CHATER 5

DISCUSSION

The results of this study show an efficacy of low dose erythromycin for treatment of feeding intolerance in premature infants. Infants in treatment group achieved full feeding faster approximately one week earlier than that of placebo group. The effect of erythromycin on the gastrointestinal motility is quite dramatic as indicated by significantly reduced gastric residuals and numbers of withhold feeds. The treatment effects could be seen even in very premature infants since almost all of the infants in this trial were less than 32 weeks of gestation supporting that motilin receptors are presented in the gastrointestinal tract in these tiny infants and that these receptors are able to response to exogenous motilin agonist.

Since the definition of feeding intolerance in infants is problematic due to lack of agreement on the definition, making it difficult to compare the results among the trials. The definition used in this trial likely indicates mild to moderate feeding intolerance, that explain why the age of enrollment is quite earlier than that of previous report.(33, 39, 40) Although, this trial recruited mild to moderate severity of feeding intolerance, it still showed the efficacy of the treatment. These findings support the strategy of treatment of symptomatic infants rather than prophylaxis strategy which has been failed to demonstrate the efficacy of erythromycin.(35, 36, 38)

Some physiological studies on gastroduodenal activity by using a gastroduodenal manometry system in preterm infants showed that infants less than 32 weeks' gestation lacked of migratory motor complex (phase III).(13, 19) However, the results of other studies and our findings indicated a dramatic response and a decrease in gastric emptying time and gastrointestinal transit time after initiation of erythromycin.(23, 30, 32, 37, 41)

The conflicting clinical outcomes of this study compared to other clinical trials using erythromycin in symptomatic infants with feeding intolerance(39, 40) may depend upon several factors: (1) Most of enrolled infants in this study involved mild to moderate

cases as noticed by earlier age at enrollment and by that almost all infants in placebo group reached full feeding within 3 weeks after enrollment as compared to a mean of 57 days in ElHennawy A, et al and a mean of 31 days in Ng SC, et al. Milder forms of feeding intolerance might indicate more mature gastrointestinal neuroendocrine network and better response to exogenous motilin agonist., (2) Dose of erythromycin used in this study was higher than that of ElHennawy's study which used a very low dose of 1.5 mg/kg/dose via nasogastric tube. It had been shown that antroduodenal motility response to erythromycin was dose dependent(13) and erythromycin of 2 mg/kg/dose intravenously had a better clinical response and higher blood level than 1 mg/kg/dose intravenously.(34), (3) Loading dose erythromycin of 10 mg/kg/dose orally every 6 hours in this study was used to ensure adequate therapeutic blood level and the previous studies showed that higher dose erythromycin stimulated antral motility and decreased gastric emptying time.(23, 30), (4) Low dose erythromycin after loading dose as used in this study would serve two different pathways in motor effects of erythromycin by which loading dose induced antral contractility by activation of motilin muscular receptors, followed by induced migratory motor activity by activation of motilin neuronal receptors with a lower maintenance dose.(50-52), (5) Other factors might involved in enhancing gastrointestinal motility such as more amount of nutrients, that passed stomach through small intestine by effect of erythromycin, would stimulate gastrointestinal peptide and neuroendocrine network.(18, 53)

With regard to the dose and dosage form of erythromycin in this trial, low dose (4 mg/kg/dose) after initial loading dose given orally was selected since it has been shown that intravenous erythromycin 1-2 mg/kg/dose was effective in treatment of feeding intolerance in premature infant and blood level of intravenous erythromycin was 4-10 times higher than oral route.(30,32,35) In addition, given low dose of drug orally is preferable, because, theoretically, it is safer and more practical than given intravenously, and also avoids any possible side-effects related to high dose intravenous erythromycin. Unfortunately, blood level of erythromycin was not measured in this study. But dramatic clinical response in treatment group could indirectly indicate that therapeutic level being

achieved. Erythromycin ethyl succinate was chosen due to it had been shown to be less reported side-effects than other forms of erythromycin used in infants.

The total course of 7 days used in this trial seems to be adequate for treatment of mild to moderate feeding intolerance. There were no rebound signs and symptoms of intolerance after completed course, unless other secondary causes like sepsis, re-opening PDA, or progressive chronic lung disease developed. However, the most appropriate and safest duration of treatment could not be concluded. It is possible that the more severe case, the longer duration may require. We believe that keeping duration as short as possible would be preferable to avoid any side-effects related to the medication.

There were no differences between the two groups with respects to cholestatic jaundice or elevated liver enzyme. There was no case of hypertrophic pyloric stenosis observed in this trial during 2-years period of the study. Hearing impairment has been reported only in high dose intravenous erythromycin lactobionate or gluceptate or high dose oral form of erythromycin estolate(42,43) , that very unlikely to occur in low dose oral erythromycin ethyl succinate. The incidence of sepsis and necrotizing enterocolitis were similar between the two groups. Two infants died in the treatment group, one died at 3 months of age from severe bronchopulmonary dysplasia which seemed not relate to given medication. The other infant died of NEC stage III which occurred 11 days after discontinuation of erythromycin. It was difficult to conclude if there was any association between erythromycin and developing NEC in this case, however, previous studies using erythromycin either prophylaxis strategy or treatment symptomatic infants with feeding intolerance have not reported this association.(29, 34-36, 38-40, 42)

Duration of parenteral nutrition was significantly shorter in the treatment group. However, the clinical magnitude of the difference could not clearly be seen, since the differences in the complications associated with parenteral nutrition and prolonged catheterization could not be demonstrated between the two groups. These findings may be due to that enrolled infants were not severe cases of feeding intolerance and we also apply gut priming or trophic feeding as our routine neonatal care of the very preterm infants. In addition, the calculated sample size primarily for the primary outcome is not enough power to detect the differences in secondary outcomes.

The limitations of small sample size of this study need to be considered to interpret the results. Significant effect of the medication may occur by chance, while type II errors may explain no significant differences in secondary outcomes such as side effects of medication or complications associated with prolonged parenteral nutrition or catheter related infection. Therefore, further study in a larger scale population is warranted.