

ROLE OF ERYTHROMYCIN IN THE MANAGEMENT OF GASTRO ESOPHAGEAL REFLUX IN INFANTS

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ABSTRACT

Regurgitation and vomiting of milk due to GER is a common problem in infants especially under 6 months of age. It is a self limiting condition and improves as the infant becomes older & starts sitting, but in some cases pharmacological treatment may be required.

Objective: This study aims to evaluate the effectiveness of erythromycin as a prokinetic agent in otherwise healthy infants with gastro esophageal reflux.

Design: Interventional study

Place & Duration of Study: Outpatient Pediatric Clinic of Govt. Kot Khawaja Saeed Teaching Hospital (KEMU) Lahore. From 1st May 2014 till 31st October 2014.

Patients & Methods: Infants (15 days to 1 year) attending Pediatric Outpatient Clinic who were otherwise healthy except for history of regurgitation and vomiting after feed were included in the study. Erythromycin drops were started in a dose 10-15 mg/kg/day for a period of 2 weeks.

Results: A total of 30 infants, 15 days to 10 months age were included in the study. Male to female ratio was 1.1:1. Twelve infants presented with history of regurgitation, twelve with history of vomiting and six with regurgitation and vomiting both. Twenty infants showed improvement within a week. Four infants showed partial improvement and four did not respond at all, while two infants were lost to follow up.

Conclusion: Erythromycin has been found a helpful drug for the management of regurgitation and vomiting in infants.

Keywords: Erythromycin, GER (gastro esophageal reflux), GERD (gastro esophageal reflux disease), LES (Lower esophageal sphincter)

INTRODUCTION

Regurgitation and vomiting is common in infants due to gastro esophageal reflux (GER) or gastro esophageal reflux disease (GERD). GER occurs in over two third of healthy infants ⁽¹⁾. GER is a normal physiological process that occurs in healthy infants several times a day. Regurgitation (spitting up) is a passive movement of stomach contents into the pharynx or mouth. Vomiting is the forceful movement of stomach contents through the mouth by autonomic and voluntary muscles contraction sometimes triggered by reflux ⁽²⁾. Gastro esophageal (GER) reflux is defined as the retrograde and involuntary passage of stomach contents into the esophagus with or without accompanied regurgitation and vomiting ⁽³⁾. The fluid reaching the proximal esophagus and mouth causes regurgitation and vomiting ⁽⁴⁾.

GER resolves on its own by one year of age due to elongation of esophagus, a more upright position, increased tone of lower esophageal sphincter (LES) and a more solid diet. Regurgitation and spitting up occurs in 50% of all infants ⁽⁵⁾. GERD encompasses troublesome symptoms or complications associated with GER, like irritability, weight loss or poor weight gain, difficulty in feeding, regurgitation with or without hematemesis, wheezing, stridor, cough or hoarseness. Sandifer syndrome is a specific manifestation of pediatric GERD and consists of abnormal posturing with head tilt, torticollis and arching of back ⁽⁶⁾.

The natural barriers or defenses to GER develop as the infant becomes older thus explaining the decrease in the incidence of GER & GERD as infant approaches one year of age. The risk factors for GER or GERD are prematurity, asphyxia, sepsis, broncho pulmonary

dysplasia, neurodevelopmental delay, congenital and acquired gastro intestinal anomalies (congenital diaphragmatic hernia, fistula, omphalocele) ⁽⁴⁾.

The presence of GER or GERD may be confirmed by specific diagnostic investigations such as esophageal pH-metry ⁽⁷⁾, multiple intraluminal impedance (MII) monitoring ⁽⁸⁾. In addition, milk scan or technetium scintigraphy, esophageal manometry, ultrasonography, endoscopy and biopsy, barium studies, pepsin assay in tracheal aspirate are done in some cases ⁽⁴⁾.

In the conservative treatment for GER and GERD positioning of infant at 30° upward in prone position or left lateral position causes less reflux ^(9,10), frequent small feeds and probiotics ⁽¹¹⁾ may help. A two weeks trial of hypoallergenic milk formula may be tried to exclude cow's milk protein allergy ⁽¹²⁾. Thickening of milk feeds is also tried but it may increase the risk of necrotizing enterocolitis ^(13,14).

The infants who do not respond to conservative treatment pharmacological treatment may be required. Erythromycin which is a prokinetic drug has been found useful in GER & GERD ⁽¹⁰⁾. Metoclopramide another prokinetic drug has been used but there are adverse effects seen in upto 34% of children like lethargy, irritability, gynecomastia and extra pyramidal reactions and has caused permanent tardive dyskinesia ⁽¹⁵⁾. There is limited evidence for its efficacy and significant potential adverse effect profile. Another prokinetic drug is domperidone. It can cause extra pyramidal central nervous system side effects. The ESPGHAN (European Society for Pediatric gastroenterology, Hepatology and Nutrition) working group on GER concluded that available data for both domperidone and metoclopramide do not support their use in GERD ⁽¹⁵⁾.

Cisapride was used previously but it was withdrawn because of concerns about fatal cardiac toxicity due to prolonged QT interval ⁽¹⁶⁾. Bethanicol can cause bronchospasm and there is no evidence to support its efficacy in reducing GER in children. Another group of medicine used for the treatment of GER and GERD are mucosal protectors. Gaviscon (Sodium-alginate) has been used but has side effects like renal impairment and congestive cardiac failure due to high sodium content ⁽¹⁷⁾. Acid suppression by buffering histamine H₂ receptor antagonists (cimetidine, ranitidine and famotidine); or by reducing secretion of gastric acid (proton pump inhibitors like omeprazole and lansoprazole). These agents can increase the risk of necrotizing enterocolitis and infections in neonates ^(18, 19, 20). H₂ receptor antagonists can cause irritability, head banging, headache, somnolence and rapid tachyphylaxis which is a draw back to their chronic use. Proton pump inhibitors have idiosyncratic reactions (up to 14%),

drug-drug interactions, drug induced hyper gastrinemia and drug induced hypochlorhydria. There may be headache, diarrhea, constipation and nausea, parietal cell hyperplasia and occasional fundal gland polyps and benign changes. Enterochromafin like cell hyperplasia is also a result. Hypochlorhydria associated with H₂RAs and PPIs may increase rates of community acquired pneumonia and gastro enteritis in children ⁽¹⁵⁾. Surgical intervention like fundoplication is reserved for infants with severe GERS who have failed aggressive medical management.

The objective of study was to use oral erythromycin for the management of regurgitation and vomiting in otherwise healthy infants.

PATIENTS AND METHODS

An interventional study was done in the Outpatient Pediatric Clinic of Govt. Kot Khawaja Saeed Teaching Hospital (KEMU) Lahore, for a period of 6 months i.e. from 01st May 2014 till 31st October 2014.

Thirty (30) infants were included in the study who had history of vomiting and / or regurgitation but were otherwise healthy. They were given antiemetic drugs in previous 2-3 weeks with no improvement. The infants with prematurity, age less than 2 weeks, congenital malformations, intestinal obstruction and infections were excluded. A detailed history was taken and a thorough physical examination was done for each infant. All the findings were recorded in a special proforma. Patients name, father's name, age, sex, date, address, registered number, presenting complaints, history, examination findings and investigations if any and follow up were recorded.

Erythromycin drops (Erythrocin Abbott) were prescribed in a dose of 10-15 mg/kg/day in two divided doses for a period of 2 weeks. Mothers were strictly advised not to give any other drug for regurgitation or vomiting.

The patients were called weekly and questions were asked about any improvement in symptoms and any side effects of erythromycin. The patients were weighed, examined and record kept in the proforma.

RESULTS

A total of thirty (30) infants were included in the study. There were 16 males and 14 females with male to female ratio of 1.1:1. The age ranged from 15 days to 10 months. Mean age was 3 ± 2.15 months. Four (13.3%) infants were less than one month. Four (13.3%) infants were of one month of age. Ten (33.3%) infants were of 2 months of age. Six (20%) infants were of 3 months of age. Two (6.7%) infants were of 4 months of age. Two (6.7%) infants were of 7 months of age. One

infant (3.3%) was of 8 months of age and one infant (3.3%) was of 10 months of age.

Five infants (16.7%) infants were weighing less than 3 kg. Ten infants (33.3%) were weighing between 3 and 4 kg. Six infants (20%) were between 4 and 5 kg. Six (20%) infants were between 5 and 6 kg. Two infants (6.7%) were between 6 and 7 kg. One infant (3.3%) was weighing 8.7kg. Twelve (40%) infants presented with history of regurgitation. Twelve (40%) infants presented with history of vomiting. Six (20%) infants presented with regurgitation & vomiting both. Eighteen infants had additional complaints also. Seven (23.3%) infants presented with history of failure to thrive also. Six (20%) infants had history of abdominal colic also. Three (10%) infants had history of constipation and two (6.6%) infants had history of arching also [Figure 1].

The physical examination findings were normal for every infant. Fifteen (50%) infants were exclusively breast fed. Six infants (20%) were getting mother's feed as well as cow's milk feed. Five infants (16.7%) were getting mother's feed and formula feed both. Four (13.3%) infants were getting formula feed only.

Twenty (66.7%) infants showed improvement in regurgitation and vomiting within a week. Four (13.3%) infants showed partial improvement regurgitation and vomiting. Four (13.3%) infants did not respond at all. Two (6.7%) infants were lost to follow up. (Table – 1)

During the study no side effects of erythromycin were observed.

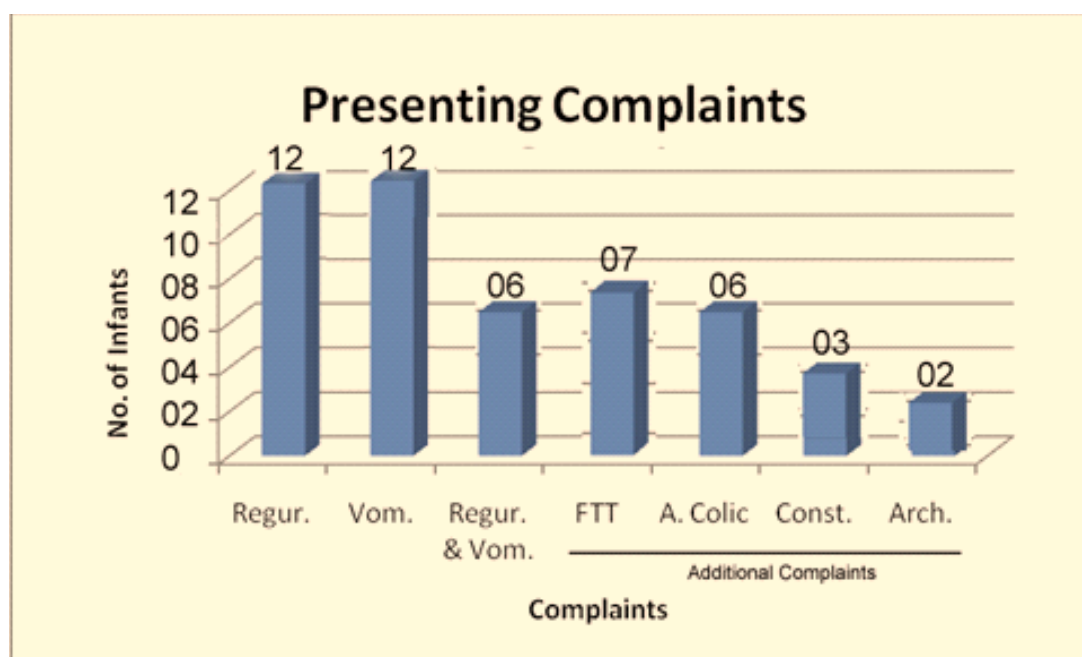


Figure 1: Number of infants with presenting and additional complaints

Table 1: Number of infants showing improvement on erythromycin treatment

Before Treatment				1 st Week After Treatment				2 nd Week After Treatment			
No. of infant	No. of Regurg	No. of Vomit	No. of Vomit & Regurg	No. of infant	No. of Regurg	No. of Vomit	No. of Vomit & Regurg	No. of infant	No. of Regurg	No. of Vomit	No. of Vomit & Regurg
12	10-12/d			8	6-8/d			2	4-6/d		
12		8-10/d		8		4-6/d		1		2-4/d	
6			4-6 Vomits & 8-10 Regurg	4			2-4 Vomits & 4-6 Regurg	1			2-3 vomits & 2-3 Regurg

DISCUSSION

Regurgitation and vomiting is common in infants due to gastro esophageal reflux (GER) or gastro esophageal reflux disease (GERD). The typical patient with GER is a well grown baby who typically feeds well and spits up milk without any discomfort or change in behavior. This is an example of 'healthy spitter'. It is benign and self-limited.

Erythromycin which is a prokinetic agent has been found useful in GER and GERD. There is enough evidence that erythromycin has its motor effect on gastrointestinal tract by activation of neural motor receptors present on cholinergic neurons and motilin receptors present on smooth muscles of upper gastrointestinal tract⁽²¹⁾. This leads to greater amplitude and frequency of antral contractions^(22,23) and increase in the tone of proximal gastrointestinal tract⁽²⁴⁾. There is suppression of pyloric pressure waves which leads to reduced pyloric outlet resistance resulting in gastric emptying and increase in duodenal contraction & its frequency. Combination of all these mechanisms produce powerful propulsive forces that effectively propel the gastric contents distally and thus improve upper gastrointestinal motility. The possible adverse effects are increased risk of pyloric stenosis when erythromycin is used within 2 weeks of life⁽²⁵⁾. Moreover, cardiac arrhythmias have been related to erythromycin intravenous administration⁽²⁶⁾.

In our study 66.7% infants showed improvement in regurgitation and vomiting within a week. In a study by Aanpreung & Vagavadul⁽²⁷⁾ all non-critically ill patients who had erythromycin improved symptoms. Similarly in a study by Zatman et al.⁽²⁸⁾ in erythromycin group most patients had negative gastric aspirates (45.9%) than in the metoclopramide group (35.1%).

Most of the studies on erythromycin are on the effect of feeding tolerance in preterm babies. In a randomized controlled study by NG et al.⁽²⁹⁾, out of 56 VLBW infants, 27 infants received erythromycin 12.5 mg per kg per day and 29 infants received the placebo solution. After 15 days of age, the infants in erythromycin group achieved enteral feeding much earlier than the placebo group.

In another study by Aly et al.⁽³⁰⁾, 25 premature infants suffering from feeding intolerance were divided in 2 groups. In the first group premature babies were given oral erythromycin 1 mg per kg per 8 hours and in the second group placebo was given (normal saline). In the erythromycin group fewer episodes of gastric residuals were seen in infants more than 32 weeks of age ($p < 0.05$).

In a study by Sekteera⁽³¹⁾, 39 preterm babies were given oral erythromycin, 9 out of 10 infants responded to treatment within 2 hours. In a study by Costalos et al.⁽³²⁾, erythromycin 10 mg per kg 8 hourly or placebo was given orally for 7 days in a double blind randomized crossover study of 20 preterm infants. It was concluded that oral erythromycin in food intolerant preterm infants enhances both enteral contractility and whole gut transit time.

In patients with dysmotility disorder associated with GERD, such a significant gastroparesis, erythromycin may be considered as described by Gremse,⁽³³⁾ Mohan⁽³⁴⁾ and Poddar⁽³⁵⁾.

In infants with dysmotility disorders associated with prematurity, in low birth weight infants recovering from abdominal surgery and in older children with a variety of their gastrointestinal disorders, prokinetic effect of erythromycin was observed in a review article by Curry et al.⁽³⁶⁾. Promotility drugs including erythromycin seem to improve gastric emptying, to reduce emesis and to enhance LES tone thus alloying to treat clinical features of GER⁽³⁷⁾.

CONCLUSION

Erythromycin has been found a helpful drug for the management of regurgitation and vomiting in infants in the study, but randomized trials are required on greater number of infants with regurgitation and vomiting to establish its usefulness.

REFERENCES

1. Ann & Lurie RH. Gastroesophageal reflux in infants & children. Children Hospital of Chicago. <http://www.2.luriechildrens.org/ce/online/article.aspx?ArticleID=325>.
2. National collaborating center for women's and children's health (UK) Gastro esophageal reflux disease. Recognition, diagnoses and management in children and young people. London National Institute for Health and Care excellence (UK) January 2015. <http://www.nice.org.uk/guidance/ng1/evidence/ng1/dyspepsiagerd-in-children-andyoungpeople-fullguidelines-1784557-accessjuly17,2015>.
3. Baird DC, Daunsen J, Harker MD and Aarsen S, Karmas DO. Diagnosis and treatment of gastro esophageal reflux in infants and children. Am Fam Physician. 2015; 92(8): 705-714
4. Kultursay N. Gastroesophageal reflux (GER) In preterms: current dilemmas and unresolved problems in diagnosis and treatment. Turkish J Pediatr 2012; 54: 561-569.

5. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med 2000; 154(2): 150-154.
6. Lehvald N, Krausch M, Franke C, Assmann B, Adam R & Knoefel TW. Sandifer Syndrome – A multidisciplinary diagnostic & therapeutic challenge. Eur J Pediatr Surg. 2007; 17(3): 206-207.
7. Birch LJ, Newell JS. Gastroesophageal reflux disease in preterm infants: current management and diagnostic dilemmas. Archives of Disease in Childhood. 2009; 94(5): F379-F383.
8. Omari IT and Davidson PG. Multipoint measurement of intragastric pH in healthy preterm infants. Archives of Disease in Childhood. 2003; 88(6): F517-F520.
9. Van Wijik MP, Benninga MA, Davidson GP, Haslam R, Omari TI. Small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral portion in infants. J Pediatr 2010; 156: 744-748.
10. Omari T. Gastroesophageal reflux in infants: can a simple left side positioning strategy help this diagnostic and therapeutic conundrum? Minerva Pediatr 2008; 60: 193-200.
11. Indrio F, Riezzo G, Raimondi F et al. *Lactobacillus reuteri* accelerates gastric emptying and improves regurgitation in infants. Eur J Clin Invest 2011; 41: 417-422.
12. Rudolph CD, Mazur LJ, Liptak GS et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32: (suppl): S1-31.
13. Wenzl TG, Schneider S, Scheele F, et al. Effects of thickened feeding on gastroesophageal reflux in infants; a placebo-controlled cross over study using intraluminal impedance. Pediatrics 2003; 111: e355-359.
14. Woods CW, Oliver T, Lewis K, Yang Q. Development of necrotizing enterocolitis in premature infants receiving thickened feeds using SimplyThick®. J Perinatol. 2012; 32(2):150.
15. Vandenplas Y, Ashkenazi A, Belli D et al. A proposition for the diagnosis and treatment of gastroesophageal reflux disease in children; a report from a working group on gastroesophageal reflux disease. Working group of European Society of Pediatric Gastroenterology and Nutrition (ESPGAN). Eur J Pediatr 1993; 152: 704-711.
16. Meclennan S, Ungood C, Cash-Gibson L, Logan S, Gilbert RE. Cisapride treatment for gastroesophageal reflux in children. Cochrane Database Systemic Review 2010; CD002300.
17. Corvaglia L, Aceti A, Mariani E et al. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-esophageal reflux disease in preterm infants. Aliment Pharmacol Ther 2011; 33: 466-470.
18. Guillet R, Stoll BJ, Cotten CM et al. Association of H₂ blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2006; 117: e137-142.
19. Bianconi S, Gudavalli M, Sutija VG et al. Ranitidine and late-onset sepsis in neonatal intensive care unit. J Perinat Med 2007; 35: 147-150.
20. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr 2007;44: 41-44.
21. Otterson M and Sama SK. Gastrointestinal motor effects of erythromycin. Am J Physiol 1990; G355-363.
22. Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. Engl J Med 1990; 322: 1028-1031.
23. Bruley des Varannes S, Parys V, Ropert A, Chayvialle JA, Roze C and Galmiche JP. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. Gastroenterology 1995; 109: 32-39.
24. Fraser R, Shearer T, Fuller J, Horowitz M, Dent J. Intravenous erythromycin overcomes small intestinal feedback on antral, pyloric and duodenal motility. Gastroenterology 1992; 103: 114-119.
25. Mahon EB, Rosenman BM, Kleiman BM. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. J Pediatr 2001; 139(3): 380-384.
26. Gouyon BJ, Benoit A, Betremieux P et al. Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. Pediatr Infect Dis J, 1994; 13(9): 840-41.
27. Aanpeung P & Vajaradul C. Clinical use of Erythromycin in children with gastro esophageal

- dysmotility. *J Med Assoc Thai* 2001; 84 (7): 1021-6
28. Zatman TF, Hall JE, Harwer M. Gastric residual volume in children: A study comparing efficacy of erythromycin and metoclopramide as prokinetic agents. *Br J Anesth.* 2001; 86 (6): 869-7
29. Ng CP, So WK, Fung CSK, Leg HC, Fok FT, Wong E, Cheung LK, Cheng BFA. Randomized controlled study of oral erythromycin for the treatment of gastrointestinal dysmotility in preterm infants. *Archives disease Childhood* 2001; 84(3): F177-F182.
30. Aly H, Abdel Hady H, Khashaba M & El-Badry N. Erythromycin and feeding intolerance in premature infants; a randomized trial. *J Perinatol* 2007; 27: 39-43.
31. Sekteera W, Nuntnarumit P, Supapannachart S. Oral erythromycin for treatment of feeding intolerance in preterm infants: a preliminary report. *J Me Assoc Thai* 2002 ;85: S1177-82.
32. Costalos C, Gounaris A, Varhalama E, Kokori F, Alexiou N, Kolovou E. Erythromycin as a prokinetic agent in preterm infants. *J Pediatr Gastroenterol Nutr.* 2002; 34(1):13-15
33. Gremese AD. GERD in the pediatric patient: management considerations. *Med Gen Med* 2004; 6(2):13. Published online May 6, 2004.
34. Mohan N. Gastroesophageal Reflux Disease. October 2010. Media/Gallery. <http://drneelammohan.com/2010/10/gastroesophageal-reflux-disease-2/>.
35. Poddar U. Diagnosis and management of Gastroesophageal Reflux Disease (GERD): An Indian Perspective. *Indian Pediat* 2013; 50: 119-126.
36. Curry JJ, Lander TD, Stringer MD. Review Article: erythromycin as a prokinetic agent in infants and children. *Aliment Pharmacol Therap* 2001; 15(5): 595-603.
37. Vandenplas Y, Rudolph CD, Rudolph DC. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric gastroenterology, Hepatology and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009; 49: 498-547.