Iran Red Crescent Med J. 2019 September; 21(9):e92790. doi: 10.5812/ircmj.92790.

Published online 2019 September 30. **Research Article**

Evaluating the Effect of the Intermediate-Dose Oral Erythromycin on the Treatment of Feeding Intolerance in Premature Neonates: A Randomized Clinical Trial Study

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Received 2019 May 02; **Revised** 2019 July 15; **Accepted** 2019 July 27.

Abstract

Background: Gastrointestinal (GI) dysmotility is a common problem among preterm neonates with very-low-birth-weight and is manifested as feeding intolerance, and in this situation, total parenteral nutrition (TPN) is needed for several complications. Erythromycin is a prokinetic antibiotic that neonatologists widely prescribe for the treatment of GI dysmotility in high and low doses.
Objectives: This study aimed to evaluate the effects of an intermediate dose of Erythromycin in the treatment of feeding intolerance in preterm neonates.
Methods: This study is a randomized clinical trial on preterm neonates admitted in two university-affiliated hospitals in Isfahan, Iran, during 2016 - 2017. Feeding is started for all neonates with 20 mL/kg/day doses and if they tolerate it, 20 mL/kg/day is added daily to receive toreach 150 mLcc/kg/day. The infants were divided into two groups, which received either Erythromycin (5 mg/kg/dose every 6 hours) or placebo for eight days. These outcomes were evaluated: time duration to reach 75, 110, and 150 mL/kg/day feeding volume, lavage count after the intervention, time duration of oxygen dependency and hospitalization, the incidence of necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus, chronic lung disease, cholestatic icterus, sepsis, and hypertrophic pyloric stenosis.
Results: Sixty-four neonates (female 38 (59.3%) and male 26 (40.6%)) with the mean gestational age 30.10 $\pm$ 2.49 weeks were evaluated. The mean time duration to reach 75, 110, and 150 mL/kg/day feeding volume was significantly lower in the Erythromycin group (4.19 vs. 6.84 days, $P < 0.001$, 6.35 vs. 9.08 days, $P < 0.001$ and 9 vs. 11.46 days, $P < 0.001$ in the Erythromycin vs. placebo groups, respectively). Also the number of lavages were significantly lower in the Erythromycin group (0.35 $\pm$ 0.56 vs. 3.03 $\pm$ 3.08 in the Eerythromycin and placebo groups; $P < 0.001$).
Conclusions: Intermediate dose of Erythromycin can reduce the time duration to reach full feeding volume and is safe for preterm neonates.

Keywords: Enterocolitis, Erythromycin, Feeding, Infant, Intolerance, Iran, Jaundice, Necrotizing, Neonates, Newborn, Parenteral Nutrition, Prematurity, Prokinetic

1. Background

Gastrointestinal (GI) Dysmotility is a common condition in very low birth weight (VLBW) neonates, which is manifested as feeding intolerance (1, 2). This feeding intolerance includes the presence of gastric residue, vomiting, recurrent regurgitation, and abdominal distention in severe cases. Abdominal X-ray in neonates with GI dysmotility shows intestinal distention, but there is no air in the intestine wall or abdominal cavity (3).

Studies reported that this clinical condition is due to ineffective, low frequent and uncoordinated intestinal movement and is secondary to prematurity of GI system in premature neonates. Although GI dysmotility is benign and uncomplicated in premature neonates, the fear of necrotizing enterocolitis and other intra-abdominal complication lead to stopped feeding and prolongation of total parenteral nutrition (TPN). Therefore, prokinetic agents that improve GI motility is probably beneficial, especially for those who do not reach complete feeding volume be-

cause of their recurrent feeding intolerance (4-6).

Erythromycin is an antibiotic with prokinetic property, and many practitioners widely use for treating gastroparesis due to diabetes, scleroderma, esophagectomy, and vagotomy in adult patients (7). This functional property had positive effects in other situations such as GI dysmotility diseases include gastro-esophageal reflux, chronic intestinal pseudo-obstruction, and ileus after surgeries (7). Moreover, the role of Erythromycin as a prokinetic agent is evaluated in preterm and VLBW neonates in several randomized clinical trials; however, there are disagreements and controversy about the effect of Erythromycin on neonate oral nutrition (6, 8-16).

Erythromycin is a macrolide antibiotic, which is used as a prokinetic agent during the last decades and improves intestinal nutrition in preterm neonates (17). Studies on Erythromycin and feeding intolerance in neonates are categorized in two groups include prophylactic (starting treatment before the presence of feeding intolerance symptoms) and therapeutic (starting treatment after the presence of feeding intolerance symptoms) (3). There are different studies in these aspects, suggesting different dosages of Erythromycin and various methods (18). Erythromycin was evaluated as a prokinetic agent in the last 20 years and was motilin receptor agonist that affected on gallbladder and intestine, stimulate the intestine nerve and smooth muscle, increase intestine motility, strength stomach contraction, and improve intestine motility complex movements (19-22).

One study on premature neonates with less than 32 weeks' gestational ages evaluated prescribing a high dose of Erythromycin and reported that this dosage or Erythromycin could improve GI dysmotility and feeding in neonates significantly (14-16). Another study was prescribed low dose Erythromycin in premature neonates and suggested that this dosage of Erythromycin improved intestinal nutrition and reduced time duration to reach complete intestinal nutrition (9, 23). In most of the studies low and high doses of Erythromycin were assessed and did not report any serious adverse effects (6, 8, 9). One study on premature neonates reported that the intermediate dosage of Erythromycin had no concerning complications such as hypertrophic pyloric stenosis and in systematic reviews reported that prescribing intermediate to high dosage of Erythromycin did not show any adverse effects (17, 24).

2. Objectives

According to different findings of previous studies concerning the use of Erythromycin in premature neonates and also different dosage of Erythromycin used in these studies, as well as limited studies that used an intermediate dosage of Erythromycin, this study aimed to evaluate the effect of oral Erythromycin with intermediate dosage on treating feeding intolerance in preterm neonates in Isfahan, Iran.

3. Methods

3.1. Study Design and Participants

This study is a Randomized Clinical Trial (RCT) on preterm neonates admitted in neonate intensive care unit and internal department of neonates in Shahid Beheshti and Alzahra Hospitals, tertiary referral hospitals of Isfahan University of Medical Science (IUMS) during 2016 - 2017. A total of 159 premature neonates were assessed for eligibility, and finally, 77 neonates were included using the convenience sampling method.

The inclusion criteria were as follows: (1) premature neonates, (2) birth weight lower than 1800 g, (3) having two or more than two episodes of the presence of more than 50% of feeding volume (lavage) or feeding volume less than 75 mL/kg/day in 14th day after birth, (4) lack of congenital anomaly and (5) parent's willingness for participation. Neonates with sepsis before the study, gastrointestinal anomaly, cyanotic heart disease, a history of surgery on gastrointestinal system in the first 14 days after birth, using medications that had interaction with Erythromycin metabolism, arrhythmia and QT interval prolongation, and parent's unwillingness to continuing this study were excluded from the study. Research Ethics Committee approved the methodology of this study in IUMS, and this study was registered in the IRCT website (IRCT20120614010026N10).

3.2. Intervention

In this study, feeding was started for all neonates with 20 mL/kg/day feeding volume and if they tolerate it, 20 mL/kg/day was added to reach 150 mL/kg/day. The participants of this study were selected by a person who was not a colleague of this study and was divided into two groups by simple randomization. In the Erythromycin group, Erythromycin syrup was used (Kimidaru®, Tehran, Iran) with a dosage of 20 mg/kg/day (5 mg/kg/dose every 6 hours) for eight days. We used distilled water in the placebo group, in an equal volume with Erythromycin syrup. The syringes of Erythromycin and distilled water were similar in appearance, color, and cover. A trained nurse who was not involved in this study numbered these syringes and gave them to colleagues of this study. The syringes were divided among neonates without any awareness of the contents of the syringes. Before starting the study, the senior investigator explained the intervention to neonate's parents, and informed consent form was completed.

3.3. Primary and Secondary Outcomes

The average time to reach 75, 110, and 150 mL/kg/day feeding volume (mL) and the frequency (number) of milk intolerance (lavage) after the intervention were considered primary outcomes. Secondary outcomes were as follows: duration of oxygen dependency (days), length of hospital stay (days), incidence of necrotizing enterocolitis (NEC) (advanced, proven, and suspected), intravascular hemorrhage (IVH), patent ductus arteriosus (PDA), hypertrophic pyloric stenosis at the age of 4 weeks, chronic lung disease (CLD) and cholestatic jaundice, QT interval before and after intervention, sepsis and, the mortality rate.

NEC and CLD diagnosed by clinical criteria whereas PDA, IVH, hypertrophic pyloric stenosis and long QT syndrome were diagnosed by echocardiography (Esaote device), sonography (Esaote device),) and electrocardiogram (2000 Bionet model), respectively. All of the information was certified in the prepared forms by one specified staff in each center.

3.4. Sample Size and Analysis

Considering the lack of a report on the efficacy of an intermediate dose of Erythromycin, a pilot study was designed, and reported assessments in the references were used to estimate the sample size. We assumed that the smallest effect size is statistically significant (d < 0.1). According to Table 1 in Bell et al. study, the minimum sample size for each group was determined 50 ($\beta = 0.2$) ($\alpha = 0.05$, $\beta = 0.2 \rightarrow n = 50$). In the Whitehood et al. study, the sample size was suggested between 24 to 70. Based on the power of the two above studies, the sample size was determined as 30 subjects in each group.

Data were analyzed using the IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, ILL., USA). For reporting quantitative data, the mean and standard deviation (SD) and for reporting qualitative variables, number and percent were used. For comparing variables between the two groups, independent *t*-test, chi-square, and Mann Whitney tests were used. A two-tailed α level of 0.05 was considered a statistically significant level.

4. Results

In this study, 159 premature neonates were assessed for eligibility, and finally, 77 neonates were included in this study (Figure 1). From those, eight neonates were excluded because their parents showed no willingness to continue to collaborate. Moreover, 69 neonates were divided into two groups, and four neonates in the Erythromycin group and one neonate in the placebo group were excluded because of their incomplete data or death, and finally, data on 64 neonates (26 in the Erythromycin group and 38 in the placebo group) were analyzed (Figure 1)

Demographic data in the two groups were not statistically different. The mean gestational age in the Erythromycin and placebo groups were 29.83 ± 2.12 and 30.30 ± 2.75 weeks, respectively (P = 0.85) and the mean birth weight in the Erythromycin and placebo groups were 1198.65 ± 297.78 g and 1236.32 ± 305.84 g, respectively (P = 0.50). Gender distribution was not significantly different between the two groups (P = 0.8) (Table 1). The age of feeding onset in the Erythromycin and placebo groups were 3.88 ± 2.95 days and 2.63 ± 1.46 days, respectively; there were no statistical differences between the two groups (P = 0.24) (Table 1).

As the primary outcome, the average time to reach 75, 110, and 150 cc/kg/day feeding volume were significantly shorter in the Erythromycin group than placebo group (4.19 vs. 6.84 days, P < 0.001, 6.35 vs. 9.08 days, P < 0.001 and 9 vs. 11.46 days, P < 0.001 in the Erythromycin vs. placebo groups, respectively) (Table 2). Moreover, the frequency of milk intolerance was significantly lower in the Erythromycin versus placebo groups (0.35 ± 0.56 vs. 3.03 ± 3.08 in the Erythromycin and placebo groups, respectively; P < 0.001) (Table 2).

Although the incidence of clinical sepsis and NEC after the intervention was lower in the Erythromycin group than the placebo group, this difference was not significant (15.4% vs. 24.3%, P = 0.45 and 3.8% vs. 16.2%, P = 0.22 in the Erythromycin vs. placebo groups, respectively) (Table 2). The incidence of PDA, CLD, and IVH was not significantly different between the two groups (19.2% vs. 10.8%, P = 0.46, 23.1% vs. 18.9, P = 0.75 and 3.8% vs. 21.6%, P = 0.06 in the Erythromycin and placebo groups, respectively) (Table 2). The mean duration of oxygen dependency and mean length of hospital stay were not significantly different between the two groups (16.69 ± 23.85 vs. 17.78 ± 17.59 days, P = 0.83 and 31.12 ± 17.5 vs. 29.73 ± 15.22 days, P = 0.39 in the Erythromycin vs. placebo groups, respectively) (Table 2). Mortality was 3.8% in the Erythromycin group and 7.9% in the placebo group (P = 0.64) (Table 2).

For evaluating the Erythromycin complication, QT interval was assessed in electrocardiograms of neonates and the mean QT interval was not significantly different between the two groups before and after the intervention (0.37 and 0.39 in the Erythromycin and placebo groups after the intervention, P = 0.20) (Table 2). Direct jaundice presented in only one neonate in the Erythromycin group and no neonates in the placebo group showed cholestatic jaundice (P = 0.41). Stool culture findings before and after the intervention were not statistically different between the two groups and normal flora were grown in both groups. Interestingly, none of the infants in the Erythromycin group showed hypertrophic pyloric stenosis.

Table 1. Basic Characteristics of Neonates

Variables	Erythromycin Group	Placebo Group	P Value
Gestational age[a]	30.30 ± 2.75	29.83 ± 2.12	0.85
Birth weight[a]	1198.65 ± 297.78	1236.32 ± 305.84	0.5
Age at start of feeding[a]	3.88 ± 2.95	2.63 ± 1.46	0.24
RDS[b]	20 (76.9)	34 (89.5)	0.29
NCPAP[b]	18 (69.2)	34 (89.5)	0.06

Abbreviations: NCPAP, nasal continuous positive airway pressure; RDS, respiratory distress syndrome.
[a]Values are expressed as mean ± standard deviations (SD).
[b]Values are expressed as No. (%).

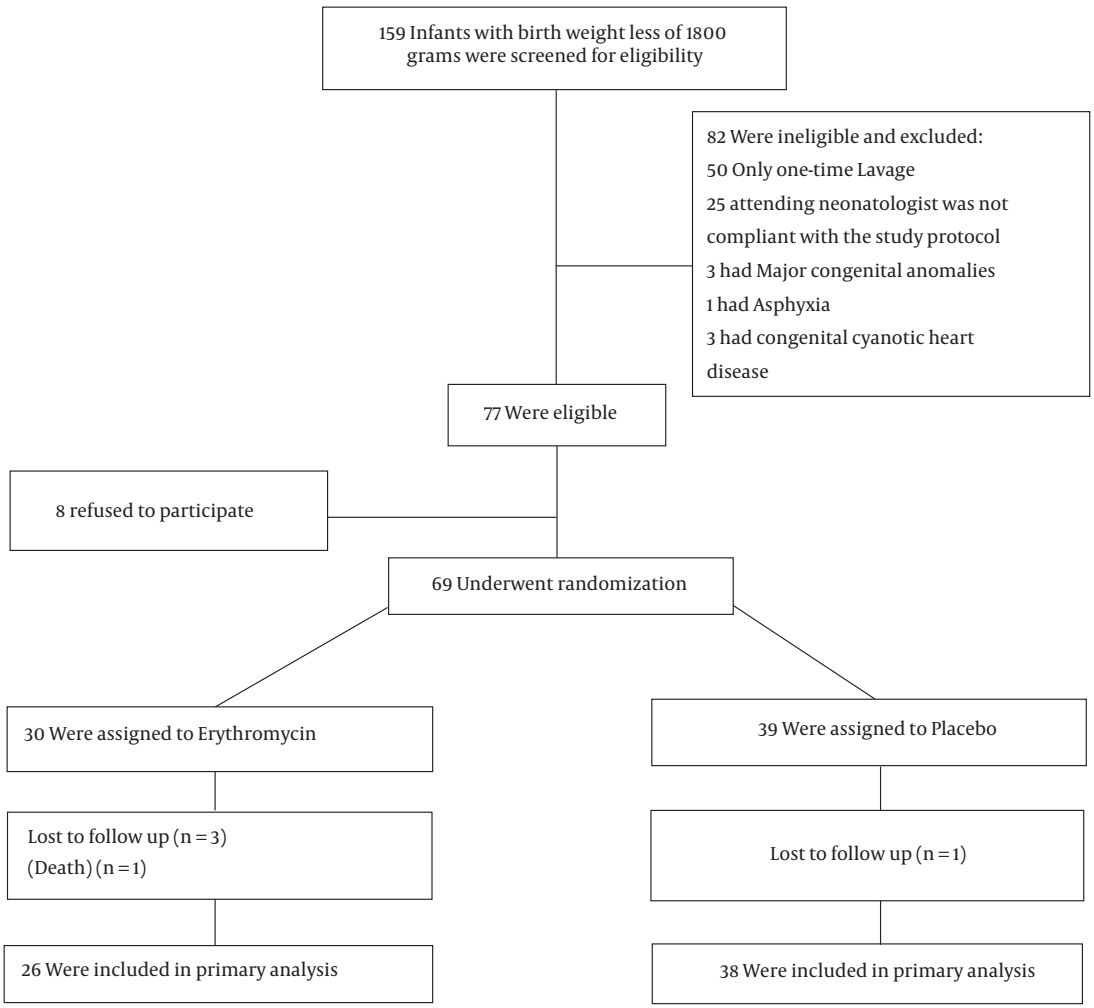

Figure 1. CONSORT diagram shows the flow of subjects in each stage of the study

5. Discussion

In this study, the effect of the intermediate dosage of Erythromycin on the treatment of feeding intolerance was assessed. In this study, the average time to reach 75, 110, and 150 mL/kg/day feeding volume were measured in neonates treated with Erythromycin and placebo and this time du-

Table 2. Primary and Secondary Outcomes in the Participants of the Two Groups

Variables	Erythromycin Group	Placebo Group	P Value
Time to reach to 75 mL/kg/day intestinal feeding volume, day[a]	4.19 ± 0.63	6.84 ± 3.83	< 0.001[b]
Time to reach to 110 mL/kg/day intestinal feeding volume, day[a]	6.35 ± 0.79	9.08 ± 4.03	< 0.001[b]
time to reach complete intestinal feeding volume, day[a]	9 ± 2.81	11.46 ± 4.14	< 0.001[b]
Feeding intolerance, lavage[a]	0.35 ± 0.56	3.03 ± 3.08	< 0.001[b]
Sepsis[c]	4 (15.4)	10 (27)	0.45
NEC[c]	1 (3.8)	6 (16.2)	0.22
IVH[c]	1 (3.8)	8 (21.6)	0.06
PDA[c]	5 (19.2)	4 (10.8)	0.46
Duration of oxygen dependency, day[a]	16.69 ± 23.85	17.78 ± 14.59	0.12
CLD[c]	6 (23.1)	7 (18.9)	0.75
QT Interval before intervention[a]	0.37 ± 0.04	0.39 ± 0.04	0.49
QT Interval after intervention[a]	0.37 ± 0.05	0.39 ± 0.03	0.5
Cholestatic jaundice[c]	1 (3.8)	0 (0)	0.41
Duration of hospitalization, day[a]	31.12 ± 17.5	29.73 ± 15.22	0.75
Death[c]	1 (3.8)	3 (7.9)	0.64

Abbreviations: CLD, chronic lung disease; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis, PDA, patent ductus arteriosus.
[a]Values are expressed as mean± standard deviations.
[b]P value < 0.05 is considered as significant.
[c]Values are expressed as No. (%).

ration was significantly lower in the Erythromycin group, suggesting the prokinetic property of this dosage of Erythromycin in feeding intolerance in preterm neonates.

Cairns et al. reported that neonates who were treated with a low dosage of intravascular Erythromycin had lower time duration to reach complete intestine feeding compared to those who received placebo (12). Moreover, Nuntnarumit et al. evaluated the high dosage of oral Erythromycin in neonates with the gestational age less than 32 weeks and showed beneficial effects of Erythromycin on feeding intolerance in comparison to placebo. The median time duration to reach a complete feeding volume was significantly shorter in the Erythromycin versus placebo groups (7 (6 - 9) vs. 13 (5 - 19) days; P < 0.001). The number of stopped feeding episodes was 1 (0 - 2) and 9 (2 - 13) in those who treated with Erythromycin and placebo (P < 0.001) (14).

However, in other studies, the average time to reach a complete feeding volume was not significantly different between neonates who received Erythromycin or placebo. In the study of Stenson et al. neonates were treated by 15 mg/kg infusion of Erythromycin 3 times a day. The average time to reach a complete feeding volume was 8 (5 - 12) and 9 (6 - 14) days in the Erythromycin and placebo groups (P = 0.45) (6). Patole et al. evaluated the effect of oral Erythromycin on 73 neonates and the time duration to reach a complete feeding volume were 93.5 and 104 hours in the Erythromycin and placebo groups (P = 0.6) (8).

In Elhennawy et al. study, the low dosage of Erythromycin was used for eight days in neonates with 29-36 weeks of gestational ages, and there was no significant difference between Erythromycin and placebo groups in terms of time duration to reach complete intestinal feeding volume (10). Although using an intermediate dosage of Erythromycin by scientists is limited, Ng and his colleagues evaluated the effect of an intermediate dosage of Erythromycin on preterm neonates and observed a significant reduction in time duration to reach complete intestinal feeding volume when compared to placebo. In their study, 45 neonates were assessed, and 5 mg/kg/dose oral Erythromycin (every 6 hours for 14 days) was prescribed. The mean time to reach complete intestinal feeding volume was 36.5 ± 7.4 and 54.7 ± 23.3 days in the Erythromycin and placebo groups, respectively (P = 0.01) (17).

According to the presence of studies that used low dosage and high dosage of Erythromycin and did not achieve appropriate findings on the average time to reach complete intestinal feeding volume and the frequency of milk intolerance, it is suggestive that very low or very high dosage of this medication has not suitable prokinetic properties, and it is better to plan more researchers on evaluating the intermediate dosage of this medication. This study finding is likely similar to limited studies that prescribed an intermediate dosage of Erythromycin, but for better decision making based on scientific evidence, more studies are needed in the fields of the intermediate dosage of Erythromycin on treating feeding intolerance in neonates.

Also, in our study, the incidence of Erythromycin com-

plications was evaluated, including prolongation of QT Interval, cholestatic jaundice, hypertrophic pyloric stenosis, and changes in the normal flora of stool. In this regard, none of them occurred in both groups, especially in the Erythromycin group suggesting the safety of Erythromycin in preterm neonates. In none of the previous studies that prescribed Erythromycin as prophylactic or for rescue, hypertrophic pyloric stenosis or changes in the normal flora of stool or other complications were reported.

This study has some strength and limitation points like other studies. In this study, the intermediate dosage of Erythromycin on feeding intolerance was evaluated that there was a limited number of studies in this situation and most of the studies evaluated low and high dosage of Erythromycin. First, limitation of this study is its small sample size that is too small for generalizing these findings to the general population and more studies with greater sample size are needed. Second, in this study, the number of NPO days before starting feeding was significantly higher in the Erythromycin group than controls and possibly affected the findings of this study. Maybe neonates in the Erythromycin group had more improvement in feeding tolerance due to more NPO days before starting feeding. In most of the previous studies, different dosages of Erythromycin were compared with placebo; there is a need to plan studies, comparing the effects of various dosages of this medication in the treatment of feeding intolerance.

5.1. Conclusions

Prescribing an intermediate dosage of Erythromycin could reduce the average time to reach complete intestinal feeding volume and the frequency of milk intolerance without indicating any complications and it may be safe for preterm neonates.

Footnotes

Authors' Contribution: Acquisition of data: Ashraf Mousavi; analysis and interpretation of data: Amir-Mohammad Armanian and Majid Mohammadizadeh; drafting of the manuscript: Ashraf Mousavi; critical revision of the manuscript for important intellectual content: Nima Salehimehr and Akbar Hassanzade; study supervision: Amir-Mohammad Armanian.

Clinical Trial Registration: This study was registered in the IRCT website (IRCT20120614010026N10).

Conflict of Interests: Authors declare that there is no conflict of interest in this study.

Ethical Approval: Research Ethics Committee approved the methodology of this study in Isfahan University of Medical Sciences (395997 / http://mui.ac.ir/).

Funding/Support: No financial support was received for this study.

Patient Consent: Before starting the study, the senior investigator explained the intervention to neonate's parents and informed consent form was completed.

References

1. Moreno Villares JM. Parenteral nutrition-associated liver disease [Parenteral nutrition-associated liver disease]. *Nutr Hosp*. 2008;**23 Suppl 2**:25–33. Spanish. [PubMed: 18714408].
2. Kim H, Lee JJ, Park SJ, Kim AR, Kim KS, Pi SY. Total parenteral nutrition-associated cholestasis in very low birth weight infants. *J Korean Soc Neonatol*. 2001;**8**(2):200–5.
3. Ng PC. Use of oral erythromycin for the treatment of gastrointestinal dysmotility in preterm infants. *Neonatol*. 2009;**95**(2):97–104. doi: 10.1159/000153093. [PubMed: 19218823].
4. Moreno Villare JM, Irastorza Terradillos I, Prieto Bozano G. [Complications of pediatric parenteral nutrition]. *Nutr Hosp*. 2017;**34**(Suppl 3):55–61. Spanish. doi: 10.20960/nh.1383. [PubMed: 29154669].
5. Andorsky DJ, Lund DP, Lillehei CW, Jaksic T, Dicanzio J, Richardson DS, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *J Pediatr*. 2001;**139**(1):27–33. doi: 10.1067/mpd.2001.114481. [PubMed: 11445790].
6. Stenson BJ, Middlemist L, Lyon AJ. Influence of erythromycin on establishment of feeding in preterm infants: Observations from a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 1998;**79**(3):F212–4. doi: 10.1136/fn.79.3.f212. [PubMed: 10194995]. [PubMed Central: PMC1720861].
7. Ng PC, Fok TF, Lee CH, Wong W, Cheung KL. Erythromycin treatment for gastrointestinal dysmotility in preterm infants. *J Paediatr Child Health*. 1997;**33**(2):148–50. doi: 10.1111/j.1440-1754.1997.tb01018.x. [PubMed: 9145359].
8. Patole SK, Almonte R, Kadalraja R, Tuladhar R, Muller R, Whitehall JS. Can prophylactic oral erythromycin reduce time to full enteral feeds in preterm neonates? *Int J Clin Pract*. 2000;**54**(8):504–8. [PubMed: 11198727].
9. Oei J, Lui K. A placebo-controlled trial of low-dose erythromycin to promote feed tolerance in preterm infants. *Acta Paediatr*. 2001;**90**(8):904–8. [PubMed: 11529540].
10. ElHennawy AA, Sparks JW, Armentrout D, Huseby V, Berseth CL. Erythromycin fails to improve feeding outcome in feeding-intolerant preterm infants. *J Pediatr Gastroenterol Nutr*. 2003;**37**(3):281–6. doi: 10.1097/00005176-200309000-00015. [PubMed: 12960650].
11. Ng SC, Gomez JM, Rajadurai VS, Saw SM, Quak SH. Establishing enteral feeding in preterm infants with feeding intolerance: A randomized controlled study of low-dose erythromycin. *J Pediatr Gastroenterol Nutr*. 2003;**37**(5):554–8. doi: 10.1097/00005176-200311000-00009. [PubMed: 14581796].
12. Cairns PA, Craig S, Tubman R, Roberts RS, Wilson J, Schmidt B. Randomised controlled trial of low-dose erythromycin in preterm infants with feed intolerance. *Pediatr Res*. INC 351 West Camden st, Baltimore, MD. INT pediatric research foundation; 2002. p. 379A–80A.
13. Aly H, Abdel-Hady H, Khashaba M, El-Badry N. Erythromycin and feeding intolerance in premature infants: A randomized trial. *J Perinatol*. 2007;**27**(1):39–43. doi: 10.1038/sj.jp.7211618. [PubMed: 17036029].
14. Nuntnarumit P, Kiatchoosakun P, Tantiprapa W, Boonkasidecha S. Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr*. 2006;**148**(5):600–5. doi: 10.1016/j.jpeds.2005.12.026. [PubMed: 16737869].
15. Ng PC, So KW, Fung KS, Lee CH, Fok TF, Wong E, et al. Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neona-*

tal Ed. 2001;**84**(3):F177–82. doi: 10.1136/fn.84.3.f177. [PubMed: 11320044]. [PubMed Central: PMC1721258].
16. Ng PC, Lee CH, Wong SP, Lam HS, Liu FY, So KW, et al. High-dose oral erythromycin decreased the incidence of parenteral nutrition-associated cholestasis in preterm infants. *Gastroenterol*. 2007;**132**(5):1726–39. doi: 10.1053/j.gastro.2007.03.043. [PubMed: 17484870].
17. Ng YY, Su PH, Chen JY, Quek YW, Hu JM, Lee IC, et al. Efficacy of intermediate-dose oral erythromycin on very low birth weight infants with feeding intolerance. *Pediatr Neonatol*. 2012;**53**(1):34–40. doi: 10.1016/j.pedneo.2011.11.007. [PubMed: 22348492].
18. Ng E, Shah VS. Erythromycin for the prevention and treatment of feeding intolerance in preterm infants. *Cochrane Database Syst Rev*. 2008;(3). CD001815. doi: 10.1002/14651858.CD001815.pub2. [PubMed: 18646077].
19. Hawkyard CV, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: Benefits versus risks. *J Antimicrob Chemother*. 2007;**59**(3):347–58. doi: 10.1093/jac/dkl537. [PubMed: 17289772].
20. Peeters TL. Erythromycin and other macrolides as prokinetic agents. *Gastroenterol*. 1993;**105**(6):1886–99. doi: 10.1016/0016-5085(93)91089-z. [PubMed: 8253365].
21. Di Lorenzo C, Flores AF, Tomomasa T, Hyman PE. Effect of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms. *Dig Dis Sci*. 1994;**39**(7):1399–404. doi: 10.1007/bf02088040. [PubMed: 8026249].
22. Jadcherla SR, Klee G, Berseth CL. Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res*. 1997;**42**(3):365–9. doi: 10.1203/00006450-199709000-00018. [PubMed: 9284278].
23. Mohammadizadeh M, Ghazinour M, Iranpour R. Efficacy of prophylactic oral erythromycin to improve enteral feeding tolerance in preterm infants: A randomised controlled study. *Singapore Med J*. 2010;**51**(12):952–6. [PubMed: 21221501].
24. So KW, Ng PC. Erythromycin and gastrointestinal dysmotility in preterm infants. *East J Med*. 2010;**15**(4):146.