Efficacy of Erythromycin and Metoclopramide in Neonates with Feeding Intolerance

Kyung Ah Seo, MD, MSc, Na Mi Lee, MD, MSc, Eung Sang Choi, MD, PhD, Byoung Hoon Yoo, MD, PhD
Department of Pediatrics, College of Medicine, Chung-ang University, Seoul, Korea

ABSTRACT

Purpose: Feeding intolerance is common in premature infants. It may extend the parenteral nutrition period and increase the risk of complications. We evaluated the efficacy of erythromycin and metoclopramide in neonates with feeding intolerance.

Methods: Between December 2006 to August 2011, 114 neonates with feeding intolerance were divided into two groups treated with either erythromycin or metoclopramide in the neonatal intensive care unit of Chung-ang University Hospital, a tertiary care center. We defined neonates with feeding intolerance as those who either could not be fully fed enterally (120 mL/kg/day) within 7 days or who skipped feeding more than twice per day because the gastric residual volume was >20% of each feed or more than 50% once. The time taken to achieve 50%, 75%, and 100% enteral feeding was estimated retrospectively.

Results: The erythromycin group achieved 50% feeding ($P=0.047$), 75% feeding ($P=0.042$), and 100% feeding ($P=0.039$) earlier than the metoclopramide group. The erythromycin group achieved 100% feeding earlier than the metoclopramide group among infants with birth weight ≥1,500 g ($P=0.036$) and those with gestational age ≥34 weeks ($P=0.008$).

Conclusion: Compared with metoclopramide, erythromycin improves feeding in neonates with feeding intolerance, especially in infants with birth weight ≥1,500 g and in those with gestational age ≥34 weeks.

Key Words: Erythromycin, Feeding intolerance, Metoclopramide, Neonate

INTRODUCTION

Feeding intolerance is one of the most common problems in newborn infants, including premature infants. The immaturities of premature infants can cause lack of coordination in sucking and swallowing, delayed gastric emptying, and dysmotility of the bowel[1,2].

Feeding intolerance can extend the parenteral nutrition period and increase the risk of the complications of parenteral nutrition-associated cholestasis and sepsis. Feeding intolerance
is also associated with morbidity and duration of hospital stay\textsuperscript{3}. Various medications are used to treat feeding intolerance. Erythromycin and metoclopramide are the currently preferred drugs. However, the optimal dosage, treatment duration, and treatment modes of these drugs are contentious. The effects of erythromycin and metoclopramide on feeding intolerance have been compared with placebo in many studies\textsuperscript{4-16}, but few comparative data have been published on the relative effects of erythromycin and metoclopramide on feeding intolerance in neonates. This study compared the efficacy of erythromycin and metoclopramide for the treatment of feeding intolerance in neonates.

\section*{MATERIALS AND METHODS}

\textbf{1. Subjects}

A chart review was performed retrospectively. We defined neonates with feeding intolerance as either those who could not be fully fed enterally (120 mL/kg/day) within 7 days or those who skipped feeding more than twice per day because the gastric residual volume was more than 20\% of each feed or more than 50\% once. A total of 172 neonates were diagnosed with feeding intolerance and were treated with erythromycin or metoclopramide in the neonatal intensive care unit (NICU) of Chung-ang University Hospital, a tertiary care center, from December 2006 to August 2011. Those who had any congenital anomaly and/or gastrointestinal tract abnormalities were excluded. Forty-one patients positive for rotaviral antigen were excluded. Seven patients who received both erythromycin and metoclopramide were also excluded. Four patients who received domperidone with erythromycin or metoclopramide were excluded. Six infants diagnosed with necrotizing enterocolitis (NEC) with intraperitoneal gas or intramural gas were excluded. A total of 114 patients were enrolled.

\textbf{2. Drug administration}

Erythromycin (Eryc cap\textsuperscript{\textregistered}, BoRyung Pharm., Seoul, South Korea) was orally administered at a dosage of 10 mg/kg every 6 hours for 2 days, and then 4 mg/kg every 6 hours. Metoclopramide (Macperan Tab\textsuperscript{\textregistered}, Dong Wha Pharm., Seoul, South Korea) was administrated at a dosage of 0.1 mg/kg every 8 hours orally or intravenously for 30 minutes.

\textbf{3. Clinical features}

Demographic features including gestational age, birth weight, gender, Apgar score at 1 and 5 minutes, delivery type, hematocrit, body temperature at birth, antenatal use of steroids or magnesium, use of fentanyl, and use of ventilator were compared for both groups. The time to the start of medication, the time to the start of enteral feeding, the days of hospitalization, and total parenteral nutrition (TPN) duration were also compared. We also compared the incidence rates of diseases that are common in premature infants: respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). The primary endpoints were the times taken to reach 50\%, 75\%, and 100\% enteral feeding (120 mL/kg/day) in the erythromycin and metoclopramide groups. The results were compared and infants were divided into two groups for two parameters: infants with birth weight $<1,500$ g and those with birth weight $\geq1,500$ g, and infants with a gestational age $<34$ weeks and those with a gestational age $\geq34$ weeks. Side effects of both treatments were assessed, and included arrhythmia, QT prolongation on electrocardiogram (EKG), and pyloric stenosis for erythromycin, and extrapyramidal symptoms for metoclopramide. The incidence rates of culture-proven sepsis and cholestasis (direct bilirubin level $>2.0$ mg/dL) were also compared.

\textbf{4. Feeding methods}

Enteral feeding was typically started as soon as vital signs were stable. Neonates were usually fed orally every 3 hours. Feeding was skipped if gastric residues of $>20\%$ of each feed were repeated or if residue was $>50\%$ once. Feeding was withheld in infants with suspected NEC.

\textbf{5. Statistical analyses}

SPSS version 18.0 (SPSS, Chicago, IL) was used for statistical analysis. Student’s t-test, Mann-Whitney U test, and chi-square test were used to compare frequencies. A $P$-value $<0.05$ was considered to be statistically significant.

\section*{RESULTS}

Seventy (61.4\%) neonates were assigned to the erythromycin group, and 44 (38.6\%) were assigned to the metoclopramide
group. All 70 neonates in the erythromycin group were enrolled between July 2009 and August 2011, and 43 of the 44 metoclopramide neonates were enrolled between December 2006 and June 2009. Mean±SD birth weight and gestational age of the 114 enrolled patients was 2,195.2±725.6 g and 34.1±3.5 weeks, respectively. Mean±SD duration of hospital stay was 29.6±23.2 days.

Table 1 shows the basic demographic data and clinical characteristics of the infants in both groups; there were no significant differences between the groups. The times to reach 50% feeding (erythromycin 1.4±3.5 vs. metoclopramide 3.0±7.8 days, \(P=0.047\)), 75% feeding (2.7±3.7 vs. 5.5±8.4 days, \(P=0.042\)) and 100% enteral feeding (4.6±5.6 vs. 8.2±10.8 days, \(P=0.039\)) were significantly shorter in the erythromycin group (Fig. 1). The duration of hospital stay was 26.5±17.0 days in the erythromycin group and 34.5±30.1 days in the metoclopramide group, with no significant difference between both groups (\(P=0.113\)). The duration of TPN was 6.0±8.3 days in the erythromycin group and 8.8±12.6 days in the metoclopramide group, with no significant difference (\(P=0.199\)). There were two cases of sepsis (2.9%) in the erythromycin group and three cases (6.8%) in the metoclopramide group, with no significant difference between the groups for this parameter (\(P=0.372\)). There were three cases of cholestasis (4.3%) in the erythromycin group and three cases (6.8%) in the metoclopramide group, again, there was no significant difference (\(P=0.675\)).

1. Neonates with a birth weight <1,500 g

Seventeen patients had a birth weight <1,500 g: eight received erythromycin and nine received metoclopramide. There were no significant differences in demographic data, clinical characteristics, and time to reach 50% feeding (\(P=0.334\)), 75% feeding (\(P=0.735\)), and 100% feeding (\(P=0.847\)) between both groups. The duration of hospital stay was significantly shorter

<table>
<thead>
<tr>
<th>Table 1. Demographic Data and Clinical Characteristics of Infants in the Erythromycin and Metoclopramide Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin group (N=70)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Cesarean section</td>
</tr>
<tr>
<td>Apgar score 1 min</td>
</tr>
<tr>
<td>5 min</td>
</tr>
<tr>
<td>Initial hematocrit (%)</td>
</tr>
<tr>
<td>Initial body temperature (°C)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>and duration, days</td>
</tr>
<tr>
<td>UAC insertion</td>
</tr>
<tr>
<td>and duration, days</td>
</tr>
<tr>
<td>UVC insertion</td>
</tr>
<tr>
<td>and duration, days</td>
</tr>
<tr>
<td>Antenatal steroid</td>
</tr>
<tr>
<td>Antenatal magnesium</td>
</tr>
<tr>
<td>Fentanyl use</td>
</tr>
<tr>
<td>RDS</td>
</tr>
<tr>
<td>PDA</td>
</tr>
<tr>
<td>BPD</td>
</tr>
<tr>
<td>Postnatal days to start of medication</td>
</tr>
<tr>
<td>Duration of medication, days</td>
</tr>
<tr>
<td>Postnatal days to start of enteral feeding</td>
</tr>
</tbody>
</table>

Abbreviations: UAC, umbilical artery catheter; UVC, umbilical venous catheter; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.
in the erythromycin group than in the metoclopramide group for neonates whose birth weight was <1,500 g (56.6±22.7 vs. 80.7±30.8 days, \( P = 0.043 \)). One case each of sepsis and cholestasis was reported in the erythromycin group (12.5%) and the metoclopramide group (11.1%). No significant differences between the 2 groups were evident for duration of TPN (20.0±12.2 vs. 22.0±13.1 days, \( P = 0.700 \)), incidence of sepsis (\( P = 1.000 \)), and incidence of cholestasis (\( P = 1.000 \)) (Fig. 2).

2. Neonates with a birth weight \( \geq 1,500 \) g

Ninety seven neonates had a birth weight \( \geq 1,500 \) g. Of these, 62 received erythromycin and 35 received metoclopramide. Among these patients, there were no significant differences in demographic data and clinical characteristics between both groups. The erythromycin group reached 100% feeding earlier (\( P = 0.036 \)). The duration of hospital stay was not significantly different between the two groups in this birth weight category (22.7±11.6 vs. 22.7±14.7 days, \( P = 0.993 \)) (Fig. 2). The duration of TPN was 4.2±5.6 days in the erythromycin group and 5.3±10.1 days in the metoclopramide group. There was one case of sepsis (1.6%) in the erythromycin group and two cases (5.7%) in the metoclopramide group. There were two cases of cholestasis (3.2%) in the erythromycin group and two (5.7%) in the metoclopramide group. There were no significant differences between the groups in the duration of TPN (\( P = 0.526 \)) and the incidence of sepsis (\( P = 0.295 \)) and cholestasis (\( P = 0.618 \)).

3. Neonates with a gestational age <34 weeks

Fifty two neonates had a gestational age <34 weeks. Of these, 33 received erythromycin and 19 received metoclopramide. Birth weight (1,816.2±370.9 g in the erythromycin group and 1,520.2±499.4g in the metoclopramide group, \( P = 0.028 \)) and postnatal age at the start of medication (9.6±5.5 days in the erythromycin group and 14.0±8.5 days in the metoclopramide group, \( P = 0.049 \)) were significantly different. The time taken to reach 50% feeding (\( P = 0.290 \)), 75% feeding (\( P = 0.101 \)), and 100% feeding (\( P = 0.130 \)) were similar in the two groups (Fig. 3). However, the mean hospital stay in the erythromycin group (45.5±33.6 days) was significantly shorter (\( P = 0.044 \)) than that in the metoclopramide group (63.4±47.6 days). The duration of TPN was 8.8±8.1 days in the erythromycin group and 14.6±12.8 days in the metoclopramide group. There were two cases of sepsis (6.1%) in the erythromycin group and three cases (15.8%) in the metoclopramide group. There were no cases of cholestasis in the erythromycin group while there was one (5.3%) in the metoclopramide group. The duration of TPN (\( P = 0.132 \)) and the incidence of sepsis (\( P = 0.342 \)) and cholestasis (\( P = 0.365 \)) were not
significantly different between both groups.

4. Neonates with a gestational age $\geq 34$ weeks

Sixty-two neonates had a gestational age $\geq 34$ weeks. Of these, 37 received erythromycin and 25 received metoclopramide. Demographic data were not significantly different between the two groups. The times taken to reach 50% feeding ($P=0.018$), 75% feeding ($P=0.047$), and 100% feeding ($P=0.008$) were consistently significantly shorter in the erythromycin group. The duration of hospital stay did not significantly differ between the two groups (18.5±13.1 vs. 20.8±24.0 days, $P=0.957$). The duration of TPN was 3.5±7.7 days in the erythromycin group and 4.3±10.7 days in the metoclopramide group. There were no cases of sepsis in either group. There were three cases of cholestasis (8.1%) in the erythromycin group and two cases (8.0%) in the metoclopramide group. The duration of TPN ($P=0.957$) and the incidence of sepsis ($P=1.000$) and cholestasis ($P=1.000$) were also not significantly different between both groups (Fig. 3).

Possible side effects of erythromycin and metoclopramide, including arrhythmia, QT prolongation on the EKG, pyloric stenosis, and extrapyramidal symptoms such as oculogyric crisis were monitored. However, no such significant adverse effects were noted.

**DISCUSSION**

Feeding intolerance in preterm infants is closely related to morbidity and duration of hospitalization. Compromised enteral feeding can cause limitation of nutritional supply and growth restriction, including in the brain. To decrease parenteral nutrition associated cholestasis and catheter-related septicemia, many medications have been studied. Cisapride, domperidone, metoclopramide, and erythromycin have been used in neonates with feeding intolerance; there are few alternative medications available. Cisapride stimulates serotonin 5-hydroxytryptamine intestinal receptors and increases lower esophageal sphincter pressure, intestinal motility, and gastric emptying. It was a first-line gastrointestinal prokinetic agent until about 10 years ago, but its use was halted for infants due to risk of QT prolongation on EKG and arrhythmias.

Domperidone is a peripheral dopamine antagonist. It shortens the gastric emptying time, but can cause QT prolongation and ventricular fibrillation.

Metoclopramide is a dopamine receptor antagonist that has antiemetic properties and stimulates gastrointestinal motility. It is used for gastroesophageal reflux disease treatment. Despite the widespread use of metoclopramide for improvement of gastrointestinal movement, data in neonates are lacking. Furthermore, side effects of concern include irritability, vomiting, dystonic reaction, oculogyric crisis, and extrapyramidal symptoms.

Many recent studies have investigated erythromycin in infants with feeding intolerance. Erythromycin is an antibiotic that also modulates gastrointestinal motility. Erythromycin acts as a motilin agonist that stimulates the cholinergic nerves of the gastrointestinal tract and increases gastric antrum contractility and the rate of gastric emptying. Many neonatal units use erythromycin as a prokinetic drug for premature infants, but there is no consensus regarding dose, duration, effects, and side effects.

More than 10 randomized controlled trials have been perform-
ed to test the effects of erythromycin in feeding intolerance. The diverse study designs may have led to different results. Many studies reported good efficacy for erythromycin\(^8\text{-}^{14}\), but the use of high doses and intravenous administration may have caused adverse effects\(^24\text{-}^{25}\). Meanwhile, other studies reported that low-dose erythromycin was not helpful in neonates with feeding intolerance\(^{15,16}\). Since a modified dose of erythromycin is thought to be safe and effective\(^23\), this approach was chosen for this study, and the drug was given orally. Furthermore, the use of erythromycin as rescue therapy, rather than its prophylactic use, was justified because the prophylactic use of erythromycin may increase the risk of adverse effects\(^23\).

Possible complications of erythromycin treatment include infantile hypertrophic pyloric stenosis (IHPS), arrhythmia, alteration of bacterial colonization of the bowel, and the emergence of antibiotic-resistant organisms\(^24\text{-}^{25}\). However, no trial of erythromycin has reported any major side effects in premature infants. Similarly, no significant side effects of erythromycin were observed in this study.

Previous studies have proven the efficacy of these medications in feeding intolerance, but only for preterm infants. Feeding intolerance is a problem not only in preterm infants but also in full-term infants, and therefore we included full-term infants in our study (21% had gestational age ≥38 weeks; 12 in the erythromycin group and 12 in metoclopramide group) and analyzed results according to various subgroups.

In this study, erythromycin showed a superior effect on feeding in neonates, especially in those whose birth weight was ≥1,500 g and whose gestational age was ≥34 weeks. Neonates are equipped with a gastrointestinal neuroendocrine network and an adult-like motilin distribution by 25 weeks’ gestation\(^2,26\), so preterm infants have shown responses to erythromycin in the treatment of feeding intolerance in many randomized controlled trials\(^8,12,13\). It is possible that motilin receptors are fewer or motilin function is less effective in infants of <34 weeks gestational age or with a birth weight <1,500 g.

There was no significant difference in duration of hospital stay between the erythromycin and metoclopramide groups in infants of ≥34 weeks’ gestational age or ≥1,500 g birth weight. The duration of hospital stay in the erythromycin group was shorter in infants of <34 weeks’ gestational age and those of <1,500 g birth weight, although the time taken reach full feeding did not significantly differ between the two groups. These results could be due to policy changes. TPN duration was longer in the metoclopramide group and the incidence of sepsis or cholestasis was higher in the metoclopramide group, although statistical significance was not reached. More patients may be needed to reveal the true effect. Alternatively, it may be that erythromycin and metoclopramide are both effective, and there may be no dramatically significant differences in complication rates or the durations of hospital stay.

There are several limitations to this study. First, ours was not a prospective study or a randomized controlled trial. Prospective randomized controlled trials should be performed with larger patient groups to better assess the differences between both treatments in their effects on hospitalization, weight gain, and incidence of sepsis and cholestasis. Second, clinicians selected the mode of metoclopramide use on a case-by-case basis, and of the nine neonates whose birth weight was <1,500 g in the metoclopramide group, three were treated intravenously and one was treated orally. For five neonates, metoclopramide was given intravenously first and then orally. Of 19 neonates whose gestational age was <34 weeks in the metoclopramide group, seven were treated intravenously and one was treated orally. For 11 neonates, metoclopramide was given intravenously first and then orally. It could be that intravenous administration of metoclopramide is preferred for patients with more serious gastrointestinal conditions. This may have introduced bias into the study, because all patients in the erythromycin group received erythromycin orally, and erythromycin was found to be more effective. Third, demographic data and clinical features were not significantly different in any subgroup except among neonates with a gestational age <34 weeks. This may have influenced the results.

In conclusion, erythromycin was generally effective for the treatment of feeding intolerance. We recommend the prudent use of erythromycin for treating feeding intolerance in neonates. However, because of the above limitations, more comparative studies are needed.

REFERENCES

수유불내증 신생아에서 Erythromycin과 Metoclopramide의 효능 비교

중앙대학교 의과대학 소아과학학교실
서경아 · 이나미 · 최응상 · 유병훈

목적: 수유불내증은 미숙아에서 흔하다. 이것은 장액영양기간을 연장시키고 이에 따른 합병증을 증가시킬 수 있다. 이에 저자들은 수유불내증이 있는 신생아에서 치료로 흔히 사용되는 erythromycin과 metoclopramide의 효능을 비교해보았다.

방법: 2006년 12월부터 2011년 8월까지 중앙대학교병원 신생아중환자실에서 수유불내증이 있는 114명의 신생아를 erythromycin과 metoclopramide로 치료하는 두 군으로 나누었다. 수유불내증 신생아는 7일 안에 완전장관영양 (120 mL/kg/day)에 도달하지 못하거나 위장류량이 각 수유의 20% 보다 많이 하루에 두 번 이상 수유를 건너뛴거나 한번이라도 각 수유량의 50%이상일 때로 정의하였다. 50%, 75%, 100% 장관영양에 도달하는데 걸리는 시간을 후향적으로 측정하였다.

결과: Erythromycin군은 metoclopramide군 보다 50% (P=0.047), 75% (P=0.042), 100% (P=0.039) 수유에 더 빨리 도달하였다. 출생체중이 1,500 g 이상인 환자군과 재태연령 34주 이상인 환자군에서 erythromycin군에서 metoclopramide 군보다 100% 수유에 더 빨리 도달하였다.

결론: Metoclopramide와 비교하였을 때 erythromycin은 수유불내증이 있는 신생아, 특히 출생체중 1,500 g 이상과 재태연령 34주 이상에서 우수한 효과를 보인다.