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Efficacy of proton pump inhibitors and H2 blocker in the treatment of symptomatic gastroesophageal reflux disease in infants

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Purpose: Gastroesophageal reflux disease (GERD) occurs in pediatric patients when reflux of gastric contents presents with troublesome symptoms. The present study compared the effects of omeprazole and ranitidine for the treatment of symptomatic GERD in infants of 2–12 months.
Methods: This study was a clinical randomized double-blind trial and parallel-group comparison of omeprazole and ranitidine performed at Children Training Hospital in Tabriz, Iran. Patients received a standard treatment for 2 weeks. After 2 weeks, the patients with persistent symptoms were enrolled in this randomized study.
Results: We enrolled 76 patients in the present study and excluded 16 patients. Thirty patients each were included in group A (ranitidine) and in group B (omeprazole). GERD symptom score for groups A and B was 47.17±5.62 and 51.93±5.42, respectively, with a *P* value of 0.54, before the treatment and 2.47±0.58 and 2.43±1.15, respectively, after the treatment (*P*=0.98). No statistically significant differences were found between ranitidine and omeprazole in their efficacy for the treatment of GERD.
Conclusion: The safety and efficacy of ranitidine and omeprazole have been demonstrated in infants. Both groups of infants showed a statistically significant decrease in the score of clinical variables after the treatment.

Key words: Gastroesophageal reflux, Infant, Omeprazole, Ranitidine

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Introduction

Gastroesophageal reflux (GER) refers to retrograde movement of gastric contents through the lower esophageal sphincter (LES) into the esophagus[1]. Studies on normal infants demonstrated episodes of reflux as much as 73 times per day[2]. Infant reflux becomes evident in the first few months of life, peaks at 4 months old and disappears in up to 88% by 12 months old and almost completely by 24 months old[1]. GER is common in infants, but gastroesophageal reflux disease (GERD) defined as reflux associated with pathologic signs and symptoms is uncommon[2,3].

GERD is manifested more often with regurgitation (especially postprandial), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion) and results in failure to thrive[1]. GERD may also predispose some infants to chronic respiratory diseases including cough, asthma and recurrent pneumonia[2]. Discrimination between physiologic and pathologic GER and its manifestations remains a challenge in infants[4]. Troublesome GERD is reported in 5% to 8% of infants[5-8].

Recent recommendations suggest that clinical history could be a sufficient and reliable tool to diagnose GERD[4,5].

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for Evaluation of Gastroesophageal Reflux in infants and children includes treatment recommendations for both nonpharmacologic therapy, such as thickened infant formula and attention to positioning and pharmacologic treatment[2,9].

Acid suppressing drugs used to treat GERD include H2 receptor antagonists (H2RAs) such as ranitidine and proton pump inhibitors (PPIs) likeomeprazol[10]. H2RAs are limited in their ability to inhibit postprandial gastric acid secretion and are ineffective in controlling reflux symptoms[11].

In contrast to H2RAs, PPIs block the final step of acid secretion, resulting in intense and long-lasting acid suppression[12]. Except for the new class of esomeprazole, efficacy of PPIs in newborns and infants aged up to 11 months for GERD has not been demonstrated despite inhibition of gastric acid secretion. This may relate to difficulties in determining what clinical signs contribute to esophagitis in this preverbal population or lack of gastric acid-mediated disease[13].

Van der Pol et al.[14], in a systematic review showed that if the primary aim is to treat GERD symptoms in infants, PPIs should not be recommended. Although PPIs seem to be well accepted in the short-term, some evidence did not support the efficiency and safety of PPIs in the treatment of GERD in children and adolescents.

The aim of this study was to compare the efficacy of commonly two most used drugs for treatment of GERD in children, including omeprazole and ranitidine.

Materials and methods

In this clinical randomized double blind trial and parallel-group study, 76 full-term infants aged 2 and 12 months enrolled with the diagnosis of GERD. In this study, two regimes of omeprazole 0.5 mg/kg/day and ranitidine 2–4 mg/kg/day in divided 2 doses were compared in Children Training Hospital in Tabriz, Iran.

Patients entered the study if had a modified total GERD symptom questionnaire (GSQ) infants of more than 16 at screening and baseline[2,5].

Exclusion criteria included: (1) children with birth weight below 2.5 kg, (2) concurrent esophageal disease or upper gastrointestinal congenital anomaly and previous gastrointestinal surgery, (3) neurologic disease, (4) significant hepatic and renal impairment or a history of significant cardiac or respiratory disease, peptic ulcer disease, proven lactose or cow's milk protein intolerance and lack of parental consent to participate in the study, (5) previous use of PPIs within 30 days or H2RAs within 7 days and discontinuation of previous H2RAs (for study eligibility or allergy to any factor or excipient of any PPIs, (6) premature discontinue drugs, (7) mother's disability to complete questionnaire and history of smoking in home.

All patients received standard treatment of GERD, including smaller, more frequent feeding with hypo-allergic milk, Thickening of infant feedings during 2 weeks. Patients remaining symptomatic after 2 weeks included in this randomized study. Study group assignment was determined by blocked random number generation. Patients were randomly assigned to the treatment group A, received ranitidine syrup at 2–4 mg/kg/day (Orbis Daru, Tehran, Iran) in divided 2 doses and group B received capsule of omeprazole 0.5 mg/kg/day (Exir Darou Armeh, Tehran, Iran). Symptoms were assessed during the 2-week treatment period.

Office visits followed one and 2 weeks after the onset of treatment. Parents completed a form daily with questions assessing the frequency of five key GERD symptoms during the last 24 hours; questions for caregiver assessment of GERD symptoms in infant[2], which have been validated to discriminate healthy infants and those with GERD[2].

A weekly GERD symptom score (WGSS) was defined as the sum of five selected individual weekly GERD symptom mean frequencies for vomiting/regurgitation (1a), irritability/fussiness (2b), choking/gagging (3a), arching back (4a), and refusal to feed (higher score of 5a and 5b).

Safety was assessed via adverse events reported by parents throughout the study. Physical examinations including growth parameter assessment performed and vital signs assessed at study visits.

The protocol for this study was reviewed and approved by all requisite independent ethics committees and Tabriz University of Medical Sciences' Review Boards.

This study was registered in Iranian clinical trial by the number 76 IRCT20111213530N2. The study was designed and conducted according to the Declaration of Helsinki.

A written informed consent was obtained from parents or guardians of all patients before their enrollment by the study investigators.

Baseline and other characteristics of the study population were compared using independent samples *t* test, chi Square or Fisher exact test as appropriate. A P value ≤0.05 was considered statistically significant. Data was analyzed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA).

Results

The study was conducted from July 2011 to December 2012. A total of 76 patients with GERD symptoms were screened by questionnaire, only 60 patients were enrolled and randomized (30 patients in the ranitidine group [Gr. A] and 30 in the omeprazole group [Gr. B]).

Sixteen cases were excluded because of loss of follow-up, severe pneumonia, premature discontinued drugs and mother's disability to complete the questionnaire.

Patients with mean symptom frequency more than 16 at screening and baseline proven GERD entered the study. Most patients were male (60% in Gr. A, 66.7% in Gr. B). 93.3% of patients in Gr. A and 86.7% of them in Gr. B had exclusively breast feeding.

Mean age in Gr. A was 6.4±3.1 months, and in Gr. B 5.2 ±2.75 months (*P*=0.1). Mean weight in Gr. A was 6,925±1,562 g and in Gr. B 6,499±1,839 g, also mean height in Gr. A was 63±6.6 cm and in Gr. B 59±6.1 cm.

GSQ before treatment in Gr. A was 47.17±5.62 and in Gr. B 51.93±5.42 with *P* value of 0.54 (GSQ-1) and after the treatment in Gr. A was 2.47±0.58 and in Gr. B 2.43±1.15 with *P* value of 0.98 (GSQ-2).

Baseline demographics and clinical characteristics are shown in Table 1.

Table 1. Baseline demographics clinical characteristics

Variable	Ranitidine (n=30)	Omeprazole (n=30)	*P* value
Age (mo)	6.4±3.10	5.2±2.75	0.10
Sex			0.78
Male	18 (60.0)	20 (66.7)	
Female	12 (40.0)	10 (33.3)	
Weight (g)	6,925±1,562	6,499±1,839	0.33
Height (cm)	63±6.6	59±6.1	0.02
GSQ-1	47.17±5.62	51.93±5.42	0.54
GSQ-2	2.47±0.58	2.43±1.15	0.98

Values are presented as mean±standard deviation or number (%).
GSQ, gastroesophageal reflux disease symptom score.

Significant cumulative reductions from baseline in mean WGSS occurred each week in all patients and in both treatment groups for 2 weeks.

In ranitidine group (Gr. A) and omeprazole group (Gr. B), the overall decrease in WGSS was primarily due to the decrease observed during the first 2 weeks of treatment (Table 1).

WGSS decreased significantly from baseline during treatment and was similar between the two groups (Table 2). *P* value of GSQ before and after treatment was 0.57. Therefore, there were no significant differences between ranitidine and omeprazole regarding efficacy in treatment of GERD (Table 2).

Discussion

GERD is one of the most frequent symptomatic clinical disorders affecting gastrointestinal tract of infants and children.

Complications of GERD in children are well recognized and include failure to thrive, anemia, esophagitis, Barrett esophagus, stricture, pulmonary disease and rarely esophageal adenocarcinoma[15,16].

Regurgitation is a common condition during the first year of life. At least two-thirds of 4 months old and 5% of 12 months old infants have regurgitation or vomiting[4].

Some infants with GERD have frequent regurgitation[4]. GERD should be suspected if the regurgitating infant has one or more other symptoms such as crying, arching back, refusal to feed, failure to thrive or hematemesis[4]. Most of these symptoms occur in healthy infants. Adequate control of acid secretion is a key way

Table 2. Mean alteration from baseline, weekly gastroesophageal reflux disease symptom scores

Group	Ranitidine (n=30)	Omeperazole (n=30)	*P* value*	*P* value†
1a: Vomiting/regurgitation				0.019
Change from baseline, week 1	17.25–24.53	21.74–32.21	0.01	
Change from baseline, week 2	7.5–13.6	5.01–11.25	0.75	
2b: Crying				0.89
Change from baseline, week 1	8.20–14.32	7.8–12.8	0.48	
Change from baseline, week 2	2.5–6.8	1.8–6.5	0.33	
3a: Chocking				0.42
Change from baseline, week 1	7.6–11.36	8.5–16.5	0.17	
Change from baseline, week 2	1.6–6.2	1.2–5.01	0.56	
4a: Arching				0.25
Change from baseline, week 1	6.8–14.5	6.5–11.7	0.40	
Change from baseline, week 2	1.6–5.9	1.8–4.03	0.72	
5a: Refusal to feed				0.18
Change from baseline, week 1	6.9–11.6	6.5–13.5	0.35	
Change from baseline, week 2	1.85–6.5	1.5–4.9	0.20	

**P* value, within group. †*P* value, between groups.

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for successful treatment of GERD[17,18].

There are different medical therapies with different medications for treatment of this disorder in infants and children. Medical treatment options include antacid, H2 receptor antagonists, sucralfate, prokinetics, and PPIs[17].

This clinical trial assessed PPIs and H2RAs efficacy in infants with symptoms attributed to GERD. The findings are important in determination of appropriate management strategies for such patients.

Published double-blind randomized placebo-controlled trials of drug efficacy for infants with GERD symptoms are few, small (10 to 50 patients) and of brief duration (1 to 2 weeks of PPIs). Nonetheless, all have established, as our study did, that PPIs and placebo or H2 receptor antagonists produced similar improvement in crying, despite significantly greater reduction of esophageal acid exposure with PPIs[19,20].

H2RAs inhibit acid secretion by competitively and reversibly blocking parietal cell H2 receptors, one of the stimulants of acid production[20]. H2RAs have a slower onset of action than antacids and suppress gastric acid for 4–8 hours, but have rapid onset of action (in 30 minutes) and can be used for on-demand therapy[1]. Due to this, most H2RAs are administrated twice a day. Acid suppression of H2RAs even with full dose is incomplete resulting in approximately 70% inhibition in day[21].

Several studies showed that H2RAs are less effective in healing esophagitis, because they cannot effectively inhibit meal stimulated acid secretion[10,17,22-24]. Moreover, tolerance occurs to H2 receptor antagonists, resulting in a significant decrease in their antisecretory effect[10,17].

Therefore, high-dose of H2RAs was superior to standard dose of H2RAs in healing erosive esophagitis[10,15]. Another advantage of PPI was its availability as syrup, which is well accepted by infants.

On the other hand, the site of action of PPIs is gastric acid pump (H/K ATPase) located in the secretory canaliculi membrane of the gastric parietal cell, which is the final common pathway for acid secretion in the stomach[17,25]. PPIs are a highly effective therapy for GERD and have little complications[25,26]. They significantly cause faster and more complete relief of heartburn symptoms than H2RAs[10,17]. Omeprazole, one of the PPIs, is effective for treatment of severe, refractory GER in children[15].

Side effects of different PPIs are almost similar and mild side effects have been reported in up to 14% of children. The most common side effects are headache, diarrhea, constipation and nausea[27].

Our study revealed that omeprazole, as well as ranitidine, significantly improved GERD symptom scores and was well tolerated.

The pharmacodynamics of PPIs in infants have not received as much study as they have in older pediatric populations, because of the challenges in studying this population. Omeprazole therapy might be an excellent therapeutic alternative to antireflux surgery in children with severe esophagitis or other complications of GER who are at high risk of failure or complications of such surgery or in children with failure in antireflux surgery[15].

Orenstein et al.[28] investigated a randomized, blinded, placebo-controlled study of lansoprazol treatment of GERD in newborns. They found no improvement in symptom scores between neonates who received placebo and those treated with lansoprazole, but response was defined as a 50% reduction in the specific clinical symptom.

One study suggests that even in patients with mild to severe esophagitis, H2RAs are less effective treatment compared to PPIs (100% vs. 64% for grade 1, 93.3% vs. 55.5% for grade 2, 59.6% vs. 17.6% for grade 3/4)[10]. Thus, PPIs are significantly more effective than H2RAs for treatment of all grades of esophagitis, including patients' resistance to H2RAs[10].

The U.S. Food and Drug Administration in 2012 revised four clinical trials evaluating proton pump inhibitors in infants younger than 12 months with GERD and concluded that PPIs are not effective in reducing GERD symptoms in infants[29].

Like our study, another survey revealed that pantoprazole significantly improved GERD symptom scores and was well tolerated. However, during DB treatment phase, there were no significant differences between pantoprazole and placebo inwithdrawal rates due to lack of effectiveness[2].

Investigations show that no study is performed on ranitidine in GERD in this group of patients. Ranitidine, in comparison with omeprazole, is more preferred due to its low price and availability as syrup or even tablet that is more tolerable by patients. For the same results, in our study and other studies described above, several possible limitations may be clarified. It is possible that severe esophagitis does not occur at these ages, but many pediatric gastroenterologists and pediatricians find it imperfect. It is also possible that the study design was unable to detect a change in esophagitis primarily based on symptoms. Possibly, esophagitis was healed during 2–4 weeks.

Finally, since two medications used in our study had approximately an equivalent efficacy and safety, the cost of a particular medication may be more important than comparable efficacy.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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