Efficacy of high-dose oral erythromycin on enhancement of feeding tolerance in premature neonates

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Abstract

Objective:

Most neonates admitted to neonatal wards do not tolerate sufficient milk. Recently the effect of erythromycin on increasing feeding tolerance in neonates has been studied. In this study the effectiveness of oral, high dose Erythromycin a prokinetic agent was used to enhance feeding tolerance in these neonates.

Methods:

This prospective randomized controlled clinical trial was conducted on 60 premature neonates with birth weight< 1800 g at Hafez and Namazi hospitals in Shiraz during a 13- month period. Those neonates who did not tolerate milk more than 75 cc/kg/day five days after starting feeding, were chosen for the study. A total of 60 neonates were studied who were divided randomly into two equal groups (control and study), and were similar in sex, birth weight, gestational age, apgar score, route of delivery, oxygen need, type of milk and corticosteroid therapy in the antepartum period. Oral erythromycin (ethyl succinate suspension) was given in a dose of 12.5mg/kg/dose every 6 hours for a maximum of 10 days, or until they tolerated full enteral feeding (150 cc/kg/day). One neonate in the erythromycin group and two neonates in the control group expired during the study.

Results:

Oral erythromycin was effective on enhancement of feeding tolerance in premature neonates with gestational age equal to or more than 32 weeks (p= 0.031) and lead to earlier discharge of these neonates from hospital (p= 0.003). Also oral erythromycin was relatively effective in enhancement of feeding and early discharge of neonates with birth weight equal to or greater than 1500 g. Erythromycin was not effective for neonates less than 32 weeks of age (very preterm). In this study, no adverse effects (necrotizing enterocolitis, sepsis, O2 dependency, patent ductus arteriosus, high-dose positive stool culture or prolonged QT interval)
were observed following erythromycin usage.

Conclusion:

High-dose oral erythromycin in premature neonates of gestational age equal to or greater than 32 weeks with feeding intolerance is effective for increasing feeding tolerance and earlier hospital discharge. However, routine use is not suggested.

Keywords:

Feeding tolerance, Oral erythromycin, Premature neonates.

Introduction

Full Enteral feeding (FEF) is an important issue in premature neonates because it may lead to feeding intolorance, vomiting and possibility of necrotizing enterocolitis (NEC) . Sometimes it takes several weeks for FEF (150 cc/kg/d) (1). Additionally, prolonged parenteral feeding increases the problems facing both the neonate and neonatologists. Thus, it is prudent to improve nourishment of premature infants. Studies

regarding the positive effect of erythromycin (EM) on better milk tolerance have recently been done. EM is a macrolide antibiotic. It has an agonist effect on motilin and vigorous prokinetic effects on the stomach and proximal part of the small intestine (4) and can induces phase III migratory motor complexes (MMCs) (2). We designed a rescue approach study for premature infants with birth weight less than 1800 g who were admitted to the hospital and given high doses of oral EM for up to 10 days to assess the prokinetic effect of EM to increase milk tolerance.

Methods

This prospective randomized controlled clinical trial was done in 13 months on premature neonates who were admitted to the Namazi and Hafez hospitals in Shiraz. In this study premature infants with birth weight less them 1800 g were assessed. Exclusion criteria were: Asphyxia, congenital cyanotic heart disease, congenital intestinal abnormalities (such as intestinal atresia), positive surgical history, NEC, electrolyte imbalances, history of indomethacin or prokinetic drugs such as metoclopramide. Oral feeding was begun for infants during the first 5 days after birth. Milk was given every 3 hours 15-20 cc/kg/d. As much as possible, breast milk was used but if it was not available milk formulas were used.

If residual milk in neonates' stomach was more then 50% of the oral intake, or if newborns had vomiting, feeding was stopped. If there was abdominal distention, the newborn was kept NPO until improvement of distention. Also, if there was tachypnea with a respiratory rate> 80 /min the newborn was kept NPO. Newborns who did not tolerate milk up to 75 cc/kg/d (half FEF) for 5 days after starting oral feeding, were included in the study. A questionnaire was filled for each neonate.

Sixty neonates, were chosen and divided into two equal groups randomly. The control group did not receive any drugs to improve milk tolerance and the case group received oral EM in ethyl succinate form. Dosage of EM was 12.5 mg/kg/dose every 6 hours and continued until milk tolerance reached 150 cc/kg/d. Maximum administration time was 10 days. Every infant was visited twice daily. All cases received parenteral nutrition (without intralipid). All newborns (except one in the control group) received parenteral antibiotics and O2.

Primary electrocardiography (ECG) was performed for all infants to assess QT interval and if they received EM, the QT interval was rechecked just after cessation of the drug. Data collection was done with SPSS software (version 10) and all statistical analysis were done using Fisher's exact test and t-test (p-Value< 0.05 was significant).

Results

During the study two cases from the control group and one infant from the case group died. All three cases had been connected to a respirator and all died of respiratory distress syndrome. Results of comparison between the 2 groups are listed in Table 1. QT interval changes were not significant. All stool cultures were negative (before and after EM administration). Only in one case pseudomonas was cultured before EM intake which became negative after EM intake. There was no sign of HPS in the infants.

Infants in both groups were subdivided (Tables 2 and 3) according to birth weight and gestational age (GA) as follows: Birth weight ($\geq$ 1500 g or < 1500 g) and GA($\geq$ 32 weeks or GA < 32 weeks).

Discussion

Prophylactic administration of EM for increasing milk tolerance has no positive effect on premature infants so it is not suggested (1,5). In one controlled trial, randomized double-blinded study on 24 very low birth weight (VLBW) premature infants with feeding intolerance low dose oral EM had no positive effects on increasing milk tolerance (2) because low doses (3-12 mg/kg/d) do not reach appropriate serum concentration levels and have no prokinetic effects (1). In another controlled randomized double-blinded placebo study on 56 VLBW premature infants with GA < 32wk and feeding intolerance, high doses of EM, decreased the duration time to attain FEF (3), however, high dose administration of EM (or antimicrobial doses > 40 mg/kg/d) for more than 14 days in premature neonates with less than 2 weeks age, increases the incidence of hypertrophic pyloric stenosis (HPS) 10 times. Thus, it is not recommended (6). To decrease complications enteral EM is preferred

Table - 1. comparison of demographic & other variables between EM group and controlled group*

variable	EM group (n=29)	Controlled group (n=28)
Gestational age(week)	30.9 (28-34)	31.5 (28-35)
Birth weight (gr)	1292 (80-1660)	1371 (900-1770)
Apgar score (5 minutes)	8 (5-10)	7 (4-10)
Duration time for O2 demand (days)	16.3 (4-47)	13.3 (5-48)
Duration time to reach to EEF (days)	14.24(6-44)	15.7(7-31)
Releasing age (day)	21.41 (10-45)	24.53 (12-50)
Sexuality (female : male)	17(58.6%):12(41.4%)	11(39.3%): 17(60.7%)
The age of starting breast feeding (day)	3.8 (1-5)	3 (1-5)
Mode of delivery :		
cesarean section	16(55.2%)	12(42.8%)
vaginal	13(44.8%)	16(57.2%)
Past hx of corticosteroid therapy in mother	7(24.1%)	6(21.4%)
Type of milk:		
formula	2(6.8%)	2(7.1%)
Breast milk	13(44.8%)	11(39.2%)
Breast milk + formula	14(48.2%)	15(53.5%)
Respirator demand	5(17.2%)	7(25%)
Need to exchange transfusion	1(3.4%)	2(7.1%)
Suspicious signs of sepsis	5(17.2%)	7(25%)
Suspicious signs of NEC	2(6.8%)	3(10.7%)
Patent ductus arteriosus	7(24.1%)	5(17.8%)
Oxygen demand duration(day)	16.3 (1-35)	13.3 (0-44)
Coffee ground secretion	17(58.6%)	20(71.4%)

* all p-values were not significant (> 0.05)

Table - 2. comparison between EM group and controlled group about duration time to attain FEF and releasing age according to gestational age(GA)

Gestational age (week)		group	N	mean	SD	P-value
GA < 32	Releasing age	EM	16	28.3	10.76	0.641
		control	15	26.4	11.04	
	Duration time to attain FEF	EM	16	18.3	11.36	0.836
		control	15	17.6	6.97	
GA ≥ 32	Releasing age	EM	13	12.92	3.2	0.003
		control	13	22.31	8.91	
	Duration time to attain FEF	EM	13	9.23	1.48	0.031
		control	13	13.5	6.27	

Table - 3. comparison between EM group and controlled group about duration time to attain FEF and releasing age according to birth weight

Birth weight(gr)		group	N	mean	SD	P-value
< 1500	Releasing age	EM	22	23.5	12.14	0.277
		control	18	27.11	10.89	
	Duration time to attain FEF	EM	22	15	10.44	0.476
		control	18	17	6.79	
≥ 1500	Releasing age	EM	7	16.29	6.05	0.283
		control	10	19.9	6.92	
	Duration time to attain FEF	EM	7	11.86	5.96	0.651
		control	10	13.3	6.6	

to the parenteral route (1). There have been many studies using EM to improve nourishment of premature infants with different doses, different durations and modes(rescue or prophylactic) and routes of drug administration (intravenous (IV) or oral). We used high doses of oral EM for up to 10 days to assess the prokinetic effect of EM to increase milk tolerance.

As shown in Tables 1, 2 and 3 both groups had similar demographics and there was no significant difference between them. The results of our study have indicate that although high doses of oral EM with rescue approach do not increase milk tolerance or expedite discharge time for premature infants with birth weights < 1800 g, when these infants are divided into two groups: GA< 32 wk and GA ≥ 32 Wk, EM decrease the time to attain FEF significantly in neonates with GA≥ 32 wk (EM group versus control group 9.23d, 13.5d respectively, p= 0.031); and significantly decreases hospital stay (EM group versus controlled group 12.92d, 22.31d respectively, p= 0.003).

EM is a motilin agonist. It induces phase 3 MMCs and has prokinetic properties. MMCs phases are: (I) no contractile activity (II) irregular contractions periods (III) regular contractions with a rate of 3/min in the antrum and 12/min in the duodenum(IV) short period of irregular contractions (1). It has been reported that although plasma motilin concentration in premature infants with GA< 32 wk is the same as adults, there are no evidence of MMCs in them. Therefore EM can not induce MMCs in this group. But, normal MMCs are observed in infants with GA> 32 wk(7), and our study indicated the same results. Also low-dose EM can not cause strong contractions (in contrast with high-dose) (7). Jadcherla et al prescribed enteral EM for 7 premature infants with GA < 32 wk and 14 with GA≥ 32 wk. They found that in the first group MMCs were not induced but in 7 infants of the second group, EM induced the appearance of migratory activity. They concluded that preterm neonates have MMCs after 32 w of GA. Although the motilin receptor is functionally present< 32 wk of GA, hormonal modulation of migrating activity by plasma motilin is absent in GA< 32 wk (8). Costalos et al in another double-blinded randomized cross over study, administered enteral EM to 20 premature infants with mean GA= 32 wk 10 mg/kg/dose every 8 hours via a rescue approach for 7 days. They concluded EM decreases gut transit time and promotes antral contractility significantly. There were no adverse drug effects in that study (9).

On the other hand, there are some studies which illustrate EM increases milk tolerance in premature infants with GA < 32 w and VLBW infants. PC Ng et al conducted a double blinded randomized controlled placebo study on 56 premature VLBW neonates with GA< 32w and feeding intolerance. They illustrated oral EM administration via a rescue approach, 12.5 mg/ kg/dose every 6 hours for 14 days, had a significant positive effect on decreasing duration time for approaching FEF in the EM group, with no adverse effects. Thus, they confirmed the hypothesis that enteral feeding in the neonatal gut causes faster detection of phase III MMCs than would be normally expected for that GA.

In preterm neonates who already have necessary anatomical and physiological organs at a very early gestation, EM can produce an effect on motilin receptors and enhance upper gastrointestinal (GI) motility (3). Also, Pak C. Ng et al in another study on VLBW premature neonates with milk intolerance concluded high-dose oral EM administration significantly decreases duration time for approaching to FEF and the incidence of cholestasis which is relevant to parenteral feeding (10). In another double-blinded placebo controlled trial study which was arranged for 46 premature infants with GA < 32wk and feeding intolerance, Pracha et al prescribed 10 mg/kg/dose enteral EM every 6 hours for 2 days and then 4 mg/kg/dose every 6 hours throughout the next 5 days. He found that EM decreases duration time for approaching FEF significantly. They stated that EM dose not have the same effect on MMCs in preterm as in term infant (4). Perhaps motilin receptors on GI smooth muscles become functional in lower GA than neuronal motilin receptors or that neuronal receptors are responsible for MMCs generation. EM in infants with GA< 32 wk increases stomach motility.

EM has prokinetic effects due to stimulation

of GI smooth muscle receptors (7). Our study confirms the hypothesis that before GA of 32weeks, MMCs are absent and motilin dose not modulate the migratory activity; thus, EM has no prokinetic effect on infants with GA< 32 weeks. Although there were no adverse drug effects in our study, our sample size was small and calculated to assess the effect of EM on increasing milk tolerance in premature infants. Further studies are therefore warranted.

Conclusion

High dose oral EM significantly improves milk tolerance and shortens hospital stay of premature infants with GA≥ 32 weeks and feeding intolerance. But routine administration can not be recommended until more research is done on premature infants regarding this issue.

Acknowledgment

We are thankfull from the research department of Iran University of Medical Sciences because of their cooperation in this study.

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