

Is Erythromycin Useful for Dysmotility of Prematurity? : A Randomised Controlled Trial in a Neonatal Unit of a Rural Medical College, India

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Abstract: ***Aim:** To find out the efficacy and safety of low dose oral erythromycin (6mg/kg/day) in gastro intestinal dysmotility of premature infants. **Methods:** A prospective double blind randomised placebo controlled study was done on 82 preterm infants admitted to the neonatal unit. The infants were randomly allocated to receive oral erythromycin or equivalent volume of normal saline as placebo. The time taken to establish quarter, half, three quarter and full enteral feed after drug treatment were compared in between two groups. Potential adverse effects of oral erythromycin were assessed. **Results:** Infants with < 30 weeks, 30- 34 weeks and 34- 38 weeks gestational age achieved full enteral feeding (FEF) at the of 19.44 days, 12.81 days and 9.36 days respectively in erythromycin group whereas in control group it took 34.33days, 21.50 days and 18.65 days. None of the infant developed cholestasis, pyloric stenosis or QT prolongation in both groups. Only 1 infant from erythromycin group and 8 from control group had developed necrotising entero-colitis.*

Keywords: erythromycin, preterm infants, gastro-intestinal dysmotility, necrotising entero-colitis

1. Introduction

Neonatal growth restriction is a major and universal problem in preterm especially low birth weight infants. It is very common to take several days to weeks to establish FEF (full enteral feed) in high risk preterm neonates, which is evidenced by adverse effects of prolonged use of parenteral nutrition. [1] Gastrointestinal dysmotility (ileus of prematurity) and necrotising enterocolitis are potential causes of feed intolerance. Erythromycin is a macrolide antibiotic that had been available since 1950. It is rarely used as an antibiotic per se now a days and primarily used for its prokinetic effect on the gastrointestinal tract. [2] Motilin a naturally occurring peptide produced by enterochromaffin cells present in duodenal and jejunal mucosa and is released periodically in the fasting condition. Premature babies do not appear to demonstrate cyclical fluctuations in plasma motilin levels. Receptor binding studies demonstrated that erythromycin has high affinity for motilin receptor, and *in vitro* a motilin receptor antagonist can block erythromycin induced antral smooth muscle contraction. [3] At lower doses (1mg/kg) an erythromycin induced motor complex was propagated distally from stomach. [4] However repetitive non propagated antral contraction can be induced by erythromycin in neonates of less than 32 weeks of gestation. [5] The purpose of the study is to evaluate the efficacy and safety of erythromycin as prokinetic agent in gastrointestinal dysmotility of prematurity.

2. Methods

A randomised controlled double blind hospital based study was done over a period of 1 year between September 2018 to August 2019 in the neonatal unit of a rural based tertiary care centre.

Patients: The preterm infants admitted in the neonatal unit of Midnapore Medical College, during the defined study period and fulfilling inclusion criteria were enrolled for the study. The preterm infants with birth weight <1500 grams having following criteria were included: i) < 75ml/kg/day of enteral feeding, ii) bile stained gastric residuals, iii) abdominal distension increase in abdominal girth > 15% of baseline, iv) gastric residuals > 25% of preceding 4 hour fed volume on 2 occasions, v) vomiting > twice in 24 hours. The preterm infants with other co-morbidities like respiratory distress syndrome, birth asphyxia, seizures and the infants with gross congenital anomalies are excluded from the study.

Sample size: Statistics of 2years data our neonatal unit before the study denotes that over 70% of the VLBW (very low birth weight) infants fail to achieve full enteral feeding (FEF) by 14th day of life mostly due to high prevalence of feed intolerance. Our previous experience of using prokinetics suggested that uncomplicated gastro-intestinal dysmotility could achieve FEF within 1 week of treatment with prokinetics drug. As about 100 to 130 VLBW infants of our unit developed dysmotility in previous year on an average, it was estimated that 41 infants would be required in each group of randomised controlled study to keep the margin of error at the 5% and confidence interval at 85%.

Randomisation: Eligible infants were assigned to receive either oral erythromycin or normal saline. A designated staff nurse not involved in newborn care performed the randomisation by minimising the three variables: gestational age, birth weight and age of introduction of feed. The attending team were unaware of the assignment.

Drug: Due to low risk of cardiac complication and easy to administer the oral route was preferred. Infants allocated to receive active drug were given oral erythromycin (Althrocin ; Erythromycin Estolate 125mg/5ml, each ml was diluted with 5 ml of sterile water to 5mg/ml solution) 6mg/kg/day 8-

12 hourly doses till the FEF achieved. Those allocated to receive the placebo solution were given an equivalent volume of normal saline. Both active drug and the normal saline mixed thoroughly with milk to mask their appearance from the attending nursing team. When oral feeding had to be withheld after the start of study the all oral medication including the active drug and placebo were also stopped.

All VLBW infants were started on parenteral nutrition from day of admission and feeding started according to the gestational age. Orogastric tube feeding was started at 1ml/kg/3hr and increased cautiously at a rate of 1ml/3h according to the tolerance. Infants were fed preferably with mother’s milk, but commercially available formulas were also used if mother’s milk was not available.

Liver function test was in done all patients for cholestasis and USG of abdomen was done to exclude pyloric stenosis as a part of adverse effect of erythromycin. All infants were kept under continuous ECG monitoring during the full course of the study.

The primary aim of the study was to find the time to reach full enteral feeding (150ml/kg/day). The secondary outcome of interest were: a) duration of parenteral nutrition, b) duration of hospital stay, c) weight at discharge, d) incidence of necrotising enterocolitis of stage 2 or worse.

Statistics: Statistical analysis was performed by windows version of software, R- Project for Statistical Computing (version 3.51). 2sample t- test and chi-squared test were performed for the comparison between 2 groups. The results were analysed on an intention to treat basis. The study was approved by clinical research ethics committee of Midnapore Medical College and informed parental consent was obtained before randomisation and enrolment.

3. Results

A total of 39 infants received oral erythromycin and 43 infants received placebo solution. Case and control population were grouped into 3 weight groups (<1kg, 1kg-1.25kg and 1.25kg-1.5kg) and 3 gestational age groups (<30weeks, 30-34 weeks, 34-38 weeks) and checked their distribution for both the case and control population. (table 1,2)

Table 1: Distribution of infants according to the birth weight

Birth weight	Case(frequency)	Control (frequency)	P –value
<1 kg	12	4	0.0827
1-1.25 kg	17	18	0.7027
1.25-1.5 kg	14	17	0.4232

Table 2: Distribution of infants according to the gestational age

Gestational age	Case(frequency)	Control (frequency)	P –value
<30 weeks	11	8	0.7785
30-34 weeks	21	11	0.0917
34-38 weeks	11	20	0.0300

The infants in the oral erythromycin group achieved quarter, half, three quarter and full enteral feeding significantly earlier in comparison to control group.

Table 2: Age of achievement of amount of feed and duration of hospital stay

Gestational age	Variable	Case (days)	Control (days)	P- value
<30 weeks	Quarter feed	12.45	20.33	0.00518
	Half feed	14.70	26.50	0.00121
	Three quarter feed	17.10	30.83	0.00083
	Full enteral feed	19.44	34.33	0.00065
	duration of hospital stay	38.22	69.83	0.00001
30-34 weeks	Quarter feed	6.71	10.64	0.06009
	Half feed	8.76	14.64	0.02563
	Three quarter feed	10.47	18.00	0.01618
	Full enteral feed	12.81	21.50	0.01264
	duration of hospital stay	30.57	39.28	0.01490
34-38 weeks	Quarter feed	5.63	9.75	0.02352
	Half feed	6.72	12.37	0.02192
	Three quarter feed	7.86	15.50	0.00872
	Full enteral feed	9.36	18.65	0.00364
	duration of hospital stay	16.18	23.12	0.02234

Table 4 summarises the comparison of potential adverse effects like cholestasis, pyloric stenosis, and cardiac arrhythmia in both case and control group with 95% confidence interval.

Table 4: Comparison of potential adverse effects

Variable	Case (n= 39)	Control (n=43)	P- value	95% confidence interval
QT interval before drug treatment (ms)	0.35	0.37	0.7339	0.34-0.40
QT interval after drug treatment (ms)	0.36	0.37	0.7263	0.35-0.38
Total serum bilirubin(mg/dl)	3.36	3.90	0.7775	(-1.126) - (0.846)
Direct bilirubin (mg/dl)	0.53	0.64	0.0285	(-0.214)- (0.012)
SGOT (U/L)	42.07	43.59	0.3658	(-4.868) - (1.827)
SGPT (U/L)	47.21	48.06	0.6141	(-4.173) - (2.487)
Pyloric muscle thickness(mm)	1.37	1.80	0.5237	(-0.464) - (0.075)
Pyloric diameter (mm)	9.54	9.85	0.3284	(-0.941)- (0.320)

2 infant from the erythromycin group and 7 infants from control group expired either due to sepsis or due to necrotising entero-colitis (NEC).

Table 5: Comparison of outcome of the infants

	Case (n = 39)	Control (n = 43)	Total (n = 82)
Survived	37(94.87%)	36(83.72%)	73(89.02%)
Expired	2(5.12%)	7(16.27%)	9(10.97%)
Sepsis	1(2.56%)	3(6.97%)	4(4.87%)
Necrotising entero-colitis	1(2.56%)	8(18.60%)	9(10.97%)

There was no significant variation in weight of the infants during discharge between 2 groups.

Table 6: Comparison of weight of infants during discharge

Gestational age	Case (mean weight in gram)	Control (mean weight in gram)	P – value
<30 weeks	1342.22	1330.83	0.3085
30-34 weeks	1373.38	1368.35	0.7949
34-38 weeks	1404	1385.87	0.3634

4. Discussion

The prokinetic action of erythromycin act at the level of stomach and the proximal small bowel of both human and animal. [6] The result of our randomised controlled trial indicate significant variation in the use of erythromycin as a prokinetics in preterm infants. Stimulation of motilin receptor results in frequent antral contraction and gastric muscular tone. This study shows allocation of infants in both erythromycin and placebo group were identical. In table no. 1 & 2 distribution of case and control in respect to the birth weight and gestation age showing no significant variation (p value >0.05). The infants in the erythromycin group achieved quarter, half, three fourth and full enteral feeding earlier than those of placebo group (p value <0.05); similar finding was showed by P C Ng et al. [7] Regarding adverse effect of erythromycin there was no significant changes in QT interval before and after this low dose oral erythromycin medication (p value 0.7). [8] None of the infants in both group showed cholestasis; the mean direct serum bilirubin were 0.53 mg/dl and 0.64 mg/dl in case and control group respectively. [9] There was no significant increase in pyloric diameter (<11mm) or pyloric muscle thickness (<3mm) in the erythromycin group. [10] In this study there were only 2 deaths in the erythromycin group whereas 7 in control group. Deaths were either due to sepsis or necrotising entero-colitis. Only 1 infant in erythromycin group had developed NEC whereas 8 infants in control group, which is a significant finding.

5. Conclusion

There is significant evidence to suggest erythromycin as prokinetics in dysmotility of prematurity in this study. Small study population and other confounding factor are the limitation of this study. Since premature babies are at risk of increase mortality and morbidity in delayed establishment of FEF more trials are needed considering the adverse effects with larger study population.

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