ethyl-succinate every 6 hrs for 10 days, or until full enteral feeding was tolerated (150 ml/kg/day), was started. No drug or placebo was given to the control group.

All infants had daily weight and routine physical examinations. The neonates did not receive any other prokinetic drugs during the study. All prematures received total parenteral nutrition. Except for one newborn in the control group, other infants received antibiotics and oxygen. Stool cultures were done for all newborns before the study and once more immediately after cessation of therapy in treatment group. All newborns had an initial ECG for evaluation of QT interval. In treatment group, a final ECG was also taken after completion of therapy.

Table 2: Baseline parameters measured in treatment and control groups.*

Parameter	Control (n=28)	Treatment (n=29)
Mean GA**(range)	31.5 (28–35)	30.9 (28–34)
Male sex (%)	17 (61%)	12 (41%)
Mean (range) Birth	1371	1292
weight (gm)	(900–1770)	(830–1660)
Mode of Delivery*	CS: 12 (43%)	CS: 16 (55%)
	NV: 16 (57%)	NV: 13 (45%)
Mean (range) 5-min Apgar Score	7 (4–10)	8 (5–10)

** GA: Gestational age (weeks)
* P value: not significant
† CS: Cesarean section, NV: Normal vaginal delivery

Feeding regulations

According to the conditions and availability, infants were exclusively breast-fed. Other alternatives included breast milk plus Perinan® formula or Perinan® alone. Protocol used for advancement of feeding amount is depicted in Table 1. If the respiratory rate was >80/min, milk was given via a nasogastric or an orogastric tube. Those with slower respiration rates, or under 32 weeks of gestation were breast- or bottle-fed, otherwise milk was given via an oro/naso-gastric tube even to those under ventilator.[6] If the respiratory rate was >80/min, in the case of vomiting, or if the gastric residual was >40%–50% of the given milk, feeding discontinued for one session. Feeding ceased until recovery, if abdominal distention or other primary clinical signs of necrotizing enterocolitis (NEC) were present.[7,8]

The statistical analyses were done using Fisher's Exact test and. Significance level was set at $p<0.05$.

Results

Newborns in the two groups were not statistically different regarding their birth weight, gestational age, sex ratio, mode of delivery, and 5-minute Apgar scores (Table 2). Six (21%) mothers in control, and 7 (24%) in the treatment group had received antenatal steroids (p=0.943).

Two newborns in control and one in the treatment group expired of severe immaturity and advanced respiratory distress syndrome while they were under ventilation therapy.

The mean time for initiating the milk after birth, for control, and treatment groups were 3 and 3.8 days, respectively (p=0.271). Twenty-four infants received breast milk exclusively of whom 11 (39%) were in control and 13 (45%) were in the treatment group. On the other hand, 29 newborns received breast milk and Perinan® formula of whom 15 (54%) were in control and 14 (48%) were in the treatment group. Moreover, four infants of whom 2 (7%) were in control and 2 (7%) in the treatment

Table 3: Comparison of groups regarding their need for supportive care and suspected side effects of erythromycin*

Need/Side effect	Control n=28	Treatment n=29
Mean (range) days needed O_2 therapy	13.3 (5–48)	16.3 (4–47)
Exchange transfusion	2 (7%)	1 (3%)
Ventilatory support	7 (25%)	5 (17%)
Oral ibuprofen intake	2 (7%)	2 (7%)
Septicemia	7 (25%)	5 (17%)
NEC	3 (11%)	2 (7%)
PDA	5 (18%)	7 (24%)
Coffee ground	20 (71%)	17 (59%)

* P value: not significant

Table 4: Mean±SD age at discharge from the hospital and days required to achieve full enteral feeding for patients.

	GA*	Control (days)	Treatment (days)	p value
Discharge	≥32	(n=13) 22.3±8.9	(n=13) 12.9±3.2	0.003
	<32	(n=15) 26.4±11.0	(n=16) 28.3±10.8	0.641
Feeding	≥32	(n=13) 13.5±6.3	(n=13) 9.2±1.5	0.031
	<32	(n=15) 17.6±6.9	(n=16) 18.3±11.4	0.836

* GA: Gestational age (weeks)

group were given Perinan® only. The differences among all three types of feedings were not statistically significant. Comparison of two groups regarding their needs for oxygen therapy, exchange transfusion, ventilatory support, postnatal oral ibuprofen intake and clinical suspicions of adverse effects of erythromycin proved to be statistically non-significant (Table 3). All stool cultures in both groups were negative with one exception in treatment group, from which *Pseudomonas aeroginosa* was isolated before starting erythromycin that turned negative following therapy. The mean QT interval in control group was 417 ms. In the treatment group the mean QT intervals before and after therapy were 408 and 401 ms respectively (p=0.628). No clinical signs or symptoms of hypertrophic pyloric stenosis (HPS) were observed.

Based on their gestational age, preterm neonates were divided into two subgroups of ≥32 and <32 wks. The time needed for reaching full enteral feeding and the age at which the neonates of these subgroups discharged from the hospital are presented in Table 4.

Discussion

The premature infants are mostly intolerant to the milk due to dismotility or inappropriate non-anatomic GI tract motilities.[8] In a randomized controlled study, no positive effects for intravenous erythromycin on enhancement of milk tolerance in preterm infants was reported.[9] Probably, the low antimicrobial doses of intravenous erythromycin used in that study had no significant prokinetic effects. The prokinetic functions of oral erythromycin are present in the stomach and the upper segments of small intestine.[5] Oral erythromycin therapy activates motilin receptors in the cholinergic neurons and smooth muscles of the upper GI tract.[11,12] Since an increase in gastric muscular tonicity lowers the pyloric resistance, it improves milk tolerance.[12] It is believed that the neuro-endocrine development of GI tract is completed by the 25th wks of gestation.[13] Some reports have shown that the immaturity and defects in the migrating constrictive activities in the premature infants of <32 wks of gestation, are the major reasons for not properly responding to erythromycin.[2] This point is verified by our findings. In this study, administration of oral erythromycin did not change the need for oxygen, nor decreased the incidence of septicemia, NEC, Patent Ductus Arteriosus (PDA), or need for blood exchange transfusions.

The maximum duration for oral erythromycin therapy was 10 days in our neonatal subjects and no signs or symptoms resembling HPS, which has been reported to occur in those receiving the drug for >10 days was observed.[14] Oral administration of erythromycin did not affect mortality rate in both groups. Oral erythromycin therapy as a routine practice or for prophylactic purposes is not yet recommended in premature infants, due to insufficient data on its safety.[12,15] The new non-antibiotic macrolides (such as ABT 229) that stimulates the motilin receptors, particularly in preterms <32 wks of gestation, are under investigations.[12,16]

The present study shows that premature infants of ≥32 wks of gestation are satisfactorily benefited by oral administration of erythromycin ethyl-succinate, for better milk tolerance with no adverse reactions, and shorter hospital stay.

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