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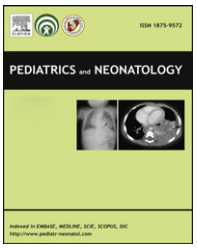

ORIGINAL ARTICLE

Efficacy of Intermediate-Dose Oral Erythromycin on Very Low Birth Weight Infants With Feeding Intolerance

Yan-Yan Ng [a], Pen-Hua Su [a,b], Jia-Yuh Chen [a,b,*], Yeak-Wun Quek [a], Jui-Ming Hu [a,c], Inn-Chi Lee [a], Hong-Shen Lee [b,d], Hua-Pin Chang [c,e]

[a] *Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan*
[b] *School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[c] *Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[d] *Department of Public Health, Chung-Shan Medical University, Taichung, Taiwan*
[e] *Department of Nursing, Chung Shan Medical University Hospital, Taichung, Taiwan*

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Key Words
feeding intolerance;
oral erythromycin;
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Background: Erythromycin is generally used as a prokinetic agent for the treatment of feeding intolerance in preterm infants; however, results from previous studies significantly vary due to different medication dosages, routes of administration, and therapy durations. The effectiveness and safety of intermediate-dose oral erythromycin in very low birth weight (VLBW) infants with feeding intolerance was examined in this study.
Methods: Between November 2007 and August 2009, 45 VLBW infants with feeding intolerance, who were all at least 14 days old, were randomly allocated to a treatment group and administered 5 mg/kg oral erythromycin every 6 hours for 14 days ($n = 19$). Another set of randomly selected infants was allocated to the control group, which was not administered erythromycin ($n = 26$).
Results: The number of days required to achieve full enteral feeding (36.5 ± 7.4 vs. 54.7 ± 23.3 days, respectively; $p = 0.01$), the duration of parenteral nutrition ($p < 0.05$), and the time required to achieve a body weight $\geq$2500 g ($p < 0.05$) were significantly shorter in the erythromycin group compared with the control group. The incidence of parenteral nutrition-associated cholestasis (PNAC) and necrotizing enterocolitis (NEC) $\geq$ stage II after 14 days of treatment were significantly lower ($p < 0.05$) in the erythromycin group. No significant differences were observed in terms of the incidences of sepsis, bronchopulmonary dysplasia, or retinopathy of prematurity. No adverse effects were associated with erythromycin treatment.

* Corresponding author. Department of Pediatrics, Chung Shan Medical University Hospital, No. 110, Chien-Kuo N. Road, Section 1, Taichung 402, Taiwan.
E-mail address: jen@csh.org.tw (J.-Y. Chen).

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Conclusions: Intermediate-dose oral erythromycin is effective and safe for the treatment of feeding intolerance in VLBW infants. The incidences of PNAC and $\geq$ stage II NEC were significant lower in the erythromycin group.

1. Introduction

Premature, very low birth weight (VLBW) infants frequently develop feeding intolerance. Neonatologists often choose to withhold feeding or hesitate to advance daily feeding volumes in these neonates. Full enteral feeding, with the aim of delivering a total daily fluid intake of 150 mL/kg/day, is difficult to achieve. Inadequate caloric intake can result in postnatal growth restriction and hasten the complications of parenteral nutrition.[1]

Although the exact mechanisms remain unclear, macrolide antibiotic erythromycin has been used for decades as a prokinetic agent to facilitate the advancement of enteral feeding in preterm infants. Data from previous clinical trials are inconsistent, possibly due to variations in times and routes of erythromycin administration, as well as varying durations of erythromycin therapy.[2,3]

In the past, metoclopramide or domperidone have been prescribed to treat feeding intolerance in premature infants. However, we were unable to treat refractory gastrointestinal motility in a VLBW infant until intermediate-dose oral erythromycin was administered on postnatal day 78. The time required to reach full enteral feeding after beginning erythromycin therapy was 15 days. No adverse effects were noted. Consequently, this prospective study was conducted to determine the effectiveness and safety of intermediate-dose oral erythromycin in VLBW infants with feeding intolerance.

2. Patients and Methods

2.1. Patients

This study was approved by the institutional review board of Chung Shan Medical University Hospital. Informed consent was obtained from all parents before the study was initiated. The trial was conducted at the neonatal intensive care unit (NICU) of Chung Shan University Hospital. Infants were eligible for this study if they met the following criteria: (I) gestational age $<$32 weeks, (II) birth body weight $<$1500 g, (III) had been receiving $<$50% of the total daily fluid intake or $<$75 mL/kg/day of milk via oral feedings after 14 days of life (DOL). Infants were excluded from this study if they had major congenital malformations, such as congenital heart disease (except persistent patent ductus arteriosus or patent foramen ovale), gastrointestinal anomalies, hypoxic injury, current or previous history of necrotizing enterocolitis (NEC) within 7 days of the onset of feeding intolerance, or suspected or confirmed sepsis. The administration of other prokinetic agents or probiotics was not allowed in the erythromycin group during the study period.

2.2. Sample size

The sample size was calculated based on the primary outcome, i.e., the time required for the infant to tolerate a full feeding. Our unit statistics revealed a consistently high prevalence of milk intolerance in preterm VLBW infants during the 2 consecutive years before this study was initiated. The mean total time required to tolerate a full enteral feedings in our unit was 50 days. Assuming that the median time to full feeding was 33 days in the erythromycin group, with an α-error of 0.05 (two-tailed) and a power of detection of 0.9, a sample size of 30 subjects (15 in each group) was required.

2.3. Medication

In the erythromycin group, the infants were given 5 mg/kg of erythromycin estolate (Ulosina in an oral suspension diluted to 20 mg/mL with sterile water; U-Liang Pharmaceutical Co., Ltd., Taiwan) every 6 hours for 14 days. Erythromycin was administered 30 minutes before feeding. Infants in the control group received 2 cc/kg of 5% dextrose water when three feedings were attempted every 3 hours, and then oral milk feedings were initiated. The medications and dextrose water were suspended if oral feedings were discontinued and then resumed afterward.

2.4. Enteral and parenteral nutrition

According to the NICU feeding protocol, parenteral fluids with glucose are required to meet the immediate fluid and energy requirements of all VLBW infants. Parenteral nutrition solutions (e.g., glucose, amino acids, calcium, vitamins, etc.) were started on DOL 2, and a 20% intralipid solution with trace elements of various supplements was supplied on DOL 3. Oral milk feedings were usually started at a volume of 10—20 mL/kg/day as soon as possible and increased to 10—35 mL/kg/day unless feeding intolerance was encountered.

The presence of any one of the following signs indicated feeding intolerance: (I) emesis, (II) increased residual on nasogastric (NG) aspiration ($>$50% of the previous feeding or $>$30% of multiple previous feedings), (III) findings of abdominal distention and tenderness on physical examination, or (IV) the presence of bloody stools.

Milk feedings were administered as a continuous infusion under gravity through an orogastric tube or nasogastric tube every 3 hours. The attending nurse aspirated the stomach once every 3 hours to measure gastric residuals, and the attending clinician would either withhold enteral feeding altogether or discontinue the advancement of feeding if intolerance was noted.

2.5. Statistical analysis

Comparisons of continuous variables were made using two-tailed independent samples, and the Student's *t* test was used to analyze normally distributed data. For comparisons of the categorical data, the Chi-square test and Fisher's exact test were used whenever applicable. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical evaluations and the level of significance was set to $p < 0.05$. All *p* values reported in this trial are two-tailed.

3. Results

A total of 51 patients were initially enrolled in this study, of which 25 were allocated to the erythromycin group and 26 were allocated to the control group. However, three infants were withdrawn from the erythromycin group during the study period due to parental concerns about the adverse effects of the medication. Two infants in the erythromycin group died and were excluded from this study because of parental refusal to allow their infants to receive further treatment after the development of severe intraventricular hemorrhage and periventricular leukomalacia, respectively. Another infant was withdrawn after 1 day of erythromycin treatment following a positive blood culture for *Streptococcus mitis*. Therefore, 45 infants completed the study. Nineteen infants received erythromycin treatment and 26 were observed without erythromycin treatment.

There were no statistically significant differences between the demographic data and clinical characteristics of the two groups (Table 1). Both groups started enteral feedings at a similar mean age.

The clinical outcomes are summarized in Table 2. All infants in the erythromycin group received an unsuspended 14-day course of treatment over the course of the study. In the erythromycin group, the mean time of enrollment in the study was 21.9 ± 7.7 DOL. The mean volume of feeding at enrollment was 24.4 ± 17.3 mL/kg/day. The mean time required to reach full feeding after the beginning of treatment in the erythromycin group was 14.6 ± 4.1 days.

Table 1 Clinical characteristics of the oral erythromycin and control groups.

Clinical characteristics	Oral erythromycin group ($n = 19$)	Control group ($n = 26$)	*p*
Gestational age (wk)	28.4 ± 2.5	28.4 ± 1.9	0.941
Birth weight (g)	1114.8 ± 296.0	1179.5 ± 275.5	0.455
Male : female	9 (47.4%):10 (52.6%)	12 (46.2%):14 (53.8%)	1
Classified as small for the gestational age	3 (15.8%)	1 (3.8%)	0.295
Mode of delivery (NSD:CS)	6 (31.6%):13 (68.4%)	8 (30.8%):18 (69.2%)	1
Surfactant used	9 (47.4%)	16 (61.5%)	0.379
Umbilical arterial catheter	12 (63.2%)	15 (57.7%)	1
duration (d)	3.7 ± 3.7	3.7 ± 3.6	0.974
Umbilical venous catheter	16 (84.2%)	20 (76.9%)	0.667
duration (d)	4.7 ± 3.4	4.8 ± 3.4	0.975
Antenatal dexamethasone	14 (73.7%)	14 (53.8%)	0.222
Apgar score			
1 min	4.9 ± 1.2	4.0 ± 1.8	0.081
5 min	6.6 ± 1.3	6.4 ± 1.4	0.482
Arterial blood analysis			
pH	7.3 ± 0.1	7.3 ± 0.1	0.893
Base excess (mmol/L)	-3.2 ± 3.4	-4.6 ± 3.5	0.196
First hematocrit after delivery (%)	47.1 ± 6.6	45.9 ± 6.6	0.555
Body temperature on admission (°C)	35.4 ± 0.7	35.4 ± 0.7	0.86
CRIB score	4.9 ± 5.0	5.0 ± 2.9	0.967
NTISS	20.6 ± 3.8	20.7 ± 4.1	0.935
Oxygenation index at admission	3.8 ± 3.5	3.7 ± 3.1	0.887
PDA			
At 72 h	9 (47.4%)	13 (50%)	1
Indomethacin	6 (31.6%)	6 (23.1%)	0.734
Ibuprofen	3 (15.8%)	9 (34.6%)	0.191
PDA ligation	2 (10.5%)	4 (15.4%)	1
Type of milk feedings (human milk/ formula milk/mixed)	8 / 4 / 7 (42.1%/ 21.1% / 36.8%)	4 / 5 / 17 (15.4% / 19.2% / 65.4%)	0.099
Age at the beginning of enteral feeding (d)	5.7 ± 3.6	6.0 ± 4.5	0.811

CRIB score = clinical risk index for babies score; CS = cesarean section; NSD = normal spontaneous delivery; NTISS = Neonatal Therapeutic Intervention Scoring System; PDA = patent ductus arteriosus.

Table 2 Comparison of the clinical outcomes of the oral erythromycin and control groups.

	Erythromycin group ($n = 19$)	Control group ($n = 26$)	p
Time enrolled the study (DOL)*	21.9 ± 7.7	20.7 ± 8.3	0.625
Mean volume of feeding at enrollment (mL/kg/d)*	24.4 ± 17.3	34.8 ± 22.9	0.103
Time to full feeding after the beginning of the study (d)*	14.6 ± 4.1	34.0 ± 23.2	0.01†
Time after birth required to achieve half enteral feeding (75 mL/kg/d) (d)	28 ± 7.7	37.5 ± 20.9	0.041†
Time after birth required to achieve 3/4 enteral feeding (115 mL/kg/d) (d)	33.0 ± 7.6	47.2 ± 22.1	0.005†
Time after birth required to achieve full enteral feeding (150 mL/kg/d) (d)	36.5 ± 7.4	54.7 ± 23.3	0.001†
Time required to regain birth body weight (d)	20.7 ± 6.7	24.8 ± 11.1	0.162
Duration of parenteral nutrition (d)	44.7 ± 10.0	63.2 ± 33.9	0.013†
Duration of lipid infusion (d)	24.2 ± 10.5	29.0 ± 15.6	0.253
Duration of mechanical ventilation (d)	33.4 ± 25.5	27.7 ± 25.4	0.462
Duration of O_2 dependence (d)	49.6 ± 32.0	48.7 ± 38.4	0.934
Duration of aminophylline therapy (d)	55.6 ± 23.2	56.1 ± 34.5	0.961
NEC $\geq$ stage IIa	0 (0%)	7 (26.9%)	0.016†
PNAC	2 (10.5%)	10 (38.5%)	0.046†
Sepsis	1 (5.3%)	0 (0%)	0.422
Suspected sepsis (CRP $\geq$2 mg/dL with unstable clinical status)	1 (5.3%)	5 (19.2%)	0.222
IVH			
none or mild	16 (84.2%)	24 (92.3%)	0.636
severe	3 (15.8%)	2 (7.7%)	
ROP with laser therapy	6 (31.6%)	9 (34.6%)	1
BPD	4 (21.1%)	9 (34.6%)	0.507
Time required to achieve body weight $\geq$ 2500 g (d)	80.9 ± 25.9	105.0 ± 40.5	0.037†

*Data presented as median $\pm$ SD (range).
†$p < 0.05$.
BPD = bronchopulmonary dysplasia; DOL = days of life; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PNAC = parenteral nutrition-associated cholestasis (direct bilirubin > 2 mg/dL); ROP = retinopathy of prematurity.

The use of erythromycin was associated with an earlier ability to tolerate full enteral feedings (36.5 ± 7.4 vs. 54.7 ± 23.3 days, respectively; $p = 0.01$). Although there was no significant difference in terms of the number days required to regain birth weight between the groups, the duration of parenteral nutrition (44.7 ± 10 vs. 63.2 ± 33.9 days, respectively; $p < 0.05$) and the time required to achieve a body weight $\geq$ 2500 g (80.9 ± 25.9 days vs. 105.0 ± 40.5 days, respectively; $p < 0.05$) were significantly shorter in the erythromycin group than the control group.

The incidence of parenteral nutrition-associated cholestasis (PNAC) was significantly lower in the erythromycin group (10.5% vs. 38.5%; $p < 0.05$). The incidence of NEC $\geq$ stage II after 14 days of treatment was also lower in the erythromycin group (0% vs. 26.9%; $p < 0.05$).

Physiological dehydration is known to predominate in preterm infants. However, there was no difference in body weight gains between the two groups or the time required to achieve a daily intake of 75 mL/kg/day. A significant increase in weight gain did occur in the erythromycin group during the time required to progress from 75 mL/kg/day to full enteral feeding (15.9 ± 5.1 g/kg/day vs. 11.1 ± 5.9 g/kg/day; $p = 0.007$). The mean body weight of the erythromycin group increased by 14.6 ± 4.3 g/kg/day during the 14 days of treatment (Table 3).

The incidences of sepsis or suspected sepsis, bronchopulmonary dysplasia, and retinopathy of prematurity (ROP) were similar in both groups. None of the typical adverse effects associated with erythromycin treatment, such as cardiac arrhythmia or infantile hypertrophic pyloric stenosis, were encountered over the course of this study.

One infant in the erythromycin group and five infants in the control group had elevated C-reactive protein (CRP) levels (> 2 mg/dL) that were also accompanied by unstable clinical findings; these infants were diagnosed with suspected sepsis. One infant in the erythromycin group

Table 3 Comparison of body weight gains in the erythromycin and control groups.

Body weight gain (g/kg/d)	Erythromycin group ($n = 19$)	Control group ($n = 26$)	p
Before enrollment	0.1 ± 4.5	-1.2 ± 4.0	0.290
Time after enrollment required to achieve full enteral feeding	14.6 ± 4.3	9.4 ± 4.8	0.01*
Time required to achieve half an enteral feeding	3.3 ± 2.7	2.7 ± 2.4	0.387
Time after achieved half enteral feeding	15.9 ± 5.1	11.1 ± 5.9	0.007*

*$p < 0.05$.

developed septicemia related to a peripherally inserted central catheter (PICC). The PICC tip culture, pleural effusion culture, and blood culture were all positive for *Candida parapsilosis*. No bacteria were isolated from the control group.

4. Discussion

Although the fetus is able to swallow amniotic fluid at as early as 11—12 weeks of gestation, many premature neonates (especially VLBW infants) cannot tolerate enteral feedings.[1] The functional immaturity of gastrointestinal motility in premature infants often takes several days or even weeks to resolve. Prolonged hyperalimentation in preterm infants increases the risk of developing cholestatic jaundice, liver impairment, rickets of prematurity, catheter-related septicemia, and postnatal growth restriction.[4—9]

The current clinical approach for the management of feeding intolerance in preterm infants includes withholding feeding, decreasing the amount of milk intake, and diluting enteral fluid mixtures.[1] Reports on medical treatment are, unfortunately, rather limited, as are reports on the efficacy and safety of treatments involving preterm infants.

Cisapride was widely prescribed in the 1980s and early 1990s because of its gastroprokinetic effects, but was withdrawn from the market in 2000 after reports of life-threatening cardiovascular side effects such as prolonged QT interval, ventricular arrhythmia, and torsade de pointes.[10,11] A prospective blinded study by Dubin et al demonstrated a higher risk of a prolonged QTc interval and arrhythmia in preterm infants.[11]

Metoclopramide, a dopamine receptor antagonist, can effectively improving gastrointestinal motility by increasing the pressure of the lower esophageal sphincter, thus enhancing esophageal peristalsis and decreasing the gastric-emptying time. However, the clinical utility of metoclopramide is hampered by its potential extrapyramidal side effects, acute dystonic reactions, and irritability, particularly in children.[12,13]

Domperidone, another dopamine antagonist, acts on the chemoreceptor trigger zone and affects the motor functions of the stomach and small intestine.[14] Unlike metoclopramide, domperidone minimally penetrates the blood-brain barrier and is not believed to exert effects on the central nervous system. Nevertheless, in premature infants, who could potentially have a leaky blood-brain barrier, neurological reactions may occur.[14,15] Several cases of arrhythmias associated with domperidone therapy, including QT interval prolongation, have been reported in infants as well.[16,17] Therefore, domperidone should be used judiciously.

Erythromycin has been studied as a prokinetic agent for over 20 years. A motilin receptor agonist that affects the gut and gallbladder, erythromycin stimulates enteric nerves and smooth muscle, increases antral motility (resulting in strong, nonpropagating gastric contractions), and triggers migrating motor complexes in newborns.[18—21]

Three studies on the use of intravenous (IV) erythromycin as a prokinetic agent in preterm neonates have been reported. As a prophylactic treatment, Stenson et al failed to show any significant differences between IV erythromycin (15 mg/kg/dose every 8 hours) and placebo in terms of the days required to achieve full feedings.[22] Cairns et al reported no significant difference in the time required to establish full enteral feedings when using IV erythromycin (3 mg/kg/day every 6 hours) as a rescue therapy.[23] A preliminary observation by Su et al indicates a good response to erythromycin treatment in VLBW infants with feeding intolerance, as assessed by the daily net orogastric balance after an IV loading dose of 30 mg/kg/day was administered over a 3-day period followed by a maintenance dose of 3—5 mg/kg once per day until full feedings (100 mL/kg/day) were established.[24]

Using oral erythromycin as a prophylactic prokinetic agent, Oei et al reported that low-dose erythromycin (2.5 mg/kg every 6 hours) effectively facilitates enteral feeding.[25] Nonetheless, in a study by Patole et al, prophylactic oral erythromycin at a dose of 12 mg/kg every 6 hours (48 mg/kg/day) failed to reduce the time required to establish full enteral feedings in preterm neonates who were <32 weeks of age ($p = 0.60$).[26]

Aly et al demonstrated that earlier full enteral feedings, fewer episodes of gastric residuals, and a shorter duration of parenteral nutrition result from the use of low-dose erythromycin (1 mg/kg every 8 hours) in infants with a gestational age >32 weeks. No effect was found in infants with a gestational age ≤ 32 weeks.[27]

Nuntnarumit et al studied intermediate-dose erythromycin therapy (10 mg/kg every 6 hours for 2 days, followed by 4 mg/kg every 6 hours for another 5 days) in preterm infants who were ≤ 35 weeks and observed a decrease in the time required to establish full enteral feedings compared with placebo ($p < 0.001$).[28] However, these infants were enrolled at an earlier age (DOL 6—8) compared with our study population, and the effectiveness of Nuntnarumit et al's protocol on infants with severe feeding intolerance remains unclear.

In a large randomized control trial, Ng et al demonstrated that infants treated with high-dose oral erythromycin (12.5 mg/kg every 6 hours for 14 days) achieved full enteral nutrition earlier than the placebo group ($p < 0.001$) and the duration of parenteral nutrition decreased by 10 days ($p < 0.001$).[29]

In 1999, Honein et al reported a cluster of seven cases of pyloric stenosis that occurred among neonates who had received erythromycin for pertussis prophylaxis.[30] In 2002, a large population-based study by Cooper et al reported that infants treated with erythromycin during the first 2 weeks of life were at an 8-fold increased risk of developing pyloric stenosis; no increased risk of pyloric stenosis was found in infants exposed to erythromycin after DOL 13.[31] Hence, in our study, oral erythromycin was given to infants with feeding intolerance who were >14 days of postnatal age. The association between erythromycin and pyloric stenosis is still not fully understood. The motilinomimetic effects of erythromycin on antral smooth muscle functions, such as the migratory motor complex (MMC), has been proposed.[32] Although MMC does not appear until week 35 of gestation, pyloric stenosis had been reported in an extremely low birth weight infant who was exposed to erythromycin.[21,27,33]

After considering the side effects of the antimicrobial dose of erythromycin (40—50 mg/kg/day) in infants and the poor effects of low-dose erythromycin (3—12 mg/kg/day)

that have been reported previous studies, intermediate-dose oral erythromycin (5 mg/kg every 6 hours for 14 days) was used in our study. Based on the protocol reported by Ng et al in their high-dose erythromycin trial, we administered erythromycin treatment for 2 weeks. The results showed the earlier achievement of full enteral nutrition ($p = 0.001$) and a shorter duration of parenteral nutrition ($p = 0.013$) in the erythromycin group, which is similar to the results obtained by Ng et al.

Parenteral nutrition remains the primary method for treating feeding intolerance in preterm infants; however, PNAC continues to be a major concern in infants who require long-term parenteral feeding. Previous studies indicate that 40—60% of infants on long-term total parenteral nutrition (TPN) will eventually develop hepatic dysfunction.[4] The factors that contribute to the development of PNAC are most likely multifactorial and include the lack of enteral stimulation, recurrent sepsis, intestinal bacterial overgrowth leading to a reduction in gut hormone secretion, and biliary stasis.[4—7]

Using high-dose oral erythromycin, Ng et al demonstrated a lower incidence of PNAC in erythromycin-treated infants compared with placebo-treated infants ($p = 0.03$).[29] Using intermediate-dose oral erythromycin, a significantly lower incidence of PNAC was also noted in our study ($p = 0.046$).

Most previous studies have failed to show any significant differences in the incidence of NEC; however, the study by Patole et al reported NEC $\geq$ stage II resolves after a standardized feeding regimen is implemented.[27—29,34] In our study, no infants in the erythromycin group, but seven infants in the control group, developed NEC $\geq$ stage II. No infants required surgery.

Despite the earlier achievement of full enteral feeding, previous studies have shown no significant difference in the number of days required to regain birth weight, length of hospitalization, and weight at discharge.[27—29] In our study, an earlier achievement of a body weight $\geq$2500 g ($p < 0.05$) was observed in the erythromycin group. Daily weight gain was also significantly improved after erythromycin treatment compared with the control group (Figure 1).

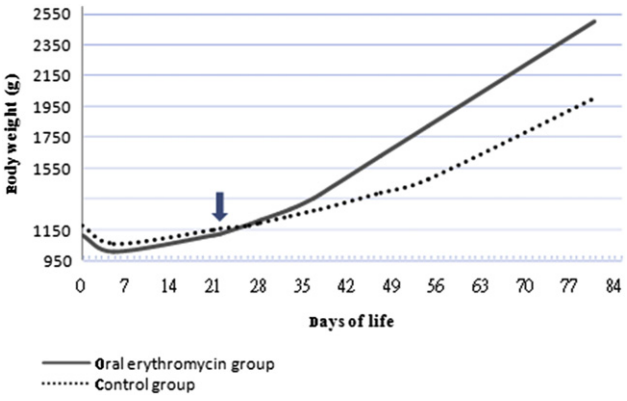

Figure 1 Mean body weight gain of the oral erythromycin and control groups from birth until time required to achieve a body weight $\geq$ 2500 g. Daily weight gain was significantly higher in the erythromycin group compared with the control group. The arrow indicates the mean age of all patients at the beginning of the study.

In conclusion, our findings suggest that oral erythromycin, when administered at 5 mg/kg every 6 hours, may be considered as an adequate, safe, and effective dose to administer for the treatment of feeding intolerance in VLBW infants. However, there are several limitations in this study. First of all, only 45 VLBW infants from a single center were enrolled in this study. The small number of participants may not be representative enough to generalize the findings of this study to all VLBW infants. In addition to the limited sample size, there is the potential for selection bias in trials that are not double blinded. Consequently, a multicenter, randomized, controlled study on the effects of intermediate-dose oral erythromycin on VLBW infants with feeding intolerance is necessary.

Acknowledgments

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