

## Efficacy of oral erythromycin to enhance feeding tolerance in preterm infants

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### Abstract

**Background** Feeding intolerance is a common condition that affects preterm infants. Erythromycin is a prokinetic agent used to treat feeding intolerance, but its efficacy remains inconclusive.

**Objective** To evaluate the effectiveness of oral erythromycin to enhance feeding tolerance in preterm infants.

**Methods** This prospective, randomized controlled trial in preterm infants was conducted at Sanglah Hospital, Denpasar, Bali, from June 2015 to January 2016. Eligible infants were randomized to receive either 12.5 mg/kg/dose oral erythromycin or a placebo, every 8 hours. The primary outcome was the time to establish full enteral feeding. The secondary outcomes were body weight at full enteral feeding and length of hospital stay.

**Results** Of 62 initial subjects, 3 infants dropped out of the study. Thirty infants were given erythromycin and 29 infants were given placebo. The baseline characteristics of the two groups were similar, with mean of gestational ages of 31.4 (SD 1.7) weeks in the erythromycin group and 32.4 (SD 2.2) weeks in the placebo group. The median times to reach full enteral feeding did not significantly differ between the two groups, with 10 (SD 5.3) days in the erythromycin group vs. 8 (SD 6.5) days in the placebo group ( $P=0.345$ ). Also, median body weights at full enteral feeding and lengths of hospital stay were not significantly different between the two groups.

**Conclusion** Erythromycin of 12.5 mg/kg/dose every 8 hours as prophylactic treatment does not significantly enhance feeding tolerance in preterm infants. Median body weights at full enteral feeding and length of hospital stay are not significantly different between the erythromycin and placebo groups. [Paediatr Indones. 2017;57:154-9 doi: <http://dx.doi.org/10.14238/pi57.3.2017.154-9>].

**Keywords:** erythromycin; feeding intolerance; preterm infants

Feeding intolerance is a common problem in managing preterm infants. Feeding intolerance presents as gastric residual, regurgitation, recurrent vomiting, or abdominal distention, in severe cases. Feeding intolerance leads to poor weight gain, longer hospital stay, and potential hospital-acquired infection, due to central inserted catheter (umbilical catheter, central venous catheter, percutaneous inserted central catheter), and long-term parenteral nutrition. The most common cause of feeding intolerance is low gut motility due to prematurity.<sup>1,2</sup>

Prokinetics are commonly used to treat feeding intolerance in preterm infants. The most widely used prokinetics are metocloperamide, cisapride, and domperidone. Some serious adverse effects have been related to these prokinetics, such extrapyramidal reactions and lethargy with metocloperamide and QT interval widening with cisapride. In addition, the use of domperidone in preterm infants remains controversial.<sup>3,4</sup>

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Erythromycin is an antibiotic also commonly used to treat feeding intolerance in preterm infants. This macrolide has a motilin-like effect and stimulates peristalsis.<sup>1,5</sup> Erythromycin works as a motiline agent, by binding to the motiline receptor at the antrum and upper duodenum and leading to increased contractions in the antrum.<sup>4,6</sup> The motiline hormone stimulates the gastric emptying process and induces phase III of migrating motor complexes (MMC) in the proximal intestine, reducing transit time in the intestine.<sup>7,8</sup> This process is not achieved until 32 weeks of gestational age.<sup>9,10</sup> Some studies in infants with intestinal dysmotility showed benefits from erythromycin,<sup>9,11,12</sup> while others gave inconsistent results.<sup>13,14</sup> We aimed to assess the efficacy of high-dose erythromycin (12.5 mg/kg) as prophylactic management to enhance feeding tolerance in preterm infants, compared to a placebo.

## Methods

This randomized controlled trial was done in preterm infants at 28 to <37 weeks gestational age and admitted to the Neonatology Ward, Sanglah Hospital, Denpasar, Bali, from June 2015 to January 2016. Subjects were randomized into two groups: one group was given a high dose of erythromycin (12.5 mg/kg t.i.d.) and the other group was given a placebo).

The sample size was calculated to be 25 per group, for 5% significance level ( $\alpha$ ) and 80% power ( $\beta$ ), based on ORs from a previous study.<sup>7</sup> Using a 10% estimate of lost-to-follow up, the minimum required sample size was calculated to be 60 subjects.

Study subjects were recruited by consecutive sampling until the minimum sample size was achieved. Exclusion criteria were: children with intestinal bleeding, necrotizing enterocolitis, major congenital anomaly, previous history of abdominal surgery, or referred to another center. Block randomization was performed using computer software (SPSS 20.0 for Mac), sealed, and kept in the Pharmacy Division until the study ended.

The treatment group was given high-dose, oral, erythromycin (12.5 mg/kg) every 8 hours while the control group was given a placebo. Erythromycin syrup and placebo syrup were prepared by the Pharmacy Division of Sanglah Hospital. Both preparations

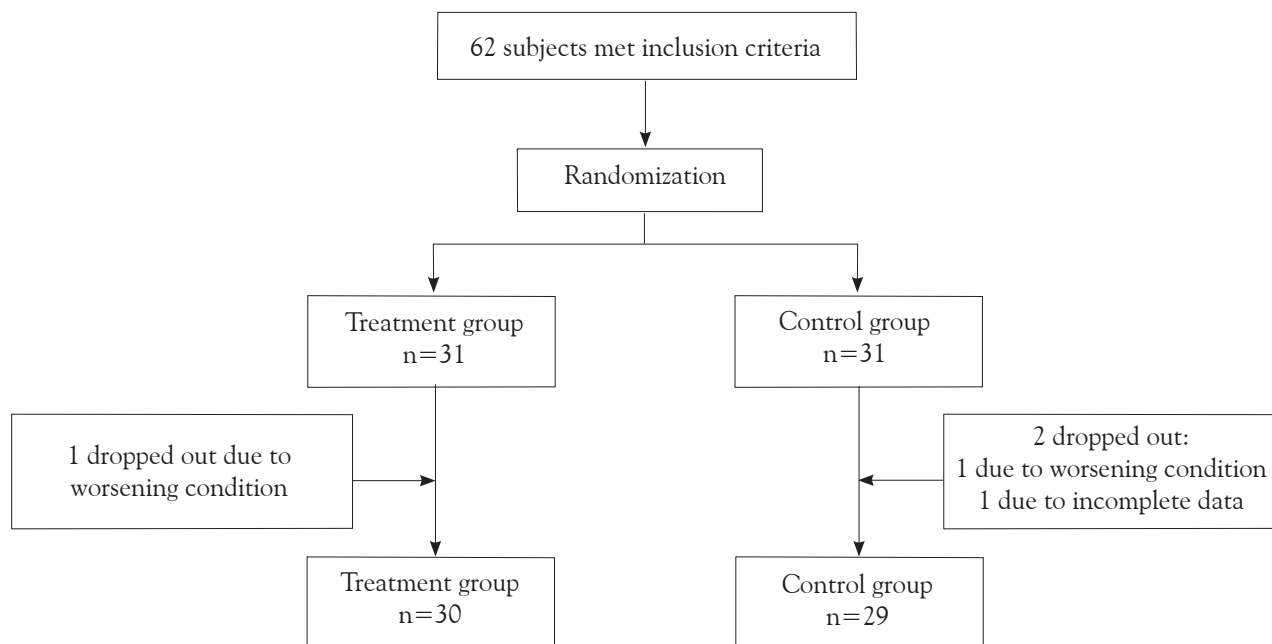
were similar in color and labeling. The investigators, clinicians, nurses, and parents were blinded to the contents during the study. Intervention was started from the initial feeding and continued until full enteral feeding was achieved. Complications such sepsis and necrotizing enterocolitis, as well as secondary outcomes of body weight when the full enteral feeding achieved, and length of stay were noted. Any adverse effects such as diarrhea, arrhythmia, and pyloric stenosis hypertrophy were noted in all subjects. Infants with serious adverse events were dropped from the study, and treated accordingly. This study was approved by the Ethics Committee of Sanglah Hospital, Denpasar. Subjects' parents provided written informed consent.

Characteristics of subjects, adverse events, and data on full enteral feeding were collected and shown in tables. Associations of time taken for full enteral feeding, body weight when full enteral feeding was achieved, length of hospital stay, and the intervention were analyzed using Mann-Whitney U test, due to non-normal distribution of data. Analyses were performed with SPSS 16.0 software.

## Results

A total of 62 subjects enrolled in the study. Three subjects dropped out: two infants in the treatment group due to worsening of condition or incomplete data during analysis, and one subject in the placebo group due to worsening condition. The remaining 59 subjects were analyzed, 30 subjects in the treatment group and 29 subjects in the control group, as seen in the flow chart in **Figure 1**.

Subjects' characteristics were similar between groups (**Table 1**). There were more males in the treatment group than in the placebo group. Modes of delivery were similar in both groups. Gestational age was younger in the treatment group than in the placebo group [31.4 (SD 1.7) vs. 32.4 (SD 2.2) weeks, respectively]. Mean birth weight was similar in both groups (about 1,550 grams). The placebo group had 3 small-for-gestational age infants and the treatment group had none. Severe asphyxia was higher in the treatment group (9/30) compared to the placebo group (2/29). Ventilator support was higher in the treatment group (10%) compared to the placebo group (6.9%).



**Figure 1.** Study flow chart

**Table 1.** Subjects' characteristics

Characteristics	Group	
	Treatment (n=30)	Placebo (n=29)
Male gender, n	18	13
Mean birth weight (SD), grams	1,549 (270)	1,543 (288)
Intrauterine growth parameter		
Appropriate-for-gestational age	30	26
Small-for-gestational age	0	3
Mean gestational age (SD), weeks	31.4 (1.7)	32.4 (2.2)
Delivery mode, n		
Vaginal	14	15
Cesarian section	16	14
Severe asphyxia, n		
Yes	9	2
No	21	27
Oxygen support, n		
No oxygen	4	4
CPAP	23	19
High-flow nasal cannula	0	4
Ventilator	3	2
Nutritional support, n		
Breast milk	15	13
Formula	3	4
Breast milk and formula	12	12

Continuous positive airway pressure (CPAP) support was also higher in the treatment group (76.7%) compared to the placebo group (65.5%).

Similar characteristics of sepsis, initial time for trophic feeding, feeding intolerance, diarrhea,

hypertrophic pyloric stenosis, and arrhythmia were found in both groups, as shown in **Table 2**.

Median full enteral feeding was achieved faster in the placebo group than in the treatment group, but the body weight when full enteral feeding was achieved

**Table 2.** Complications and adverse events

Complications	Group		P value*
	Treatment (n=30)	Placebo (n=29)	
Sepsis (clinical, culture), n	16	20	0.288
Mean initial time for trophic feeding (SD), days	4.6 (3.1)	6.0 (6.6)	0.286
Vomiting, n	4	2	0.671
Gastric residual, n	7	5	0.748
Diarrhea, n	0	0	0
Hypertrophic pyloric stenosis, n	0	0	0
Arrhythmia, n	0	0	0
Cholestasis, n	1	7	0.026

\*Chi-square tests

was higher in the treatment group. Length of hospital stay was longer in the treatment group compared to the placebo group. However, none of these differences were statistically significant, as shown in **Table 3**.

**Table 3.** Analysis of time taken to full enteral feeding, body weight at full enteral feeding, hospital length of stay, and interventions

Complications	Group		P value*
	Treatment (n=30)	Placebo (n=29)	
Time taken until full enteral feeding, day			
Median (interquartile range)	10 (5.3)	8 (6.5)	0.345
Minimum – maximum	2-34	2-39	
Median body weight at full enteral feeding, grams (interquartile range)	1,600 (283.0)	1,540 (433)	0.305
Length of hospital stay, days			
Median (interquartile range)	25.5 (24.0)	24.0 (20)	0.710
Minimum – maximum	4-68	9-8.6	

**Table 4.** Time to achieve full enteral feeding according to gestational age, enteral nutrition, and history of severe asphyxia

Variables	Mean time to achieve full enteral feeding (SD), days	
	Treatment (n=30)	Placebo (n=29)
Median enteral nutrition		
Breast milk	9.0 (4.9)	10.0 (6.1)
Formula	6.0 (7.3)	8.0 (10.8)
Breast milk + formula	11.0 (9.0)	10.0 (8.4)
Median gestational age		
≤ 32 weeks	11.0 (9.6)	11.0 (8.2)
> 32 weeks	8.0 (6.1)	9.0 (6.5)
Severe asphyxia		
Yes	13.0 (9.6)	13.0 (10.5)
No	8.0 (7.0)	9.0 (4.2)

Subjects given formula achieved full enteral feeding faster than subjects given breast milk exclusively or a combination of breast milk and formula in both the treatment and placebo groups. Subjects with gestational age >32 weeks also achieved full enteral feeding faster compared to subjects with lower gestational age, in both groups. Subjects with severe asphyxia took longer to achieve full enteral feeding compared to subjects without severe asphyxia, in both groups, as shown in **Table 4**.

## Discussion

Past studies have evaluated the efficacy of erythromycin as a prokinetic in preterm infants, be it therapy or prophylaxis. In this study, high-dose erythromycin was given as prophylaxis for feeding intolerance to preterm

infants with gestational age less than 37 weeks. No sub-group analysis for gestational age was made due to the large sample size and long period of study required for such analyses.

Baseline characteristics of subjects were similar between groups. Sub-group analysis for enteral feeding revealed that subjects given formula achieved full enteral feeding faster than subjects given breast milk. This result may have been due to lack of available breast milk in the first few days after admission, since our hospital does not have breast milk bank. As such, the initial time for trophic feeding in breast milk subjects may have been delayed.

Full enteral feeding was achieved faster in the

placebo group than the treatment group (8 vs. 10 days, respectively), but this result was not significant. Studies with low-dose erythromycin as a prokinetic have had inconsistent results. Previous studies found that low-dose erythromycin gave no prophylactic benefit in infants born at <32 weeks with feeding intolerance.<sup>9,11</sup> In contrast, Oei *et al.* found that low-dose erythromycin (2.5 mg/kg q.i.d) was beneficial as a prophylactic against feeding intolerance,<sup>14</sup> with significantly shorter time to reach full enteral feeding in the treatment group than in the placebo group [6.0 (SD 2.3) vs. 7.9 (SD 3.5) days, respectively]. This difference may have been due to different sample sizes and methods among studies.

Inconsistent results were found in some studies about the use of erythromycin as a rescue protocol in feeding intolerance in preterm infants. Most studies have shown a benefit with high-dose erythromycin (>10 mg/kg t.i.d.),<sup>12,15,16</sup> but no significant benefit with low-dose erythromycin, in management of feeding intolerance.<sup>7,17,18</sup> One study found a significant benefit with high-dose erythromycin (12.5 mg/kg q.i.d) compared to placebo for treating feeding intolerance in preterm infants with birth weight <1,500 grams [13.5 (8-22) vs. 25 (16-33) days, respectively].<sup>5</sup> Also, Madani *et al.* reported that a significant benefit was found in preterm infants >32 weeks who took high-dose erythromycin (12.5 mg/kg q.i.d) compared to placebo.<sup>2</sup> Similarly, Aly *et al.* found a significant benefit in preterm infants >32 weeks [10.5 (4.1) vs. 16.3 (5.7) days, respectively, with low-dose erythromycin (1 mg/kg t.i.d) compared to placebo.<sup>1</sup> Furthermore, a Jakarta study found no significant difference in the use of low-dose erythromycin (3 mg/kg q.i.d.) in preterm infants compared to placebo.<sup>4</sup>

In this study, we found no significant difference in the use of high-dose erythromycin as prophylaxis for feeding intolerance in preterm infants <37 weeks, compared to placebo. Two types of motilin receptors (neural and smooth muscle) have been found and the efficacy of erythromycin depends on the dose and gestational age.<sup>6,12</sup> Low-dose erythromycin (1-3 mg/kg) can stimulate neural motilin receptor (cholinergic nerves of the gut at both preganglionic and postganglionic levels) and induce phase III of MMC. But the motilin receptor in smooth muscle can only be stimulated by high-dose erythromycin.<sup>6,12,13</sup> The MMC is immature before 32 weeks of gestation.

Higher dose erythromycin is needed in preterm infants <32 weeks gestational age to stimulate antrum contraction and antro-duodenal coordination.<sup>11,13</sup>

We found no benefit of high-dose erythromycin for preventing feeding intolerance in preterm infants. Our findings may have been due to insufficient intestinal dysmotility in our subjects to show the effects of erythromycin. Sub-group analysis showed that preterm infants >32 weeks reached full enteral feeding faster compared to those with gestational age <32 weeks, in both the treatment and placebo groups. We also found that preterm infants in the treatment group had higher body weight at full enteral feeding compared to the placebo group [1,600 (SD 249) vs. 1,540 (SD 269) grams, respectively], but the treatment group also had a longer length of stay [25.5 (SD 24.0) vs. 24 (SD 20.0) days, respectively]. This difference may have been due to the younger gestational age of subjects in the treatment group.

Complications of parenteral nutrition are sepsis and cholestasis. In our study, sepsis and cholestasis were higher in the placebo group. Nevertheless, the placebo group took a shorter time to achieve full enteral feeding, indicating that the sepsis and cholestasis were not related to parenteral feeding. With regards to safety of erythromycin, we found no diarrhea, arrhythmia, or hypertrophic pyloric stenosis in the treatment group, similar to other studies.<sup>16,19,20</sup>

Long-term erythromycin can change the normal intestinal flora, with high-dose or therapeutic doses leading to diarrhea and sepsis.<sup>21,22</sup> However, Ng found no intestinal microorganism changes after the use of erythromycin for 10 days and 4 weeks. He also found no infection or necrotizing enterocolitis outbreaks during the 69-month study.<sup>12</sup> We did not examine our subjects' intestinal microorganisms before or after erythromycin.

In conclusion, no significant differences in the time to reach full enteral feeding, Body weight when full enteral feeding is achieved, or length of stay are observed in the use of high-dose erythromycin as a prophylactic for feeding intolerance in preterm infants compared to placebo. Further study with sub-groups of various gestational ages can give us a better understanding of the efficacy of erythromycin as a prophylactic for feeding intolerance in preterm infants. A study on changes in intestinal normal flora

after erythromycin use is also needed.

## Conflict of Interest

None declared.

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