Efficacy of prophylactic oral erythromycin to improve enteral feeding tolerance in preterm infants: a randomised controlled study

Mohammadizadeh M, Ghazinour M, Iranpour R

ABSTRACT

Introduction: Enteral feeding intolerance is a major problem in preterm infants. This study evaluated the safety and efficacy of prophylactic low-dose oral erythromycin, a motilin agonist, as a prokinetic agent in reducing the incidence of this problem.

Methods: From February to May 2008, a prospective randomised controlled trial was conducted at the Isfahan University of Medical Sciences, Isfahan, Iran. 70 uncomplicated preterm infants (28–34 weeks' gestation) weighing 1,000–1,500 g were randomly assigned to either a case group receiving low-dose oral erythromycin (6 mg/kg/day, in four doses over ten days) or a control group (n is 35 in each group) until they were fully fed enterally (150 ml/kg/day). Gavage feeding of the mother's milk was started within the first three days of life, and erythromycin was given simultaneously. The time taken to reach full enteral feeding and the total duration of feeding interruption due to intolerance were compared.

Results: The time taken to reach full enteral feeding was significantly shorter in the erythromycin group than the control group (10.11 +/− 2.51 versus 12.71 +/− 5.76 days, p is 0.01). In the control group, the mean duration of feeding interruption was significantly longer (84.00 +/− 62.58 versus 32.57 +/− 11.93 hours, p is 0.005) and more episodes of abdominal distention and significant gastric residue were also noted (p less than 0.05). No infant in the erythromycin group developed cardiac arrhythmias or pyloric stenosis.

Conclusion: The prophylactic use of erythromycin may be warranted in very low birth weight infants, provided the efficacy and safety of the drug can be confirmed in further studies.

Department of Paediatrics, Al-Zahra Hospital, Isfahan University of Medical Sciences, Sofe Bolvar, Isfahan 8174675731, Iran

Mohammadizadeh M, MD
Assistant Professor

Ghazinour M, MD
Resident

Iranpour R, MD
Assistant Professor

Correspondence to:
Dr Majid Mohammadizadeh
Tel: (98) 311 6249032
Fax: (98) 311 6681555
email: m_mohammadizadeh@med.mui.ac.ir

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INTRODUCTION

Enteral feeding intolerance is a major problem in premature infants, resulting in prolonged hospitalisation and a predisposition to serious complications due to prolonged use of parenteral nutrition,[1,2] It can be attributed to the immaturity of gastrointestinal motility,[3,4] as small intestinal motility and phase-3 activity of the migrating motor complex (MMC) are more immature in preterm infants, especially those with a gestational age of less than 32 weeks.[3,5]

Erythromycin and its derivatives act as nonpeptide motilin agonists by binding to motilin receptors. Motilin initiates phase-3 activity of the interdigestive MMC in the upper gastrointestinal tract, participates in regulating gastrointestinal motility, and stimulates postprandial gastric muscle contractions and gastric emptying.[5-7] The drug also enhances the release of endogenous motilin and stimulates cholinergic nerves of the gastrointestinal tract at the pre- and post-ganglionic levels, resulting in the release of calcium and contraction of muscles of the gut.

Diverse results have been reported on the use of erythromycin as a prokinetic agent to stimulate gastrointestinal motility in premature neonate. This diversity seems to be related to the different designs used in the various studies: prophylactic vs. rescue approach, low vs. antimicrobial dose, oral vs. intravenous route of drug administration, and the varied gestational age of the infants enrolled in the study. Some of these studies have evaluated the efficacy of prophylactic administration of low-dose oral erythromycin.[8] The aim of this prospective study was to evaluate the efficacy of prophylactic low-dose oral erythromycin on feeding tolerance in stable preterm infants.

METHODS

From February 2008 to May 2008, 70 preterm neonates

Table I. Demographic data of infants in the erythromycin and control groups.

Demographic	No. (%)		95% CI	p-value
	Erythromycin (n = 35)	Control (n = 35)		
Mean birth weight ± SD (g)	1307.14 ± 150.55	1252.85 ± 130.82	−12.99, 121.56	0.11
Mean gestation ± SD (wk)	31.54 ± 1.65	30.94 ± 1.64	−0.18, 1.38	0.13
Gender				
Male	16 (45.7)	18 (51.4)		0.40
Female	19 (54.3)	17 (48.6)		
Delivery				
Vaginal	14 (40.0)	19 (54.3)		0.80
Caesarean	21 (60.0)	16 (45.7)		

CI: confidence interval; SD: standard deviation

born in Shahid-Beheshti and Al-Zahra Hospitals, two teaching hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, were enrolled in this study. The Ethics Committee of Isfahan University of Medical Sciences had approved the study. Parental informed consent was obtained before the infants were enrolled in the study.

The neonates were born at 28 to 34 weeks' gestation (calculated on the basis of the first day of the last menstrual period), with a birth weight of 1,000–1,500 g. Exclusion criteria were significant congenital anomalies, structural anomalies of the gastrointestinal tract, respiratory failure with ventilatory support, necrotising enterocolitis, infants who did not require other prokinetic agents (such as cisapride or metoclopramide), theophylline or opioids, and severe asphyxia (defined as the presence of all of the following criteria: profound umbilical artery metabolic or mixed acidaemia [pH < 7], persistence of an Apgar score of 0–3 for more than five minutes, neonatal neurologic sequelae [e.g. seizures, coma or hypotonia] and multi-organ system dysfunction).

The infants were randomly allocated to either the erythromycin or the control group by a simple randomisation method using a table of random numbers. The placebo was not administered in the control group. Infants in the erythromycin group received a daily oral dose of 6 mg/kg (divided in four doses) of erythromycin ethylsuccinate suspension 200 mg/5 ml (Loghman Co, Tehran, Iran). The nurse who conducted the randomisation of the infants and administered the drug was not involved in the other aspects of the study. The neonates in both groups received breast milk. Feeding was started within the first three days of life, as soon as the infants were stable. Erythromycin was administered simultaneously and continued for ten days. Based on our institution's neonatal care policy, feeding was started at 15 ml/kg/day via the nasogastric tube, and increased by 20 ml/kg/day as tolerated. The interval between feedings was three hours. Human milk fortifier Similac HMF (Abbott Nutrition Laboratories, North Chicago, IL, USA) was added after the first week of life when the milk volume reached 100 ml/kg/day. Parenteral nutrition was started on the first day of life and discontinued when the infant was receiving 120 ml/kg of milk per day.

Feeding and erythromycin were discontinued based on the following conditions: milk vomiting ≥ two times a day, any bilious or bloody vomiting, gastric residues of at least one-third of the previous gavage volume, and clinical signs and symptoms suggestive of necrotising enterocolitis. They were resumed 24 hours after the problem was resolved. Full enteral feeding was defined as receiving milk as much as 150 ml/kg body weight per day. Electrocardiogram monitoring was conducted to detect cardiac arrhythmias. All infants were followed up for a month after discharge and evaluated for signs and symptoms of pyloric stenosis, the main side effect of the drug.

Data on the infant's gestational age, birth weight, gender, age at starting feed and at full feed, episodes of any kind of vomiting, the volume of gastric residues, cardiac arrythmias, and the time taken to reach full enteral feeding was recorded, stored in a computer database and analysed after data management in order to exclude outliers. The Statistical Package for the Social Science version 10.5 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Independent sample *t*-test and chi-square test were used to compare the mean values and determine the distribution of categorial variables, respectively. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Table I shows the basic demographic data of the infants in both groups. There were no significant differences in the mean birth weight and gestational age, gender distribution and mode of delivery. Hence, the main data

Table II. Comparison of feeding details in the erythromycin (as a prophylactic prokinetic agent) and control groups.

	No. (%)		95% CI	p-value
	Erythromycin (n = 35)	Control (n = 35)		
Age at starting feed (day)*	2.94 ± 0.93	2.91 ± 0.88	−4.79, 0.46	0.89
Age at reaching full enteral feeding (day)*	13.02 ± 2.93	15.62 ± 5.79	−4.79, −0.40	0.02
Time taken to reach full enteral feeding (day)*	10.11 ± 2.51	12.71 ± 5.76	−4.72, −4.77	0.01
No. of feeds withheld due to:				
Bilious residue	2 (5.7%)	3 (8.6%)		0.64
Bloody residue	3 (8.6%)	3 (8.6%)		0.60
Abdominal distension	2 (5.7%)	8 (22.9%)		0.04
Significant residual volume of gastric lavage	6 (17.1%)	14 (40.0%)		0.03
Total duration of withheld feed (hr)*	32.57 ± 11.93	84.00 ± 62.58	−86.30, −16.55	0.005

* Data is presented as mean ± standard deviation
CI: confidence interval

of the study was comparable. As shown in Table II, the start age of enteral feeding was not significantly different in the two groups (p = 0.89), but both the the mean time taken to reach full enteral feeding and the mean age of the infants at that time were significantly lower in the erythromycin group than in the control group (p = 0.02 and p = 0.01, respectively).

Enteral feeding and erythromycin were temporarily withheld 13 and 28 times in the erythromycin and control groups, respectively. The total mean duration for which oral feeding was withheld was significantly longer in the control group than in the erythromycin group (Table II). The number of infants with marked episodes of gastric lavage or abdominal distention was also significantly higher in the control group (Table II). There was no significant difference between the two groups in terms of episodes of bilious or bloody gastric residues (Table II). No infant developed cardiac arrhythmia, pyloric stenosis or other side effects such as changes in the frequency of stools. All the infants in the two groups completed the study.

DISCUSSION

According to the results of this study, prophylactic administration of low-dose oral erythromycin as a prokinetic agent has significant beneficial effects on the feeding tolerance of preterm infants (< 34 weeks' gestation) with no complications and very low birth weight (1,000–1,500 g). Marked episodes of abdominal distention and gastric residue as well as the mean time taken to reach full enteral feeding were significantly higher in the control group compared to the erythromycin group.

Reports concerning the efficacy of erythromycin in the feeding tolerance of preterm infants are controversial. As mentioned earlier, the diversity of results may be due in part to the different study designs with regard to dose (low vs. antimicrobial), route (intragastric vs. intravenous) and mode of administration of the drug (prophylactic vs. rescue), as well as due to the gestational age of the infants enrolled in these study. Some authors have used the drug in low doses for prophylactic or rescue purposes. In one study, prophylactic use of the drug resulted in beneficial effects on feeding tolerance in preterm infants,[8] while in another, the rescue approach resulted in the same benefits only in infants with > 32 weeks' gestation.[9] In some other studies, no such benefits were observed.[1,10,11] High-dose erythromycin has been used in some studies; authors who used it as rescue noted that it helped to reduce the time taken to reach full enteral feeding.[12-14] However, studies that utilised the prophylactic approach reported no such benefits.[15,16]

A recent systematic review included ten randomised controlled studies (three prophylactic and seven rescue studies). Based on the conclusions, the authors have emphasised that future research is needed to determine a more precise dose range of the drug to be effective as a prokinetic agent in preterm infants, especially in those with > 32 weeks' gestation.[17] According to the findings of another systematic review, the author similarly suggested that future research should be directed to resolve these controversies and to confirm whether the beneficial effects of erythromycin are applicable to other ethnic populations. The author also postulated that the action of erythromycin may be dose- and gestational-age-dependent.[18]

Erythromycin is a motilin receptor agonist, whose function on the gasterointestinal tract is the same as motilin. It also enhances the release of endogenous motilin. The reason for the different responses to various doses of erythromycin is not completely understood. Some studies conducted in full-term infants, children and adults but not preterm neonates reported that the differences may be due to the presence of two different

types of motilin receptors; the "neural" receptor is induced by low-dose eryrthromycin that enhances the phase-3 MMC, whereas the "muscle" receptor is stimulated by higher doses of the drug that trigger sustained antral contraction and inhibit MMCs. Thus, drug effects may be influenced by the nature of the underlying disorder. In one study, the use of low doses of erythromycin resulted in the induction of phase-3 MMCs in neonates with > 32 weeks' gestation but not in those who were more premature. The authors concluded that early drug administration may not be useful in very preterm infants, but it may be partially useful in older preterm infants and full-term infants. In another study performed in very preterm infants, in whom MMCs were not present, researchers found that non-propagating antral clusters of contractions were significantly increased, indicating the presence of functioning motilin receptors in preterm neonates and effects other than the enhancement of phase-3 MMCs on the gastrointestinal tract.[19]

Our results confirmed previous findings that low-dose erythromycin is effective in reducing the time taken to reach full enteral feeding. The gestational age of our infants in the erythromycin group was 30–33 weeks. Moreover, to reach an acceptable serum concentration, low-dose erythromycin must be used in an efficient amount in order to demonstrate a prokinetic effect. We used a low dose of 6 mg/kg/day, which resulted in a clinically significant beneficial effect. As observed in most studies using oral erythromycin, no instances of cardiac arrhythmias were noted in our study as well.[13,14] Intravenous administration of erythromycin, however, may be dangerous because all potential life-threatening cardiac events have occurred with this form of the drug.[19]

Although many clinicians prefer to use erythromycin as a rescue rather than as a prophylactic treatment, this study has revealed that the drug can be used prophylactically. A large number of preterm neonates develop feeding intolerance, especially during the first days of life, and no potential adverse effect has been reported when low doses of oral erythromycin are used. Prophylactic use can be considered an appropriate option, provided further randomised controlled trials can confirm the results of our study. A placebo was not administered to the control group in our study, as a suitable one was not available. This was a problem in the majority of the previous studies. Normal saline or dextrose water was used as a placebo in some trials. Since these are different from erythromycin in colour and odour, further studies should seek to find a better alternative placebo.

In summary, our data indicates that prophylactic low-dose oral erythromycin effectively reduces the time required to reach full enteral feeding in stable preterm infants weighing between 1,000–1,500 g. In addition, we found that low doses of the drug are safe, as no infant developed any potential adverse effects such as pyloric stenosis or cardiac dysrythmias. However, more extensive research is required before the routine use of prophylactic low-dose oral erythromycin can be recommended for preterm infants in neonatal intensive care units.

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