CHAPTER 2

REVIEW OF RELATED LITERATURE

Cycle of gastrointestinal motility during fasting include period of quiescence (phase1), irregular activity (phase 2), and regular propagating activity (phase 3). Phase 3 is also known as the migrating motor complex (MMC). The MMC is closely involved in gastric elimination and fasting contraction. The three phase of intestinal motor activity are present in term infants, but lack of the propagative phase III of the MMC in the duodenum of preterm infants less than 32 weeks gestational age(13, 19). The interdigestive activity of preterm infants consists of random periods of quiescence and non-propagated contractions. This functional immaturity predisposes them to feeding intolerance. Further studies have shown that gastrointestinal motility matures as gestational age increases(19, 20).

Motilin, a gastrointestinal hormone, is a polypeptide of 22 amino acids residues, stimulates propagative contractile activity during phase III of the MMC in the interdigestive state. In-vitro studies have shown that erythromycin (EM), a macrolide antibiotic is a motilin agonist(21, 22). Its prokinetic effect is seen at doses much lower than the antimicrobial dose in humans.(23) Animal studies have shown that the prokinetic effect of EM is dose dependent. At a low intravenous dose (1mg/kg), EM was shown to induce phase III of the MMC along the small intestine. At higher doses (7-10mg/kg), however, EM was shown to cause sustained contractile activity in the small intestine, followed by a prolonged disruption of the baseline MMC.(24, 25)

Clinical trials have shown its efficacy in various gastrointestinal disorders e.g., chronic functional pseudo-obstruction, gastroesophageal reflux, postoperative intestinal dysmotality and gastroparesis secondary to diabetes or vagotomy(26-28). It also has been reported to promote antroduodenal coordination(12). Clinical trials using EM for feeding intolerance or promoting feeding in preterm infants are very limited and inconclusive due to lack of standard regimen and wide heterogeneity of the studies. (13, 29-41)

Clinical trials as shown in table 1 were conducted by Oei et al, Patole et al, and Stenson et al using EM for promoting enteral feeding in preterm infants less than 32 weeks gestation(35, 36, 38).

Table 1. Clinical trials of erythromycin for promoting enteral feeding (prophylaxis strategy) in preterm infants

Study	Sample	Design	Dose	Duration	Outcomes	Results
Oie J, et al. (2001)	≤ 32 wks 22 EM 21 Placebo	RCT	EES, oral 2.5 mg/kg/dose every 6 hr.	10 days	Time to FF (day) (150 ml/kg/day) Episodes of large gastric residual	6.0±2.3 in EM vs. 7.9±3.5 in placebo (p=0.04) 1.1±1.9 in EM vs. 3.6±2.2 in placebo (p=0.0007) One infant in each group died of NEC No EM related side effects observed
Patole SK, et al (2000)	< 32 wks 36 EM 37 Placebo	RCT	EES, oral 12 mg/kg/dose every 6 hr.	Until FF or 2 wks was reached	Time to FF (hour) (150 mg/kg/day)	Median; 93.5 in EM vs. 104 in placebo (p=0.60) No EM related side effects observed
Stenson BJ,et al (1998)	<31 wks 35 EM 41 Placebo	RCT	EES, intravenous 15 mg/kg/dose every 8 hr.	7 days	Time to FF (day)	Median (quartile); 8(5-12) in EM vs. 9(6-14) in placebo (p=0.45) NEC: 2 in EM and 4 in placebo (p=0.4) Died: 7 in EM and 8 in placebo (p=0.9) No EM related side effects observed

RCT= randomized clinical trial, EM=erythromycin, EEC= erythromycin ethyl succinate, FF= full feeding, NEC= necrotizing enterocolitis

EM was initiated at time of starting enteral feed with the dosage varies from low dose of 2.5 mg/kg/dose to antibiotic dose (10-12 mg/kg/dose). Duration of EM also varies from 7 days to 14 days or until full feeding. They found no significant differences in time to full feeding, episode of vomiting and incidence of necrotizing enterocolitis, except for reduced gastric residues in treatment group compared to placebo group. Of note, all these three studies performed in asymptomatic infants who did not have feeding intolerance and involved rather small sample size.

Nogami al et(34) conducted a quasi-randomized trial using EM for treatment feeding intolerance in 14 preterm infants (mean age of 30 weeks gestation) with low dose of 1-2 mg/kg/dose intravenously compared with 12 historical controlled infants. The treated infants were able to feed successfully and to establish full feeding earlier (15 $\pm$4 days vs. 23 $\pm$6 days). No significant side effects were found.

The randomized controlled trial (as shown in table 2) in moderately severe feeding intolerance preterm infants was conducted by Ng et al(33). Fifty-six preterm (27 in EM group and 29 in placebo) infants with birth weight less than 1500 grams, who could tolerate enteral feeding less than 75 ml/kg/day by 14 days of age, were enrolled. EM was given with an antibiotic dose (12.5 mg/kg/dose) every 6 hours for 14 days. The study showed that treated infants were able to advance feeding and reach full feeding 10 days earlier. No significant side effects related to EM were detected, and more infants in placebo group had cholestatic jaundice associated with prolonged parenteral nutrition. However, infants in this study were limited to moderately severe cases and treated infants had to expose to high dose (antibiotic dose) for rather long period of time (14 days) making them increased risk for EM-related side effects.

However, the recent clinical trials using low dose EM in preterm infants with feeding intolerance showed contradictory results. ElHennawy et al(39) conducted the study using very low dose EM of 1.5 mg/kg/dose every 6 hours in 15 preterm infants compared to 12 infants in placebo group and showed no difference in time to full enteral feeding. The other study(40), which involved a small sample size of 24 infants, 13 in EM and 11 in placebo, using low dose EM of 5 mg/kg/dose every 8 hours, showed that infants in EM group reached full feeding faster than that of placebo, but not statistically significant.

A preliminary observation of low dose oral EM for treatment feeding intolerance in preterm infants at the Ramathibodi Hospital showed a dramatic response in 9 out of 10 infants, and responded infants were able to advance to full feeding within 5-7 days after treatment(42). No significant side effects were found. We believe that by using low dose EM would avoid side effects reported in infants(43-48).

Due to contradictory results and lack of systematical data of low dose EM for treatment feeding intolerance infants, thus, randomized clinical trials of EM for preterm infants with this condition are in need. If such studies show the efficacy, the benefits are not only reaching full feeding faster, but also would reduce complications associated with prolonged parenteral nutrition and would reduce hospital costs.

Table 2. Clinical trials of erythromycin for feeding intolerance (treatment strategy) in preterm infants

Study	Sample	Design	Dose	Duration	Outcomes	Results
Nogami k, et al (2001)	≤ 32 wks 14 EM 12 Controls	Observation	EM, intravenous 1-2 mg/kg/dose every 8 hr.	10±2.9 days	Time to feeding at 100 ml/kg/day (day)	15.2±4.0 in EM vs. 23±6.2 in controls ($p<0.01$)* No EM related side effects observed
Ng PC, et al (2001)	< 1500 g. if feed <75 ml/kg/day by 2 wk of age 27 EM 29 Placebo	RCT	EES, oral 12.5 mg/kg/dose every 6 hr.	14 days	Time to FF (day) (150 ml/kg/day)	Median (quartile) 13.5(8-22) in EM vs. 25(16-33) in placebo ($p<0.005$)* No NEC Reduce cholestatic jaundice in EM No serious EM side effect observed
ElHennawy A, et al (2003)	29-36 wk if severe abdominal distention or gastric residual>25% 15 in EM 12 in Placebo	RCT	EES, oral 1.5 mg/kg/dose every 6 hr.	8 days	Time to FF (day) (150 ml/kg/day) Gastric emptying time at 20 min. Transit time duodenum to anus	31±15 in EM vs. 36±16 in placebo (NS) No difference No difference
Ng SC, et al (2003)	≤ 1500 g. if fail to attain at least 20 ml/kg/day enteral feeding by 1 wk after initiating feeds 13 EM 11 Placebo	RCT	EES, oral 5 mg/kg/dose every 8 hr.	D/C 1 wk after FF	Time to FF (day) (≥130 ml/kg/day) Cholestasis	24.9±2.9 in EM vs. 30.8±4.1 in placebo ($p=0.17$) 4/13 in EM vs. 7/11 in placebo ($p=0.11$) One in placebo developed NEC No dysrhythmia, pyloric stenosis, sepsis with multi-resistant organism observed

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