COMPARISON OF MEAN TIME OF ACHIEVING FULL ENTERAL FEED WITH ORAL ERYTHROMYCIN AS COMPARED TO PLACEBO FOR THE TREATMENT OF GASTROINTESTINAL DYSMOTILITY IN LOW-BIRTH-WEIGHT PRETERM NEONATES

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ABSTRACT

Objective: To compare the mean time to receive a full feed with oral erythromycin compared with placebo for the treatment of intestinal dysmotility among low birth weight preterm neonates**.**

Methods: It was randomized controlled trial & 100 preterm neonates were randomly allocated to two groups using lottery method. Group A received erythromycin (12.5mg/kg/dose every 6 hour through oral route or nasogastric tube) while Group B received placebo solution (equivalent volume of normal saline orally 6 hourly). Both groups received erythromycin and placebo for 14 days. If patient developed necrotizing enterocolitis or deteriorated after start of study, erythromycin and placebo solution was discontinued.

Results: The mean age of all cases was 6.74 ± 2.29 days while mean age in Erythromycin group was 6.66 ± 2.48 days and in placebo group was 6.82 ± 2.10 days. In erythromycin group there were 35(70%) male and 15(30%) female cases while in placebo group there 21(42%) male and 29(58%) female cases. In erythromycin group 19(38%) cases were on mother feeding and 31(62%) cases were formula feeding and in placebo group 23(46%) cases were on mother feeding while 27(54%) cases were on formula feeding. The mean time to achieve enteral feeding in erythromycin group was 23.04 ± 4.42 days and in placebo was 26.46 ± 4.95 days. The mean time to achieve enteral feeding was statistically less in erythromycin group was statistically less as compared to placebo group, p-value < 0.001.

Conclusion: The mean time of achieving full enteral feed with oral erythromycin was significantly less as compared to placebo for treatment of gastrointestinal dysmotility in low-birth-weight preterm neonates. So, therapeutic effects of erythromycin can be utilized to achieve early feeding. This can also help to minimize the related morbidity and hospital stay.

Keywords: Gastrointestinal dysmotility, preterm birth, prematurity, low birth weight, enteral feeding, oral erythromycin

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INTRODUCTION

The World Health Organization (WHO) defines low birth weight (LBW) as birth weight Infants born 'immediately' are referred to as preterm, defined by the WHO as gestational age at birth <37 weeks complete. Infants can also be LBW because they are born 'very young' according to their age (minimum gestational age,

SGA), which has several meanings, most of which are birth weight less than 10 percent of the gestational age of pregnancy. time, SGA, or both. But babies can be born prematurely without having an LBW. About 15 million babies are born preterm per year i.e. before completion of 37 weeks of gestation[1]. The rate of preterm birth is 5% to 18% across 184 countries[1]. In Pakistan there were 750000 preterm births in 2010, the ranking of Pakistan was at fourth number in global ranking list in term of preterm births[2]. Premature birth is associated with certain complications like respiratory distress syndrome, apnoea, patent ductus arteriosus, poor gut motility, liver immaturity, hyperbilirubinemia, hypoglycaemia and susceptibility to infections etc. which cause almost 1million neonatal deaths every year [1]. In preterm low birth weight neonates gastrointestinal dysmotility is a major issue.

Active or non-gastrointestinal dysfunction (GI) is characterized by an intolerance to increased feeding with increased abdominal residues, occasional relapses or vomiting and in severe cases severe abdominal distension. In contrast to crotizing enterocolitis (NEC) and GI perforation alongside postpartum corticosteroids and prostaglandin inhibitors, bloody stools, abdominal erythema and signs and symptoms suggesting peritonitis are usually absent. Abdominal radiograph shows normal intestinal separation but no pneumatosis intestinalis or free gas in the stomach9.

Infectious biomarkers, including serial serum C-active proteins and neutrophil CD64 levels are not elevated10. The stomach easily shrinks 24-48 h after stopping the milk supply but the condition usually returns during the re-feeding of internal food. This clinical association is believed to be the result of abnormal, dysfunctional and incompatible intestinal flaws and immaturity GI11.

Although GI dysmotility of prematurity per se is a very serious condition, fear of NEC and other serious gastrointestinal disorders leads to dietary restriction and chronic hyperalimentation. Long-term malnutrition is associated with an increased risk of serious illness and sometimes life-threatening complications, including parenteral-related malnutrition (PNAC) cholestasis, recurrent catheter-related septicemia, malnutrition, and rickets. biochemical, and pain and anesthetic risks associated with repeated insertion of the long and middle line 12.

Achieving optimal enteral feeding in preterm low birth weight neonates is difficult because of poor gut motility and risk of developing necrotizing enterocolitis. Delay in achieving optimal enteral feeding prolongs hospital stay and baby may require total parenteral nutrition which has serious complications e.g. hepatic injury, cholestatic jaundice, portal fibrosis, nutrient deficiency and catheter related septicaemia etc.[3] Delayed enteral feeding leads to growth restriction and failure to thrive.

In preterm neonates who have gastrointestinal dysmotility, prokinetic therapy can be considered. Erythromycin, a macrolide antibiotic, has prokinetic property. Erythromycin has been used for treatment of gastro-oesophageal reflux, post-op gut dysmotility, diabetic gastropathy etc. and can be used for the treatment of intestinal dysmotility in the preterm. Erythromycin act on neural motilin receptors on cholinergic neurons and smooth muscle motilin receptors of stomach and small intestine, stimulation of these receptors result in antral contractions [3]and enhance gastric motility. So as a result gastric contents are pushed distally thus reducing gastric emptying time.A randomized controlled study was done in Prince of Wales Hospital, Chinese university of Hong Kong in which neonates in treatment group had attained full enteral feeding 10 days earlier as compared to placebo group 3A study conducted at the Nonatal Intensive Care Unit, Zekai Tahir Burak Maternity and Teaching Hospital, Ankara, Turkey showed that the time to get a complete diet was short in erythromycin group 22.46 ± 3.4 days compared to the placebo group 27.00 ± 5.8 days 4. Another study in Neonatology Section, Department of Paediatrics, Shiraz University of Medical Sciences, Shiraz, Iran has shown in results that oral erythromycin increase feeding tolerance in premature neonates control group (13.5±6.3), erythromycin group (9.2±1.5) ($p<0.032$) 5. Erythromycin is an effective option for treatment of gastrointestinal dysmotility, however there are limited studies done at local and international level. As no local study is available and international studies suggest that time to achieve full enteral feeding is shorter in erythromycin group[4-5], so this study aimed to determine whether use of erythromycin in preterm babies is beneficial in improving gastric emptying and establishing early enteral feeding.

METHODS

This study was a randomized controlled trial conducted over 6 months from December 19, 2017 to June 19, 2019 in the Department of paediatrics, Lahore general hospital, Lahore. Sample size of 100 (50 in each group) is calculated with 90% power of test and 95% confidence interval. Non-probability consecutive sampling was used to achieve the required sample size of 100 preterm low birth weight neonates. All babies aged 3rd day to 10th day of life of either gender born preterm infant with birth weight 1000gm -1500 gm having gastrointestinal dysmotility were included in the study. Infant with severe congenital abnormalities e.g. cleft palate, congenital heart disease (as per clinical examination and echocardiography), neonate with gastrointestinal abnormalities such as oesophageal atresia, intestinal stenosis or atresia, hirschsprung's

disease (as per history, clinical record and diagnostic imaging modalities), neonates with necrotizing enterocolitis (as per clinical findings and diagnostic imaging modalities) and neonates with septicaemia (C reactive protein is > 6 mg/L) were excluded from the study. 100 preterm neonates who present in the paediatrics neonatal unit and emergency department of LGH fulfilling the inclusion criteria were selected. After an informed consent from the parents, the preterm neonates were randomly allocated to two groups using lottery method into Group A and group-B. Preterm neonates assigned to group A received erythromycin (12.5mg/kg/dose every 6 hour through oral route or nasogastric tube). Those allocated to group B received placebo solution (equivalent volume of normal saline orally 6 hourly). Preterm was given oral feed according to protocol (via nasogastric tube, orogastric tube or oral route). Both groups received erythromycin and placebo for 14 days. If patient develop necrotizing enterocolitis or deteriorate after start of study, all oral medicine including erythromycin and placebo solution was discontinued. The duration of achieving full enteral feeding, type of milk used was noted in questionnaire along with demographic details of neonate by researcher herself.

All the collected data was entered and analysed in SPSS version 20. The numerical variables like age and duration of achieving full enteral feed i.e. 150ml/kg/day, gestational age and weight were measured as mean and standard deviation. Gender and type of milk as categorical variable was measured in frequency or percentage. Independent sample t-test was applied for comparison of mean duration of achieving full enteral feeding between two groups, taking p $\leq$0.05 as statistically significant. Data was stratified for age, gender, duration, weight gestational age and feeding type (formula feed and mother feed) to address effect modifiers. Post stratification student t-test was applied.

RESULTS

The mean age of all cases was 6.74 ± 2.29 days while mean age in Erythromycin group was 6.66 ± 2.48 days and in placebo was 6.82 ± 2.10 days. Table-1 In erythromycin group there were 35(70%) male and 15(30%) female cases while in placebo group there were 21(42%) male and 29(58%) female cases. Table -2' In erythromycin group 19(38%) cases were on mother feeding and 31(62%) cases were formula feeding and in placebo group 23(46%) cases were on mother feeding while 27(54%) cases were on formula feeding. Table -3. The mean birth weight of babies in Erythromycin and placebo group was 1252.54 ± 131.82 g and 1264.94 ± 149.04 g. The mean gestational age in Erythromycin was 32.66 ± 2.27 weeks and in placebo group was 32.48 ± 2.31 weeks. Table -4. The mean time to achieve enteral feeding in erythromycin group was 23.04 ± 4.42 days and in placebo was 26.46 ± 4.95 days. The mean time to achieve enteral feeding was statstically less in erythromycin group was statistically less as compared to placebo group, p-value < 0.001. Table -5. In age group of 3-6 days the mean time to achieve enteral feeding in erythromycin group was statistically lower (23.17 ± 4.76 days) as compared to placebo group (26.12 ± 5.24 days), p-value < 0.05. In 7-10 days of age groups, the mean time to achieve enteral feeding in erythromycin group was statistically lower (22.92 ± 4.17 days) as compared to placebo group (26.76 ± 4.76 days), p-value < 0.05. Table -6. In male cases the mean time to achieve enteral feeding in erythromycin group was statistically lower (23.14 ± 3.88 days) as compared to placebo group (25.48 ± 4.59 days), p-value < 0.05. In female cases, the mean time to achieve enteral feeding in erythromycin group was statistically lower (22.80 ± 5.63days) as compared to placebo group (27.17 ± 5.16 days), p-value < 0.05. Table -7. In cases with weight < 1300 g the mean time to achieve enteral feeding in erythromycin group was statistically lower (23.54 ± 4.10 days) as compared to placebo group (26.84 ± 5.11 days), p-value < 0.05. In cases of 1300-1500 g, the mean time to achieve enteral feeding in erythromycin group was statistically lower (22.41 ± 4.83days) as compared to placebo group (26.08 ± 4.86 days), p-value < 0.05. Table -8. In cases with gestational age of 28-32 weeks the mean time to achieve enteral feeding in erythromycin group was statistically lower (23.65 ± 4.37 days) as compared to placebo group (27±5.44 days), p-value < 0.05. In cases with 32-36 weeks of gestation the mean time to achieve enteral feeding in erythromycin group was statistically lower (22.52 ± 4.48 days) as compared to placebo group (26±4.56 days), p-value < 0.05. Table -9. In cases on mother fed the mean time to achieve enteral feeding in erythromycin group was statistically lower (22.89 ± 4.93 days) as compared to placebo group (26.61 ±5.02 days), p-value < 0.05. In cases on bottle feeding the mean time to achieve enteral feeding in erythromycin group was statistically lower (23.13 ± 4.16 days) as compared to placebo group (26.33 ± 4.98 days), p-value < 0.05. Table -10.

Table -1 Descriptive Statistics of age in both groups

Study groups	Mean	S.D	Minimum	Maximum
Age (days)				
Erythromycin (n=50)	6.66	2.48	3.00	10.00
Placebo (n=50)	6.82	2.10	3.00	10.00
Total (n=100)	6.74	2.29	3.00	10.00

Table -2 Frequency distribution of gender in both groups

		Study groups		Total
		Erythromycin	Placebo	
Gender	Male	35(70.0%)	21(42.0%)	56(56.0%)
	Female	15(30.0%)	29(58.0%)	44(44.0%)
Total		50(100.0%)	50(100.0%)	100(100.0%)

Table -3 Frequency distribution of types of feeding in both groups

	Study groups		Total
	Erythromycin	Placebo	
Types of feeding			
Mother feeding	19(38%)	23(46%)	42(42%)
Formula feeding	31(62%)	27(54%)	58(58%)
Total	50(100%)	50(100%)	100(100%)

Table -4 Descriptive Statistics of weight and gestational age (years) in both groups

Study groups	Mean	S.D	Minimum	Maximum
Birth Weight (g)				
Erythromycin	1252.54	131.82	1041.00	1487.00
Placebo	1264.94	149.04	1001.00	1489.00
Total	1258.74	140.12	1001.00	1489.00
Gestational Age (weeks)				
Erythromycin	32.66	2.27	28.00	36.00
Placebo	32.48	2.31	28.00	36.00
Total	32.57	2.28	28.00	36.00

Table -5 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups

Study groups	Mean	S.D	Minimum	Maximum
Days to achieve enteral feed (days)				
Erythromycin	23.04	4.42	16.00	34.00
Placebo	26.46	4.95	17.00	34.00
Total	24.75	4.98	16.00	34.00

t-test = -3.64 p-value < 0.001

Table -6 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups with respect to age groups

Age groups	Study groups	Mean	S.D	p-value
3-6	Erythromycin n=24)	23.17	4.76	0.046
	Placebo (n=24)	26.12	5.24	
7-10	Erythromycin (n=26)	22.92	4.17	0.003
	Placebo (n=26)	26.76	4.76	

Table -7 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups with respect to gender

Gender	Study groups	Mean	S.D	p-value
Male	Erythromycin (n=35)	23.14	3.88	0.047
	Placebo (n=21)	25.48	4.59	
Female	Erythromycin (n=15)	22.80	5.63	0.013
	Placebo (n=29)	27.17	5.16	

Table -8 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups with respect to birth weight (g)

Weight (g)	Study groups	Mean	S.D	p-value
< 1300 g	Erythromycin (n=28)	23.54	4.10	0.012
	Placebo (n=25)	26.84	5.11	
1300-1500 g	Erythromycin (n=22)	22.41	4.83	0.013
	Placebo (n=25)	26.08	4.86	

Table -9 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups with respect to gestational age (weeks)

Gestational age	Study groups	Mean	S.D	p-value
28-32 weeks	Erythromycin (n=23)	23.65	4.37	0.026
	Placebo (n=23)	27.00	5.44	
32-36 weeks	Erythromycin (n=27)	22.52	4.48	0.007
	Placebo (n=27)	26.00	4.56	

Table -10 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups with respect to types of feeding

Types of feeding	Study groups	Mean	S.D	p-value
Mother fed	Erythromycin (n=19)	22.89	4.93	0.021
	Placebo (n=23)	26.61	5.02	
Bottle fed	Erythromycin (n=31)	23.13	4.16	0.010
	Placebo (n=27)	26.33	4.98	

Table -11 Descriptive Statistics of Days to achieve enteral feed (days) in both groups in both groups with respect to duration

Duration	Study groups	Mean	S.D	p-value
< 6 days	Erythromycin (n=22)	23.41	4.33	0.028
	Placebo (n=26)	26.42	4.77	
≥6 days	Erythromycin (n=28)	22.75	4.55	0.008
	Placebo (n=24)	26.50	5.25	

In cases with duration of < 6 days the mean time to achieve enteral feeding in erythromycin group was statistically lower (23.41 ± 4.33 days) as compared to placebo group (26.42 ± 4.77 days), p-value < 0.05. In cases with ≥ 6 days the mean time to achieve enteral feeding in erythromycin group was statistically lower (22.75 ± 4.55 days) as compared to placebo group (26.50 ± 5.25 days), p-value < 0.05. Table -2

DISCUSSION

Feeding intolerance is a common problem in treating premature babies. Nourishing intolerance manifests itself as abdominal cramps, recurrence, recurrent vomiting, or abdominal cramps, in severe cases. Feeding intolerance leads to poor weight gain, long hospital stay and infections that may be hospitalized due to intermediate catheters (umbilical catheter, central venous catheter, intravenous catheter), and long-term nutrition. The most common reason to feed into intolerance is lower abdominal movement due to 23 maturations.

Premature, low birth weight infants (LBW) often increase nutritional intolerance. Neonatologists often choose to withhold nutrition or are reluctant to advance the daily diet rolls for these children. Whole foods, with the aim of delivering 150 mL / kg / day of daily fluids, are difficult to achieve. Inadequate caloric intake can lead to birth defects and accelerate parental nutrition[14].

Although the exact mechanisms remain unclear, macrolide antibiotic erythromycin has been used for decades as a prokinetic agent to facilitate the continuation of the internal diet in premature babies. Data from previous clinical trials are inconsistent, probably due to differences in the times and routes of erythromycin administration, as well as the different duration of erythromycin[15] treatment. Prokinetics is often used to treat nutritional intolerance in premature babies. Prokinetics are widely used by metocloperamide, cisapride, and domperidone. Other serious side effects are related to prokinetics, extrapyramidal reactions and weakness with metocloperamide and a QT-enhanced QT interval. In addition, the use of domperidone in premature babies remains controversial[16].

Erythromycin is also an antibiotic commonly used to treat nutritional intolerance in premature babies. This macrolide has a motilin-like effect and stimulates peristalsis. Erythromycin acts as a motilin agent, by binding to the motilin receptor in the antrum and the upper duodenum and leading to increased resistance to antrum[24]. The motilin hormone stimulates the digestive system and attracts phase III migraine (MMC) in nearby intestines, reducing bowel movement to 62. This process is not available until 32 weeks of gestation[17]. Some studies in children with intestinal dysmotility have shown benefits from erythromycin, while others have provided inconsistent results[18-19].

The study reported that the basic features of both groups were similar, with gestational periods of 31.4 weeks (SD 1.7) in the erythromycin group and 32.4 weeks (SD 2.2) in the placebo group. The intervals between receiving full nutrition were not significantly different between the two groups, with 10 days (SD 5.3) in the erythromycin vs. placebo group. 8 (SD 6.5) in the placebo group (P = 0.345) [20]. In the present study the age of pregnancy at Erythromycin was 32.66 ± 2.27 weeks and in the placebo group it was 32.48 ± 2.31 weeks.

The study reported the days required to achieve full nutrition (36.5 ± 7.4 vs. 54.7 ± 23.3 days, respectively; p = 0.01), the length of parental maintenance (p <0.05), and the time required to achieve weight ≥2500 g (p <0.05) were the shortest in the group of erythromycin compared to the control group. The incidence of parental food-related cholestasis (PNAC) and crotizing enterocolitis (NEC) - phase II after 14 days of treatment was significantly lower (p <0.05) in the erythromycin group. No significant differences were observed in cases of sepsis, bronchopulmonary dysplasia, or premature retinopathy. There are no side effects associated with erythromycin treatment. Therefore, studies have concluded that moderate doses of oral erythromycin are effective and safe in the treatment of intolerance in VLBW infants. The incidence of PNAC and phase II NEC was significantly lower in the erythromycin21 group. The median duration of intake in the erythromycin group was 23.04 ± 4.42 days and placebo were 26.46 ± 4.95 days. The mean time to internal intake was statistically lower in the erythromycin group was lower statistically compared to the placebo group, p-value <0.001.

One study reported that the erythromycin group received full nutrition before the placebo group (10.5 ± 4.1 vs 16.3 ± 5.7 days, respectively; P = 0.01) had fewer episodes of abdominal residue (P <0.05) and shorter parental feeding (PN) (PN). <0.05)[23]. One study reported that the time taken to establish half, three-quarters, and a full diet after drug treatment was significantly shorter in the group receiving oral erythromycin than those receiving placebo (p <0.05, p <0.05 and p <0.0001 respectively.). There was also a trend that suggested that more children with chronic food allergies developed cholestatic jaundice instead of a placebo than the oral erythromycin group (10v 5 infants). None of the children receiving oral erythromycin have heart disease, dysrhythmia, pyloric stenosis, or septicemia caused by drug-resistant organisms. Therefore, this study suggested that oral erythromycin is effective in facilitating intrauterine nutrition in low-risk preterm infants with very severe intestinal dysmotility. Treated infants can

reach full feeding 10 days in advance, and this can lead to significant savings in hyperalimentation. However, until the safety of erythromycin in preterm infants is confirmed, this treatment should be continued. Prophylactic or regular use of this drug for the treatment of minor cases of intestinal dysmotility may not be permitted in this category[22].

CONCLUSION

The study concludes that the mean time of achieving full enteral feed with oral erythromycin was significantly less as compared to placebo for treatment of gastrointestinal dysmotility in low-birth-weight preterm neonates. So, therapeutic effects of erythromycin can be utilized to gain early feeding. This can also help to minimize the related morbidity.

ETHICAL APPROVAL

The study was approved by the Institutional Review Board of Postgraduate Medical Institute / Ameer-ud-Din Medical College/Lahore General hospital, Lahore via Research No. 00-54-22.

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