http:// ijp.mums.ac.ir
Original Article (Pages: 18506-18516)

The Effectiveness of Omeprazole and Esomeprazole in Infants with Gastroesophageal Reflux Disease: A Comparative Study

Seyyed Ramin Madani [1], Mohammad Mahdi Heidari [1,2,3], Mohammad Ali Sabahi [1], Mahdi Salehi [3], Davood Kheirkhah [1,2], * Abbas Taghavi-Ardakani [1,2], Somayeh Jamei [4],Amir Mahdi Shafiei [3], Hamidreza Gilasi [5]

1 Department of Pediatrics, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

2 Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran.

3 Student Research Committee, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

4 Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

5 Department of Biostatistics and Public Health, Kashan University of Medical Sciences, Kashan, Iran.

Abstract

Background: Gastroesophageal Reflux Disease (GERD) is common in infants and its treatment remains extremely challenging in this age group. Therefore this study aimed to compare the efficacy and safety of omeprazole and esomeprazole in infants, aged 1-11 months old, presented with GERD.

Methods: This double-blind randomized controlled trial was conducted on 80 infants. All patients were randomly divided into omeprazole and esomeprazole treatment groups for four weeks. The signs, symptoms, and disease severity based on the Visual Analog Scale (VAS) of GERD were evaluated after treatment in both groups. The data were then analyzed using the SPSS Statistics software (version 21).

Results: The results of this study did not show significant differences between the mean disease severity based on VAS of both omeprazole- (81.1±55.7) and esomeprazole-receiving (79.1±77.6) groups (p=0.091). However, in each group, the mean disease severity after one month of treatment was significantly lower as compared to baseline (p<0.01). The recovery rates were similar in both groups (75% and 70% for omeprazole and esomeprazole groups, respectively) (p=0.799).

Conclusion: Omeprazole and esomeprazole did not have significant differences in signs, symptoms, and disease severity of GERD, however, we observed a significant reduction in disease severity in both groups indicating that these two drugs could be used interchangeably for the treatment of GERD disorder.

Key Words: Esomeprazole, Gastroesophageal Reflux Disease, GERD, Infant, Omeprazole.

* Please cite this article as: Madani SR, Heidari MM, Sabahi MA, Salehi M, Kheirkhah D, Taghavi-Ardakani A, Jamei S, Shafiei AM, Gilasi H. The Effectiveness of Omeprazole and Esomeprazole in Infants with Gastroesophageal Reflux Disease: A Comparative Study. Int J Pediatr 2024; 12 (01):18506-18516. DOI: **10.22038/ijp.2024.76553.5401**

Corresponding Author:

Abbas Taghavi-Ardakani, Department of Pediatrics, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran. Email: drtaghavia@gmail.com

Received date: Dec.01,2023; Accepted date: Jan.17,2024

1- INTRODUCTION

Gastroesophageal Reflux Disease (GERD) has been defined as the involuntary movement of the stomach content into the esophagus and interstitial regions. It seems that gastric reflux stems from the transient relaxation of the sphincter muscle at the lower end of the esophagus, and it is typically reported as a physiological event in infants and children aged less than seven years (1-4). The most common physiological manifestation of gastric reflux in children with ages lower than 7 years is recurrent episodes of vomiting which is observed in 50% of this age group (5).

Studies have reported that 50% of infants aged 0-3 months, 67% of those with 4-months of age, and 21% of those at 6-7 months have physiological gastric reflux at least once a day, which is reduced or eliminated in older ages (2, 5). However, 5% become pathological and turn into GERD (6, 7). In these cases the clinical symptoms of GERD include recurrent vomiting, no weight gain at the expected rate, irritability, swallowing difficulties (namely, dysphagia), discomfort, dyspepsia, and breathing problems (4, 5, 8).

Accordingly, a wide variety of Proton-Pump Inhibitors (PPIs) has been so far certified for GERD treatment in infants and children. In this respect, esomeprazole and omeprazole are two forms of PPI, confirmed by the Food and Drug Administration (FDA) for the treatment of infants aged 1-11 months old suffering from GERD, which are available in oral and intravenous formulations. The novel S-isomer of omeprazole, esomeprazole, is used to decrease gastric acid output more effectively (9).

Pharmacodynamic findings indicate that, in contrast to omeprazole, esomeprazole is mostly metabolized by CYP3A4 in human liver microsomes, with reduced dependence on CYP2C19. This finding suggests that esomeprazole metabolism varies less between individuals than omeprazole (10, 11). Furthermore, research has shown that esomeprazole has a much higher bioavailability than omeprazole, which results in a larger suppression of gastric acid secretion (12). Consequently, numerous Western-conducted research studies have verified that esomeprazole is more effective than omeprazole in treating GERD patients (9, 13).

To date, few clinical studies on the therapeutic effects of omeprazole and esomeprazole on GERD in infants below one year of age, children, or adolescents have revealed controversial findings (14-20). Recent clinical trials are also difficult to interpret and they have failed to prove the effectiveness of gastric acid inhibitors in infants of 0-11 months old (19, 20). So far, no study has been conducted on infants suffering from GERD, to the best of authors' knowledge, aimed at comparing omeprazole and esomeprazole use; however, limited and contradictory reports have separately examined the efficacy of these drugs.

Given the lack of similar research and with regard to the inconsistency of previous investigations on the effectiveness of these drugs, to the best of the authors' knowledge, this study was an attempt to compare the efficacy and safety of omeprazole and esomeprazole use in infants aged 1-11 months old presented with common signs and symptoms of GERD.

2- MATERIALS AND METHODS

2-1. Design and Participants

This double-blind randomized controlled trial was conducted on infants aged 1-11 months-old referred to gastroenterology clinics located in the city of Kashan, Iran, in 2019. Based on their medical history and clinical examinations

by the physician fulfilling this project, these patients were suffering from GERD (based on signs, symptoms and the clinical diagnosis of children's gastroenterologist). The patients with at least one sign and symptom of GERD including vomiting, irritability, extraesophageal manifestations (i.e., cough, wheezing, stridor, and respiratory distress), nutrition-related respiratory failure, food sensitivity, suffocation, and hiccups lasting more than one hour a day, at least two times a week, for four weeks, were included in this study.

2-1.1. Sample size

The sample size was accordingly determined to be 80 cases based on the study by Srikanth et al. (2014) (21) with 95% confidence interval (CI) and 80% test power, of which 40 patients were placed in the omeprazole group and 40 individuals received esomeprazole. The study population was selected using a simple random sampling method.

2-1.2. Inclusion and exclusion criteria

The inclusion criteria consist of infants aged between 1 and 11 months, diagnosed with GERD who had failed in the routine anti-reflux treatment (e.g., concentrate infant formula, instant knockout nutrition, and sleep switching). The exclusion criteria consist of the consumption of a PPI within the last seven days, receiving histamine H2-receptor antagonists (H2-blockers), prokinetics, and antacids containing bismuth as treatments for the reflux symptoms within the 24 hours before the intervention, as well as the patients suffering from active gastrointestinal bleeding, apnea, allergic gastroenteritis, eosinophilic gastroenteritis (EGE), bleeding disorders, pyloric stenosis, active seizure disorder, acute pancreatitis, meningitis, allergies, impaired anatomy, or other factors aggravating or inducing the reflux and unwillingness to cooperate during the study.

2-2. Procedure

After obtaining informed consent and explaining the goals of project to patients' parents, the patients were randomly divided to two groups (omeprazole and esomeprazole) and treated for four weeks through oral doses in an equal manner, in which the participants' parents and guardians, as well as the researchers, and the pharmacists became blinded to treatments. The signs and symptoms including vomiting, contraction, extraesophageal manifestations (i.e., cough, wheezing, stridor, and respiratory distress) and nutritional problems (e.g., retching and suffocation) were compared between two groups. Pathological crying was also defined as that lasting more than one hour. Vomiting/regurgitation volume was similarly classified as small (5-15 ml), medium (15-30 ml), or large (more than 30 ml) (19-20). Furthermore, recovery rate represented reduced severity of the symptoms in more than half of the primary symptom scores (the pre-intervention stage).

2-3. Data analysis

Only the data of patients with complete information were analyzed. SPSS version 22 software (SPSS Inc., Chicago, IL, USA) was used to do statistical analysis on the data. Chi-square test was used to compare qualitative features between the two groups. To determine the normal distribution of all quantitative parameters, Kolmogorov-Smirnov test was used. The Student t-test was used for variables with normal distributions, while Mann-Whitney U-test was used for variables with non-normal distributions. P-values less than 0.05 were regarded as significant.

3- RESULTS

In this study, a total number of 80 infants allocated to two groups of 40 patients received omeprazole and esomeprazole. Demographic features in the terms of age (p=0.445), sex (P=0.653),

weight (P=0.149), treatment history (P=0.34) and having siblings with GERD, reflux or allergies (P=0.813) did not differ between the two groups (**Table 1**).

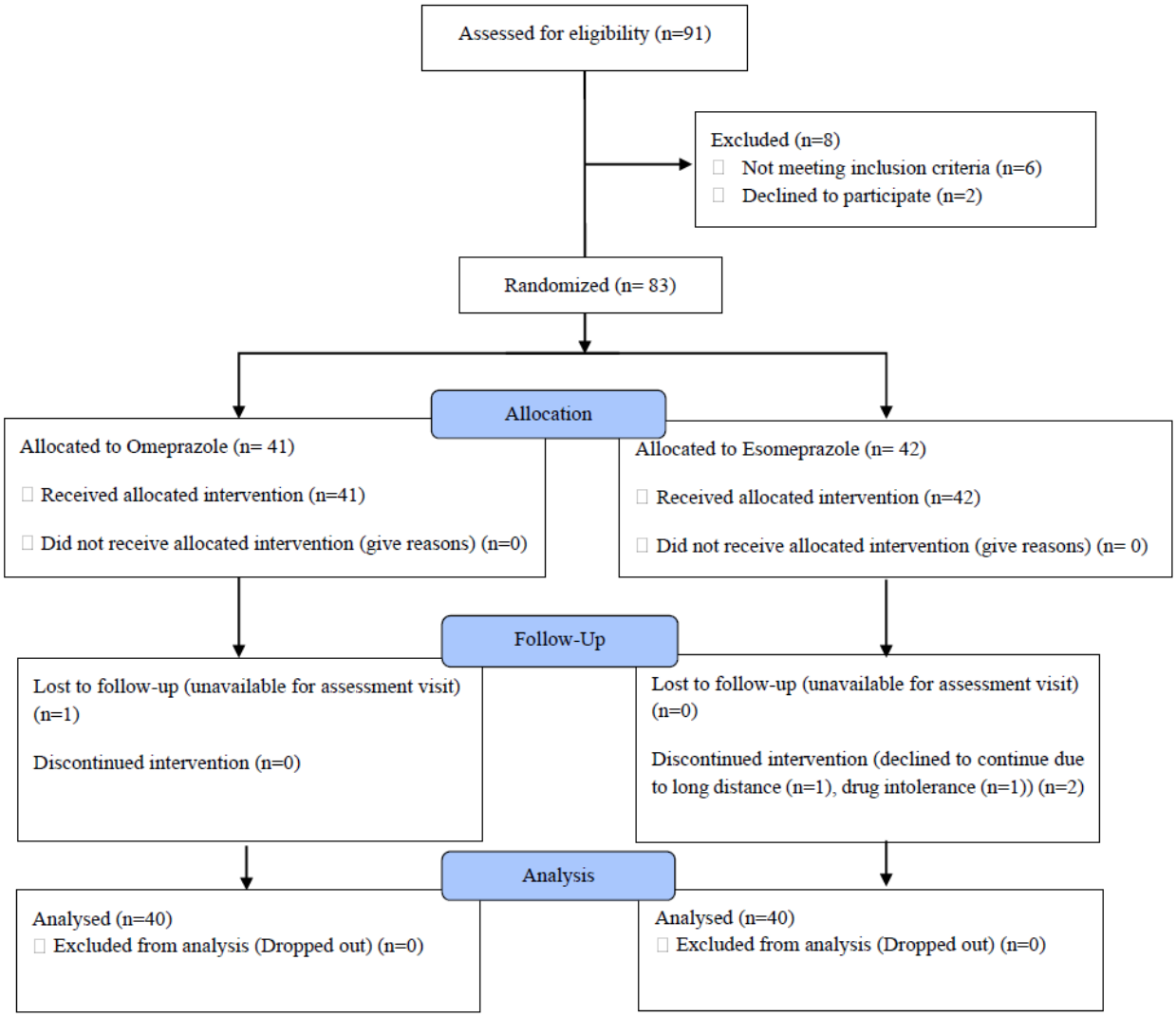

Fig. 1: Study flowchart (CONSORT format)

Our results showed signs and symptoms of GERD before and one month after the treatment, and the recovery rate did not show a significant difference ($p<0.05$) (**Table 1**). Moreover, one month after the treatment, the recovery rate in both groups taking omeprazole and esomeprazole was, respectively, 76.7% and 58.6% in terms of frequency of vomiting. Furthermore, we found recovery rates of, respectively, 77.8% and 72.8%, 3.7% and 6.1%, 20% and 30%, and 83.3% and 66.7% for vomiting volume, vomiting content, vomiting pathway, weight gain and respiratory symptoms in both groups, which were not significantly different ($p>0.05$) (**Table 2**).

The mean disease severity and the recovery rate between the omeprazole and esomeprazole groups showed no significant difference ($p>0.05$). However, in each group, the mean disease severity after one-month treatment was significantly lower than the baseline ($p<0.001$).

Table-1: Demographic and basic variables in Omeprazole and Esomeprazole groups

Group Variables		Omeprazole (n=40)	Esomeprazole (n=40)	P-value
Age (day)		89.27±58.72	79.25±58.00	0.445
Gender (Male)		17 (42.5)	19 (47.5)	0.653
Weight (gr)		5930.07±1430.88	5450.52±1513.36	0.149
Treatment history		29 (72.5)	25 (62.5)	0.340
Siblings with GERD, reflux or allergies		14 (35)	13 (32.5)	0.813
Number of vomiting	1 to 3 times a day	10 (25)	11 (27.5)	0.631
	4 or 5 times a day	8 (20)	11 (27.5)	
	>5 times a day	22 (55)	18 (45)	
Vomiting volume	<10 cc	18 (45)	22 (55)	0.301
	10-30 cc	9 (22.5)	11 (27.5)	
	>30 cc	13 (32.5)	7 (17.5)	
Vomiting contents	Liquid	13 (32.5)	7 (17.5)	0.121
	Liquid and solid	27 (67.5)	33 (82.5)	
Vomiting pathway	Through mouth	30 (75)	30 (75)	1
	Through mouth and nose	10 (25)	10 (25)	
Weighing	Inappropriate	6 (15)	9 (22.5)	0.39
	Appropriate	34 (85)	31 (77.5)	
Breathing disorder	Yes	12 (30)	7 (17.5)	0.189
	No	28 (70)	33 (82.5)	
Nasal congestion	Yes	28 (70)	30 (75)	0.617
	No	12 (30)	10 (25)	

Table-2: Recovery rates of gastrointestinal and respiratory symptoms between Omeprazole and Esomeprazole groups after the intervention

Group Variables	Omeprazole	Esomeprazole	p-value
Number of vomiting	18 (81.8)	11 (61.1)	0.293
Vomiting volume	11 (84.6)	7 (100)	0.681
Vomiting contents	1 (3.7)	2 (6.1)	0.677
Vomiting pathway	2 (20)	3 (30)	0.606
Weighing	5 (83.3)	6 (66.7)	0.475
Breathing disorder	0 (0)	0 (0)	-
Nasal congestion	0 (0)	1 (3.3)	1.000

Moreover, the recovery rate between the groups taking omeprazole (72.5%) and esomeprazole (75%) revealed no significant difference (p=0.799). In spite of this, the proportion of the recovered patients in each group was significantly high (p<0.01) (**Fig. 2**).

The behavioral symptoms were additionally examined in this study (**Table 3**). Based on these results, one month after the treatment, the recovery rates in the omeprazole and esomeprazole groups in terms of feeling discomfort during vomiting were, respectively, 29% and 24.1%. These values were 29% and 24.1%, 50% and 54.5%, 13% and 41.2%, 22.7% and 28%, and 40.6% and 46.4% for refusing to eat even if hungry, crying

during and after eating, excessive crying, and daily crying duration in both groups, respectively. The recovery rates of hiccups, back arching, and nighttime restlessness were, respectively, 71.4% and 80%, 10.8% and 22.9%, and 9.7 and no full recovery was observed in any of the groups. It should be noted that the two study groups showed a significant difference only in terms of recovery rate in crying during and after eating (p=0.042).

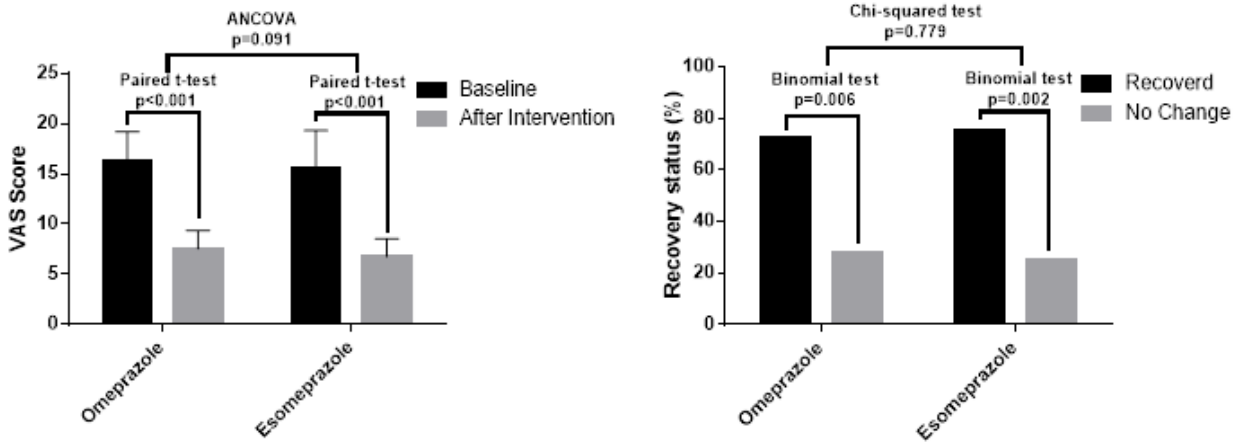

Fig. 2: The mean disease severity and the recovery rates between the omeprazole and esomeprazole groups

4- DISCUSSION

This study aimed to compare the effectiveness of omeprazole and esomeprazole in 1 to 11 month-old infants suffering from GERD. Our findings showed no significant differences in terms of signs, symptoms recovery and disease severity between omeprazole and esomeprazole after one month from the intervention. However, in each group, the mean disease severity and recovery rates after a one-month treatment were acceptable.

GER is known as the most common digestive disorder in all age groups and takes place when stomach contents come back up into the esophagus causing heartburn as short attacks that induce no signs and symptoms and even damage to the esophagus (22). On the other hand, GERD is the pathological and aggravated form of this problem accompanied by signs and symptoms as well as complications. In this sense, physiologic reflux is one of the causes of non-bilious vomiting during infancy, whose incidence can be mostly observed at four months of age, which gradually becomes much less and reaches 21% in 6-7-month-old infants. This type of reflux can be normally observed during infancy, particularly, in the first six months and mostly in the second half of the first year of life, which improves spontaneously as solid foods are consumed, so there is no need to receive diagnostic and therapeutic treatments (23). In fact, GER occurs in infants due to their undeveloped digestive system and the neurological development of infants up to one year of age, which goes away as they grow up to one year of age and when the muscular-physiological system of gastrointestinal reflux region is developed. Among other factors affecting GER would be liquid diet, long-term sleeping horizontally, narrow- or small-caliber and short esophagus, small stomach with low-volume acceptance, frequent feedings with relatively high volumes, and immature sphincter muscle at the lower end of the esophagus.

Table-3: Comparing the frequency of behavioral symptoms between Omeprazole and Esomeprazole groups after the intervention

Time	Baseline					After 1 Month				
Group	Omeprazole		Esomeprazole		p-value	Omeprazole		Esomeprazole		p-value
Variables	Yes	No	Yes	No		Recovered	No change	Recovered	No change	
Discomfort when vomiting	31 (77.5)	9 (22.5)	29 (72.5)	11 (27.5)	0.301	9 (29)	22 (71)	7 (24.1)	22 (75.9)	0.668
Do not eat when hungry	18 (45)	22 (55)	22 (55)	18 (45)	0.371	9 (50)	9 (50)	12 (54.5)	10 (45.5)	0.775
Crying while and after eating	23 (57.5)	17 (42.5)	17 (42.5)	23 (57.5)	0.180	3 (13)	20 (87)	7 (41.2)	10 (58.8)	0.042
Cry too much	22 (55)	18 (45)	24 (60)	16 (40)	0.651	5 (22.7)	17 (77.3)	5 (20.8)	19 (79.2)	0.876
Hiccups more than other children	5 (12.5)	35 (87.5)	7 (17.5)	33 (82.5)	0.531	4 (80)	1 (20)	5 (71.4)	2 (28.6)	0.735
Arc back	37 (92.5)	3 (7.5)	35 (87.5)	5 (12.5)	0.456	4 (10.8)	33 (89.2)	8 (22.9)	27 (77.1)	0.170
Night restlessness	31 (77.5)	9 (22.5)	26 (65)	14 (35)	0.217	3 (9.7)	8 (90.3)	0 (0)	26 (100)	0.424

The GERD symptoms in infants and children may include excessive crying, nighttime restlessness, anorexia, bad breath, wheezing, dry cough, recurrent vomiting with agitation, especially in the first few weeks after birth, hematochezia, excessive belching, chest pain, swallowing difficulties, hoarseness, aspiration pneumonia, failure to thrive (FTT), otitis media, rhinosinusitis, anemia, secondary hypoalbuminemia, and esophagitis (24).

Based on the study results, omeprazole and esomeprazole led to a significant difference in terms of their effects on GERD, and they could be used interchangeably for treatment. Similarly, Abbasi et al. compared the impact of omeprazole, esomeprazole, and lansoprazole in the treatment of GERD on infants aged 2 to 24 months old, and showed that there was no significant variation between disease symptoms at pre- and post-treatment stages. It seems that all three drugs of omeprazole, esomeprazole, and lansoprazole were effective in the control of GERD attacks in these infants (25). In another investigation by Armstrong et al. on the stomach acid suppression in patients with GERD, receiving esomeprazole and omeprazole, showed that after the four-week treatment, the proportion of the treated patients by both drugs was not different, which was quite consistent with the findings of the present study. They had also insisted that three separate studies with administration of esomeprazole 40 and 20 mg once a day, and omeprazole 20 mg once a day, had all led to significant elimination of the symptoms, which had resulted in complete relief of heartburn after four weeks in patients with Non-Erosive Reflux Disease (NERD). However, there was no significant difference between the symptoms attributable to omeprazole and esomeprazole doses in any of the studies (26).

In a study by Röhss et al., investigating the efficacy of the use of esomeprazole 40 ml versus omeprazole 40 ml on the stomach 24-hour pH in patients with symptomatic GERD, it was revealed that the disease severity of patients treated with esomeprazole was significantly lower compared with those taking omeprazole. Esomeprazole had been accordingly well tolerated by the patients, and the authors suggested that esomeprazole 40 mg could effectively control gastric acid than standard doses of omeprazole (27). Olbe et al., in a case history of omeprazole and esomeprazole use as inhibitors and PPIs, had further established that esomeprazole in combination with antibiotics, prescribed for curing helicobacter pylori infections, known as the main cause of stomach ulcers, could lead to a higher recovery rate (28). Moreover, Lind et al., in a study on acid control using esomeprazole versus omeprazole in patients with symptomatic GERD had found that esomeprazole had more effectiveness compared with omeprazole, since it could reduce the symptoms and provide the potential for improved efficiency in acid-related diseases (29). To explain the discrepancies between the investigations cited and the present one, it can be argued that such studies could be different because of their various sample sizes, patient selections, and intervals in treatments. On the other hand, it should be noted that due to the difference in the cost of esomeprazole compared with omeprazole, it was better to choose omeprazole as the first-line treatment to minimize patients' expenses.

It should be noted that the two groups had a significant difference only with regard to the recovery rate in crying during and after eating. According to the related literature, crying had been mentioned as one of the GERD complications. For example, Vanwing et al. had noted that omeprazole, despite being desirable as a PPI, might cause adverse behavioral reactions in

patients, which corresponded to the results of the present study. Based on such findings, it can be concluded that the presence of crying and restlessness in patients could be due to pain, as one of the main esophageal symptoms, manifested in infants in the form of crying (30). Furthermore, the findings showed that the groups had no significant difference with other children in terms of hiccups. Accordingly, hiccups were observed in 15% of the cases, but it was eliminated within 15 months of the treatment, which was in line with the results reported by Duncan (31).

4-1. Strength and limitations of the study

This study was conducted on a population of infants below one year of age as the main strength, because most investigations on the effects of the drugs concerned on GERD had been previously conducted on adults. One of the limitations of this study was the comparison of the effectiveness of different doses of these drugs due to the restrictions of the treatment centers.

5- CONCLUSION

Omeprazole and esomeprazole did not show a significant difference in terms of their effectiveness on GERD signs, symptoms and disease severity; so, both groups of drugs could be used interchangeably in the treatment of GERD in infants. Due to the difference in the cost of esomeprazole compared with omeprazole, it would be better to choose omeprazole as the first-line treatment. It is also suggested to compare the effectiveness of different doses of these drugs in future studies.

6- ETHICAL CONSIDERATIONS

This study was approved (code 98086) by the Research Council of Kashan University of Medical Sciences as a research project, and then confirmed by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.REC.1398.037).

7- CONFLICTS OF INTEREST

None.

8- ACKNOWLEDGMENTS

The authors would like to thank the Clinical Research Development Unit of Shahid Beheshti Hospital in Kashan University of Medical Sciences**.**

9- REFERENCES

1. Vandenplas Y, Sacre-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old. J Pediatr Nutr 1987; 6:220–4.

2. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med 1997; 151:569–72.

3. 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; 154:150–4.

4. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, Gerson WT, Werlin SL; North American Society for Pediatric Gastroenterology and Nutrition. 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:S1–31.

5. Gold BD. Gastroesophageal reflux disease: could intervention in childhood reduce the risk of later complications? Am J Med 2004; 117:23S–9S.

6. Sherman PM, Hassal E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S,

Orenstein S, Rudolph C, Vakil N, Vandenplas Y. A global, evidence based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol 2009; 104:1278-95.

7. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG, North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. 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.

8. Orenstein SR, Shalaby TM, Kelsey SF, Frankel E. Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy. Am J Gastroenterol 2006; 101:628–40.

9. Lindberg P, Keeling D, Fryklund J, Andersson T, Lundborg P, Carlsson E. Review article: Esomeprazole--enhanced bioavailability, specificity for the proton pump and inhibition of acid secretion. Aliment Pharmacol Ther. 2003; 17:481–488.

10. Sjövall H, Björnsson E, Holmberg J, Hasselgren G, Röhss K, Hassan-Alin M. Pharmacokinetic study of esomeprazole in patients with hepatic impairment. Eur J Gastroenterol Hepatol. 2002; 14:491–496.

11. Lind T, Rydberg L, Kylebäck A, Jonsson A, Andersson T, Hasselgren G, Holmberg J, Röhss K. Esomeprazole provides improved acid control vs. omeprazole In patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000; 14:861–867.

12. Andersson T, Hassan-Alin M, Hasselgren G, Röhss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet. 2001; 40:411–426.

13. Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, D'Amico D, Hamelin B, Joelsson B. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther. 2000; 14:1249–1258.

14. Springer M, Atkinson S, North J, Raanan M. Safety and pharmacodynamics of lansoprazole in patients with gastroesophageal reflux disease aged < 1 year. Paediatr Drugs 2008; 10:255–63.

15. Khoshoo V, Dhume P. Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr 2008; 46:352–4.

16. Omari T, Davidson G, Bondarov P, Nauclér E, Nilsson C, Lundborg P. Pharmacokinetics and acid suppressive effects of esomeprazole in infants 1-24 months old with symptoms of gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2007; 45:530–7.

17. 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; 44:41–4.

18. Bishop J, Furman M, Thomson M. Omeprazole for gastroesophageal reflux disease in the first 2 years of life: a dose-finding study with dual channel pH

monitoring. J Pediatr Gastroenterol Nutr 2007; 45:50–5.

19. Orenstein SR, Hassal E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr 2009; 154:514–20.

20. Winter H, Kum-Nji P, Mahomedy SH, Kierkus J, Hinz M, Li H, Maguire MK, Comer GM. Efficacy and safety of pantoprazole delayed-release granules for oral suspension in a placebo controlled treatment-withdrawal study in infants 1–11 months old with symptomatic GERD. J Pediatr Gastroenterol Nutr 2010; 50:609–18.

21. Srikanth G, Jagadishbabu D, Junied S, Sriharsha M. Comparative study of pantoprazole and esomeprazole for erosive gastroesophageal reflux disease: a prospective study.International Journal of Basic & Clinical Pharmacology. 2014; 3 (3): 460-464.

22. Candela NM, Lightdale JR. Therapies for Gastroesophageal Reflux in Infants. InInfectious Disease and Pharmacology 2019 Jan 1 (pp. 261-277). Content Repository Only.

23. Mousa H, Hassan M. Gastroesophageal reflux disease. Pediatric Clinics. 2017 Jun 1; 64(3):487-505.

24. El-Mahdy MA, Mansoor FA, Jadcherla SR. Pharmacological management of gastroesophageal reflux disease in infants: current opinions. Current opinion in pharmacology. 2017 Dec 1; 37:112-7.

25. Abbasi R, Abbasi F, Mosavizadeh A, Sadeghi H, Keshtekari A. comparison of the effect of omeprazole, esomeprazole and lanzoprazole on treatment of gastroesophageal reflux disease referred children aged 2 to 24 months to shahid-mofatteh clinic of yasuj-2015. JCCS. 2020; 1 (3).

26. Armstrong D, Talley NJ, Lauritsen K, Moum B, Lind T, Tunturi-Hihnala H, Venables T, Green J, Bigard MA, Mössner J, Junghard O. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Alimentary pharmacology & therapeutics. 2004 Aug; 20(4):413-21.

27. Röhss, K., Hasselgren, G. & Hedenström, H. Effect of Esomeprazole 40 mg vs Omeprazole 40 mg on 24-Hour Intragastric pH in Patients with Symptoms of Gastroesophageal Reflux Disease. Dig Dis Sci 47, 954–958 (2002). https://doi.org/10.1023/A:1015009300955

28. Olbe, L., Carlsson, E. & Lindberg, P. A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole. Nat Rev Drug Discov 2, 132–139 (2003). https://doi.org/10.1038/nrd1010.

29. Lind T, Rydberg L, Kylebäck A, Jonsson A, Andersson T, Hasselgren G, Holmberg J, Röhss K. Esomeprazole provides improved acid control vs. omeprazole In patients with symptoms of gastro-oesophageal reflux disease. Alimentary pharmacology & therapeutics. 2000 Jul; 14(7):861-7.

30. Shreef K. Chronic Gastric Volvulus: Is it a Missed Cause of Gastro-Esophageal Reflux in Children? A Single Institution Study. EC Gastroenterology and Digestive System. 2019; 6:280-6.

31. Duncan DR, Larson K, Rosen RL. Clinical Aspects of Thickeners for Pediatric Gastroesophageal Reflux and Oropharyngeal Dysphagia. Current gastroenterology reports. 2019 Jul 1; 21(7):30.