

Role of oral erythromycin for feed intolerance in neonates - A randomized controlled trial

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ABSTRACT

Objective: The objective of this study was to compare the effect of high and low dose of erythromycin with placebo and to determine the efficacy and safety of oral erythromycin for feed intolerance in neonates admitted to the neonatal intensive care unit. **Methodology:** The study was a double-blind, randomized, and placebo-controlled trial. Term and preterm babies having feed intolerance were included in the study, and babies with congenital malformations, necrotizing enterocolitis, and sepsis were excluded from the study. After parental consent, the subjects were randomized into Groups 1, 2, or 3 to receive low-dose (3 mg/kg/dose) or high-dose (10 mg/kg/dose) oral erythromycin estolate or the placebo (equal volume of 5% dextrose). Feeding of all the study neonates was managed as per the unit protocol and babies were monitored for the complications. The primary outcome was the time to reach full feeds of 150 ml/kg/day, without significant gastric residuals. **Results:** Of 58 eligible babies, 84.5% were preterm babies. The median time for reaching full feeds with placebo was 6 days with interquartile range 3–4 days, for high dose was 4 (3–7) days and for low dose 6 (4.3–7) days ($p=0.47$). The total duration of erythromycin for placebo, high-dose, and low-dose group was median days 11 (7–14), 9 (7–13), and 9 (7–14), respectively, with $p=0.86$. There was no difference in the incidence of raised liver enzymes, vomiting, sepsis, and need for intravenous fluids, total parenteral nutrition, and duration of hospital stay between the groups. None of the babies had adverse events such as fatal arrhythmias and pyloric stenosis. **Conclusion:** There was no significant difference in the time to reach full feeds after erythromycin and the duration of study medication between the high-dose and low-dose erythromycin with the placebo group. No adverse effects were seen in any of the groups.

Key words: Adverse effects, Feed intolerance, Neonates, Oral erythromycin

Feed intolerance is a common problem in the neonatal intensive care unit (NICU), more so with preterm infants. It is a major factor affecting duration of hospitalization, results in caloric deprivation and growth restriction requiring prolonged parenteral nutrition and, hence, associated with adverse effects of the same [1].

The etiology of feed intolerance can be (1) physiological - common with prematurity and (2) pathological - associated with sepsis, necrotizing enterocolitis (NEC), idiopathic, surgical, babies on invasive ventilation, and asphyxia. Factors causing feed intolerance in premature infants are immature intestinal motility, digestive enzymes immaturity, consequence of ineffective, infrequent, and uncoordinated bowel activity. This is attributable to the absence of migratory motor complex (MMC), resulting in delayed gastric emptying, and prolonged gastrointestinal transit time. Functional immaturity is also a predominant cause.

The drugs used commonly to establish the full enteral feeds quickly in NICU are metoclopramide and domperidone. Erythromycin is a potent analog of the gastrointestinal hormone motilin. It promotes gastric emptying and induces

intense bursts of Phase III MMC contractile activity in proximal intestine, which are thought to be responsible for the transit of luminal contents through the gut [2-5]. The use of erythromycin as a prokinetic agent has become fairly common in NICUs.

There are studies [6], which conclude, that erythromycin is effective only in >32 weeks and some studies [7-9] have concluded that erythromycin acts as a prokinetic agent in babies with gestation both <32 weeks and >32 weeks in a dose-dependent manner. Studies have used drugs at different doses - high dose (40 mg/kg/day) and the low dose at 3–12 mg/kg/day [10-12] and both as a prophylactic [13-15] and rescue [10-12] and by different routes and have concluded differently. Erythromycin has been also shown to be useful in conditions other than functional immaturity [2,16-20] and in term neonates with feed intolerance. Erythromycin has been used currently in pediatric and in adult age group as an antibiotic. We wish to study the different doses of erythromycin as a prokinetic in both term and preterm neonates and safety of erythromycin as a prokinetic agent in babies with feed intolerance.

MATERIALS AND METHODS

This was a double-blind, randomized and placebo-controlled trial conducted at a Level III NICU. The duration of the study was from January 2009 to June 2010. Institutional ethics committee clearance was taken before starting the study. Neonates (term/preterm) admitted to NICU, having feeding intolerance based on the following inclusion criteria: (1) A neonate having any one of the following for a 24 h period; gastric residuals more than 50% of previous feed on one occasion or >30% of previous feed on more than three occasions or >10% of total daily feed volume [1,14] and (2) the presence of abdominal distension or blood in the stools in the absence of sepsis. Babies with major congenital anomalies, anatomic gastrointestinal abnormalities, and stage 2 or above NEC, treatment with medications such as fentanyl/indomethacin/pancuronium or vecuronium at the onset of feeding intolerance and sepsis, were excluded from the study.

Eligible babies were included after parental consent. Study neonates were screened for the maternal risk factors, which predispose to small for gestational age (SGA) and compromised gut - abruptio placenta, oligohydramnios, non-reactive stress test, and uteroplacental/fetoplacental insufficiency, as diagnosed by Doppler. Fetal and neonatal risk factors were recorded. They were hypoxia, respiratory distress syndrome or pneumonia requiring ventilation, patent ductus arteriosus, perinatal asphyxia, apnea, polycythemia, shock, aminophylline use, and magnesium toxicity.

Computer-generated randomization in blocks of six was done. The subjects were randomized into Groups 1, 2, and 3, to receive low-dose (3 mg/kg/dose) and high-dose (10 mg/kg/dose) oral erythromycin or placebo (5% dextrose) medication given 8th h. The coding was done by a person who was not involved in the patient care, and the allocation concealment was achieved by keeping in serially numbered opaque sealed envelopes. Investigators and patient care team were blinded for the treatment allocation. The study medication erythromycin estolate of concentration (Syrup Eltocin, 125 mg/5 ml was used as available in the pharmacy) was prepared to the final volume of 1 ml in a glass syringe and covered with aluminum foil, to mask the pink color of medication, which was administered by orogastric route. The feeding volume and progression of feeds were as per NICU feeding protocol for all the groups (Table 1).

Expressed breast milk was used and if milk was not available, then 5% dextrose was used to make up the volume till mother expresses the adequate milk volume, as our unit had a protocol of not using the formula feeds. The enteral feeds were adjusted for both term and preterm babies according to the gastric residuals:

If the residual was >50% volume per feed - discarded, one feed skipped, blood sugars were monitored. If >50% with altered aspirates with other symptoms - started on intravenous fluids and the baby was kept nil by mouth for 6 h. Feeding was stopped when there was feed intolerance and restarted as soon as the above signs and symptoms subside. When the babies were kept nil per oral, study medicine was continued. Babies who persisted to have feed intolerance even after 48 h of study medication, the conventional prokinetic, oral domperidone at 0.3 mg/kg/dose was

given. Those babies continued to have feed intolerance, even after domperidone, were started on infusions feeds and the need for continuous infusions was documented.

Study medication was given for 7 days after they reach full feeds or for a period of total 14 days or the day of discharge whichever is earlier. Babies were examined at least twice a day and were closely monitored for vomiting, gastric residuals, abdominal girth, and gastric aspirates every prefeeds. To monitor for the safety, the babies were monitored by a pulse oximeter, to look for variations in the heart rate and a cardiac monitor if needed. Bilirubin assessment (total and conjugated fraction) or aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/alkaline phosphatase (ALP) was done at baseline and after 7 days of erythromycin. Before inclusion, septic workup was done to rule out sepsis in babies who had feed intolerance, and as required based on symptoms. Ultrasound examination was planned if the baby had persistent vomiting >2 times/day, to look for the complications like pyloric stenosis.

Primary Outcome

Time to reach full feeds of 150ml/kg, without having significant gastric residuals.

Secondary Outcome

Occurrence of sepsis, NEC, adverse effects (hypertrophic pyloric stenosis, arrhythmias), need of domperidone, infusion feeds, abnormality of liver enzymes, vomiting, and duration of hospital stay.

Babies were considered to have sepsis when they had clinical picture with the presence of any two of the following - complete blood count or C-reactive protein or positive blood culture. If the septic parameters were negative, babies were included in the study. If the isolate was coagulate negative *Staphylococcus*, they were included when repeat blood culture was negative. NEC was confirmed by clinical, biochemical, and radiographic methods [21]. Cholestasis was diagnosed when conjugated bilirubin is >15% of the total, AST, ALT, or ALP more than the reference values for that age [22].

Sample Size

Sample size was calculated based on the previous study [23]. Mean time taken to reach full feeds was taken as 5 days for treatment group and 10 days for control groups, with standard deviation (SD) 1, with 5% of level and 80% power. Sample size required was 35 in each group.

All analyses were done using SPSS software. Descriptive data were reported as mean \pm SD, median with interquartile range (IQR), and number with percentages. Categorical data were analyzed using Chi-square/Fisher's exact test. Kruskal-Wallis test was done to compare the median of three arms. ANCOVA was done to compare the time for reaching full feeds between the study groups, for aminophylline as a variable. Results were

considered statistically significant if $p < 0.05$. All the analyses were done with SPSS version 21.0.

RESULTS

The total number of babies admitted to NICU during the study period was 1653. Of which 97 babies had feed intolerance and 60 babies eligible for the study, were randomized. Flow diagram of the recruitment is shown in Fig. 1. Two babies were excluded from the study as they were on fentanyl and domperidone at the time of randomization. A total number of babies in placebo, high, and low dose EM were 19, 19, and 20, respectively.

Demographic characteristics of the babies were similar between the three groups as shown in Table 2. Total babies who were exposed to maternal risk factors and neonatal risk factors for feed intolerance in the study group were 46 (79.3%) and 49 (84.4%) (Table 3).

Of 58 babies, 40 (68.9%) babies received first feeds as breast milk and 18 (31%) babies were fed initially with 5% dextrose fluids, 49 (84.4%) babies had received bolus feeds and 9 (15.5%) babies received infusion feeds during the study period. There were 9 (15.5%) babies on aminophylline. The median age at start of feeds was day 2 with interquartile range of 1–2, 1–4, and 1–3 days in placebo, high-dose, and low-dose groups, respectively. The postnatal day of reaching full feeds was the median day 11 (8–15), 14 (10, 22), and 11 (9.25–17.8),

respectively ($p=0.50$) and time to reach full feeds after medication was median day 6 (3–9), 4 (3–7), and 6 (4.3–7) in placebo, high, and low-dose groups, respectively ($p=0.47$). The duration of study medication with the placebo, high, and low-dose group was the median of 11 (7–14), 9 (7–13), and 9 (7–14) days, respectively ($p=0.86$). One baby died in placebo

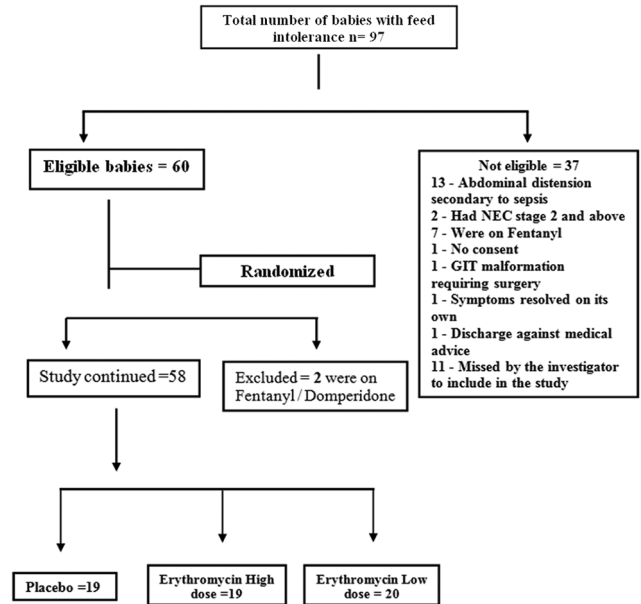


Figure 1: Study flowchart

Table 1: Increment of feeds

VLBW babies without risk factors for NEC	Sick VLBW babies with risk factors for NEC	Sick term babies
Oral feeds - 20 ml/kg/day when hemodynamically stable and increased at 20–35 ml/kg/day as bolus as per the tolerance	Hemodynamically stable babies: Feeds started as trophic feeds, at 10 ml/kg/day, divided into 4–6 times/day and increased in increments of not more than 20 ml/kg/day	Intravenous fluids - 60 ml/kg and feed was started when hemodynamically stable at 20–30 ml/kg/d

VLBW: Very low birth weight, NEC: Necrotizing enterocolitis

Table 2: Demographic details between the groups

Variables	Placebo (n=19)	High dose (n=19)	Low dose (n=20)	p value
Mean gestation	33.21 (2.2)	33.16 (3.65)	33.6 (3.218)	0.705
Mean birth weight	1616±553	1621±724	1663±556	
AGA:SGA	9:10	13:6	15:5	0.175
Male:female	11:8	10:9	12:8	0.893
Preterm:term	18:1	14:5	17:3	0.200
Maternal risk factor	16 (84.2)	13 (68.4)	17 (85)	0.35
Postnatal risk factor	15 (78.9)	17 (89.4)	17 (85)	0.66
Received antenatal steroids (n=43)	14 (87.5)	10 (71.4)	13 (100)	0.09
Aminophylline use	4 (23.5)	3 (16.7)	2 (10.0)	0.540
Age at enrollment median (25 th , 75 th)	6.0 (3–10)	8.0 (5–14)	5.5 (4–8.8)	0.144

SGA: Small for gestational age, AGA- Appropriate for gestational age

Table 3: Primary outcome: Feeding detail between the groups

Variables median (25 th , 75 th)	Placebo	High dose	Low dose	p value
Postnatal day for reaching full feeds	11.0 (8, 15)	14.0 (10, 22)	11 (9.25, 17.8)	0.509
Day for full feeds after study medicine	6.0 (3, 9)	4.0 (3, 7)	6.0 (4.3, 7)	0.477
Total duration of study drug in days	11.0 (7, 14)	9.0 (7, 13)	9.0 (7, 14)	0.869

Table 4: Secondary outcomes

Outcomes	Placebo n=19 (%)	High dose n=19 (%)	Low dose n=20 (%)	p value
Requirement of domperidone	6 (31.6)	2 (10.5)	6 (30.0)	0.24
Requirement of infusion	4 (21.1)	2 (10.5)	3 (15.0)	0.66
Side effects				
Sepsis (n=10)	5 (26.3)	3 (15.8)	2 (10)	0.39
Abnormal LFT (n=5)	1 (7)	2 (15)	2 (14)	0.81
Arrhythmias (clinical)	0	0	0	
NEC	1 (5.3)	0	0	0.35
Pyloric stenosis	0	0	0	
Duration of hospital stay (days)	16 (12–23)	27 (11–32)	15.5 (11.25–27)	0.36
Weight gain during study median (g)	3.58 (–47.5–22)	3.33 (–25–25.7)	4.22 (–250–25)	0.90

group. No mortality was noted in high-dose and low-dose group (Table 4).

DISCUSSION

Feed intolerance is a major problem in neonates; especially, in preterm infants admitted to NICU. Erythromycin, an antibiotic which is also a prokinetic, has been used to promote feed tolerance. Erythromycin exerts its gastrointestinal motor effects through activation of motilin receptors on cholinergic nerves, which are stimulated by low dose (1–3 mg/kg/dose) and augment Phase III MMC and smooth muscle motilin receptor of upper gastrointestinal tract [24], which can be stimulated by high dose (10 mg/kg/dose) and produce sustained antral contractions, promoting antroduodenal coordination [4,25–27]. The combinations of these actions are likely to produce propulsive forces, which effectively propel the gastric luminal contents distantly toward small and large bowel.

There are many randomized controlled trials since decades, which have studied the prokinetic effect of erythromycin at different doses, routes, and modes comparing with the placebo. Till now, there are no conclusions and recommendations drawn from these as the results are inconsistent and contradictory [10,22,28,29]. Studies have shown the adverse effects and emergence of multidrug resistance microflora in GIT at early age with high dose.

The present study was an RCT to compare the effect of high dose and low dose of erythromycin with the placebo in both term and preterm infants with feed intolerance. We have included babies with gestation of <32 and >32 weeks even though some studies which have concluded feed intolerance occur only in babies with gestation >32 weeks [6,30]. There are studies concluding feed intolerance has been seen in preterms with both <32 weeks [6,30] and >32 weeks gestation [25,31].

Erythromycin estolate oral preparation was used in our study, in view of concerns about side effects of arrhythmias with intravenous preparation [32]. Erythromycin ethyl succinate, which other studies used [11,12,32–34], was not available. There were no differences in the baseline characteristics, maternal and neonatal risk factors such as gestational age, birth weight, perinatal asphyxia, and severity of initial pulmonary diseases between the groups in our study. There were more male babies and higher mean gestation and mean birth weight in our study

than others. The placebo group had more preterm and SGA babies as compared to other groups, which can influence the outcome.

Many RCTs have used EM as a rescue treatment in the recent past. Some authors have used low dose - 3–15 mg/kg/d [10–12,33] and high dose - 50 mg/kg/d, [12,22,29] and found that erythromycin was effective at high doses. In the present study, most of the babies were fed with human milk and most feeds were given as bolus. There were no differences between the three groups regarding the age at starting the feeds and age at enrollment. As compared to the studies [23,34,35], time to reach full feeds in our study was similar to Ng *et al.* pilot study. Babies, who received high dose, required less time to reach full feeds after study medication, and lesser duration of medication as compared to the placebo and low-dose group; however, it did not reach statistically significant.

In the high-dose group, the median postnatal day for reaching full feeds was 14 (IQR - 10, 22) days, which was longer in this group, the reason could be the medication was started at a later age than in the other groups. In the low-dose group, age of enrollment was earlier than the other groups. The median postnatal day of reaching full feeds was 11 (IQR -9.25, 17.75) days and mean was 15.2±10.4 days and time to reach full feeds after study medication was median of 6 (IQR - 4.25, 7) days which was similar to the placebo in all the variables except the duration of study medicine which was less and is not significant statistically. Similarly, many other studies also showed no benefit. Hennawy *et al.* [10] showed that the mean postnatal day of reaching full feeds was 31±15 days; Ng *et al.* showed it 24±2.95 days [11] and Cairns *et al.* showed 13.0±14.1 days in their study [12]. Aly *et al.* have shown a positive effect with erythromycin at 1 mg/kg Q8H in babies both >32 weeks and <32 weeks gestation and have also shown shorter days of TPN requirement [33]. Nagomi *et al.* have used low-dose IV preparation and found it useful; however, it was not a prospectively RCT [31].

We also studied the requirement of IV fluids, domperidone, and glycerine syringing for irregular stools and side effects such as vomiting, cholestasis, sepsis, NEC, and adverse events such as hypertrophic infantile pyloric stenosis and arrhythmias and weight gain and duration of hospital stay. Requirement of domperidone and infusion were less in high-dose group ($p>0.05$). An abnormal liver enzyme level was not significantly different between the groups. The duration of hospital stay and weight gain was not significant

between the groups. Time to reach full feeds for those who received methylxanthine was prolonged as compared to those who did not receive methylxanthine ($p=0.003$). No adverse effects were seen in the erythromycin group, and there was no significant difference in any of the secondary outcomes between the three study groups.

None of the babies developed adverse effects such as arrhythmias or hypertrophic pyloric stenosis. In the placebo group, one baby developed NEC Stage III, and died in the course of the illness, which had been excluded earlier after the diagnosis of NEC-II. Many babies in the placebo group had sepsis, but the number was statistically insignificant as compared to other two groups. Prolonged liver enzymes seen in the study babies could be because of antibiotics or sepsis or related to medication itself, but it resolved spontaneously in all these babies.

Ng *et al.* showed that the number of withheld feeds, duration of parenteral nutrition, cholestasis, and incidence of sepsis was less in the erythromycin group and increased incidence of parenteral nutrition-associated cholestasis in the placebo group [34]. Aly *et al.*, who used low-dose erythromycin, reported decrease in TPN days [33], but Ng *et al.* and Nuntnarumit *et al.* did not show any difference in their studies [11,23]. TPN-related cholestasis reported by Aly *et al.* [33] was 13% and sepsis was 13% in the erythromycin group ($p=1.0$). Ng *et al.* [34] reported one case of NEC in the placebo group, and Nuntnarumit *et al.* [23] reported one baby with NEC in erythromycin group and three babies in the placebo group. None of the other studies have reported the same. Ng *et al.* [34] showed no difference between erythromycin and placebo in the QT interval. None of the studies reported that incidence of sepsis including a Cochrane meta-analysis showed no difference [36].

A Cochrane meta-analysis in 2008 concluded that there is insufficient evidence to recommend the use of erythromycin in low or high dose of preterm infants with or at risk of feeding intolerance and recommends for future research on erythromycin as a prokinetic agent [36]. Even though there was no difference between the study groups in postnatal day of reaching FF, all babies reached full feeds within 2 weeks of life, which is quite acceptable in preterm infants. The fact that the placebo group also reached the full feeds within the acceptable time may be the babies who were recruited had mild-to-moderate feed intolerance. Even though placebo group had more number of preterm, small for gestation babies, and high-dose group has more number of term babies, there was no statistical difference in time for reaching full feeds. Babies with high-dose erythromycin required less time to reach full feeds and lesser duration of study medication as compared to the placebo and low-dose group; however, it did not reach statistically significant. To show the positive effect of high-dose erythromycin and difference in variables between the study groups, we need to meet the required sample size, which could be the limitation of the study.

CONCLUSION

There was no significant difference in the time to reach full feeds and the duration of study medication between the high-dose and

low-dose erythromycin and the placebo group. There was no significant difference in any of the secondary outcomes between the three study groups.

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