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Original Article

Oral erythromycin for treatment of gastrointestinal dysmotility in premature infants

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Abstract

Background Functional immaturity of gastrointestinal (GI) motility predisposes preterm infants to feeding intolerance. Erythromycin as a prokinetic agent has been given to preterm infants for the management of non-obstructive GI dysmotility.

Objective To evaluate the efficacy of oral erythromycin for the treatment of GI dysmotility in preterm infants.

Methods A randomized controlled clinical trial was done at Adam Malik Hospital and Pirngadi Hospital, Medan, between October 2004 – March 2005. Fifty preterm infants with feeding intolerance were randomly assigned to either receive oral erythromycin (12.5 mg/kg, every 6 hours) or placebo for 7 days. Improved tolerance for enteral feedings was evaluated by the amount of gastric residue before feeding.

Results On the sixth day, there was a significant difference in the amount of residue from gastric residue between the oral erythromycin group and placebo group (mean 21.7 and 29.4; $P<0.05$) and so were results on the seventh day (mean 14.1 and 26.9; $P<0.05$).

Conclusion Oral erythromycin reduces the amount of gastric residue before feed in premature infants. **[Paediatr Indones 2007;47:234-237]**.

Keywords: *erythromycin, gastrointestinal dysmotility, preterm infants*

Gastrointestinal (GI) dysmotility, a common problem in preterm infants is thought to be due to immature nerves and muscle control of the GI tract which predisposes them to feeding intolerance.[1,2] Preterm infants usually take several days to tolerate full enteral feeding.[3] The slow advancement often leads to complications such as necrotizing enterocolitis and insufficient weight gain.[4]

Various medications have been used to enhance the coordination and propulsive movement of GI tract in preterm infants.[5,6] Prokinetic therapy might improve gastrointestinal motility in preterm infants after anatomical obstruction of the GI tract has been excluded.[7] Erythromycin, a prokinetic agent,[8,9] is a potent analogue of the gastrointestinal hormone motilin.[10] This hormone stimulates gastric emptying and induces phase 3 migrating motor complexes in the proximal intestine which are responsible for the transit of luminal contents through the gut.[11-13] Ng *et al*[7] reported that preterm infants with feeding

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intolerance due to non-anatomically obstructive gastrointestinal dysmotility achieved full enteral feeding significantly earlier after treatment with oral erythromycin. We conducted a randomized, double blind, placebo-controlled trial to evaluate the efficacy of oral erythromycin for treatment of GI dysmotility in preterm infants.

Methods

We studied premature infants admitted to the neonatal unit at H. Adam Malik Hospital, Medan and Pirngadi Hospital, Medan between October 2004 – March 2005. The inclusion criteria were: gestational age below 36 weeks (Ballard criteria) who had feeding intolerance defined as >50% gastric residue before feed. Written parental consent was obtained. Preterms with asphyxia, cyanotic heart disease, previous GI surgery, or other congenital GI anomalies were excluded.

The enrolled subjects were randomly assigned into treatment and control group by block randomization. All infants received milk feeding on the 2nd hour of life via nasogastric tube. The protocol used for advancement of feeding amount is depicted in **Figure 1**. Infants allocated to receive active drug were given oral erythromycin ethyl-succinate 12.5 mg/kg, every six hours for seven days (Erythrocin granules 200 mg/5 ml, Abbott Indonesia). The placebo solution was the equivalent volume of normal saline. The drug and normal saline were both mixed thoroughly into the milk to mask their appearance from the attending clinical team. Administration of other prokinetic agent (cisapride, metoclopramide) and antibiotic drugs were not allowed during the study period. This procedure was performed by two designated staffs not involved in the clinical management of these infants and who were not aware that the feeding patterns would later be studied. In addition, the oral drug was identified only by a code number to ensure effective blinding. Another staff not involved in clinical care performed the randomization.

Full enteral feeding was defined as the point when milk intake of 150 ml/kg/day was achieved. If abdominal distension, bloody stools or other primary clinical signs of necrotizing enterocolitis were present, the feeding would be withheld until recovery.

	Amount of cow's milk formula given (ml/kg/day)				
Day	1	2	3	4	5
Body Weight (g)					
≥1500	60	80	100	120	150
<1500	80	100	120	140	150

Figure 1. Protocol used for advancement of feeding[14]

We used SPSS for WINDOWS 10 (SPSS Inc, Chicago) for all statistical computations. Analysis for differential in characteristics of sex, mode of delivery, gestational age between the two groups were based on independent t-test. Birth weight, Ballard scores, Apgar scores, temperature and gastric residue with Pearson chi square. Significance level was set at $P<0.05$.

Results

Fifty eligible preterm infants were randomly assigned to the two treatment groups, divided into 25 infants for oral erythromycin and 25 infants for placebo group. There was no significant difference between the two groups in terms of sex, mode of delivery, gestational age, or birth weight (**Table 1**).

There was also no significant difference in terms of birth weight, Ballard scores, perinatal asphyxia indices, and temperature **(Table 2)**.

On the sixth and seventh days, the mean differences between the amount of gastric residue between the two groups was significant (**Table 3**).

Table 1. Demography of the participating infants

Characteristics	Oral erythromycin	Placebo
Sex		
Boy	15/25	11 /25
Girl	10/25	14 /25
Mode of delivery		
Vaginal	13/25	18/25
Caesarean section	12/25	7/25
Gestational age (weeks)		
26-	0	2/25
28-	6/25	3/25
30-	8/25	8/25
32-	7/25	12/25
34-36	4/25	0

Table 2. Baseline characteristics of the participating children

Characteristics	Oral erythromycin (n=25)	Placebo (n=25)
Birth weight (g) Mean, (SD)	1862 (377.2)	1744 (317.3)
Ballard scores; Mean (SD)	18.9 (3.9)	19.1 (4.2)
Apgar scores; Mean (SD)		
1 min	7.8 (0.4)	7.8 (0.5)
5 min	9.8 (0.4)	9.7 (0.4)
Temperature (°C) Mean (SD)	36.7 (7.0)	36.7 (0.1)

Table 3. The amount of gastric residue between treated and control group (mean, SD)

Day	Oral erythromycin group	Placebo group	P
	Mean (SD)	Mean (SD)	
I	51.5 (10.3)	50.6 (12.2)	0.78
II	42.2 (10.5)	42.5 (12.1)	0.93
III	37.4 (8.6)	39.1 (12.0)	0.56
IV	31.6 (8.2)	36.7 (12.8)	0.10
V	28.2 (6.7)	34.6 (17.1)	0.09
VI	14.1 (5.6)	26.9 (22.9)	0.02*
VII			0.009*

Discussion

We have shown that oral erythromycin could increase gastric motility in premature infants with intestinal dysmotility.

Stenson *et al*[3] doubted the benefit of erythromycin in the introduction of enteral feeding. Erythromycin was successful as a prokinetic agent in young infants with intestinal dysmotility, but its role in preterm infants is less clear. After erythromycin infusion, infants <30 weeks gestation have shown increased gastric motility but not increased duodenal motility. Intragastric erythromycin induced migrating motor activity in infants beyond 32 weeks of gestation but not in less mature infants.[3]

Despite some reports suggesting immaturity and a paucity of migrating contractile activity in infants below 32 week gestation, Ng *et al*[7] summarized that premature infants with non-anatomically obstructive gastrointestinal dysmotility achieved full enteral feeding significantly earlier after treatment with oral erythromycin (12.5 mg/kg/6 hours).

Madani[4] shows that premature infants over 32 weeks gestation benefit from oral erythromycin for better milk tolerance, no adverse reactions, and shorter hospital stay. They compared gastric and duodenal contractions for 30 minutes before and after the initiation of erythromycin, and proved the antral motility index increased 4-fold indicating the presence of functioning motilin receptors in preterms neonates.[15] In our study, we found that on the 6th and 7th days there were significantly decreasing amounts of gastric residue in infants receiving oral erythromycin.

The potent prokinetic action of erythromycin has been shown to act principally at the level of the stomach and the proximal small bowel in both human and animal studies. Erythromycin exerts its gastrointestinal motor effects through activation of the neural motilin receptors on cholinergic neurons and the smooth muscle motilin receptors of the upper GI tract. Stimulation of the motilin pathway results in greater amplitude and more frequent antral contractions, an increase in proximal gastric tone, suppresion of pyloric pressure waves, which is associated with reduced pyloric outlet resistance, and an increase in duodenal contraction frequency. In fact, the distribution pattern of motilin in the GI tract at 20 weeks gestation closely resembles adult patterns, and the development of the gastrointestinal neuroendocrine network is almost complete by 25 weeks gestation. It has also been shown that infusion of exogenous motilin may promote an earlier appearance of the migrating motor complex, and the introduction of enteral feeding to the neonatal gut has resulted in premature detection of phase III motor activity than would normally be expected for the gestational age. These studies illustrate that preterms are already equipped with the necessary anatomical and physiological apparatus at a very early gestation, and it is possible that erythromycin, act on motilin receptors and enhance upper GI motility.[15,16]

Recently, enteral feeding initiated soon after birth in prematures resulted in more rapid achievement of full feedings and weight gain and no increase in necrotizing enterocolitis. Milla[1] demonstrated that normal migratory motor complexes develop in preterm infants within three weeks of initiating regular feedings.[1] We performed this study for only one week based on former reviews that erythromycin is effective within 1 week of treatment.[3]

The oral route of drug administration was preferred since all life threatening complications related to erythromycin are associated with the parenteral route.[2,7] The peak serum concentration in iv infusion is 4-10 times higher than that by oral route and the safe dosage limit of iv erythromycin in preterm infants has not been determined. With regard to the dose of oral erythromycin,

we opted to use a higher dose (12.5 mg/kg/dose) than the lower dose regimen (3-5 mg/kg/dose) commonly used for the management of gastrointestinal dysmotility because (a) previous cases in similar situation indicated that the higher dosage was effective, (b) in former studies using a lower dose regimen often required large intravenous loading dose of erythromycin (15-30 mg/kg/day) for the initial few days.[7]

Patole *et al*[15] thought the significant variations of erythromycin as a prokinetic in preterm neonates made it difficult to reach clear conclusions or recommendations. Researchers suggested that neonatologists should limit the use of erythromycin as a rescue rather than prophylactic therapy. Although in our study oral erythromycin was safe, we also caution against prophylactic or routine use in preterms.

In conclusion, we found significantly less amount of gastric residue on the 6th and 7th days in premature infants receiving oral erythromycin. Further studies with a larger sample would be needed.

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