INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH AND ANALYSIS

ISSN(print): 2643-9840, ISSN(online): 2643-9875

Volume 06 Issue 09 September 2023

DOI: 10.47191/ijmra/v6-i9-16, Impact Factor: 7.022

Page No. 4057-4061

The Safety and Efficacy of Acid Suppression Therapy in Neonatal GERD

Peymaneh Alizadeh Taheri

Department of Neonatology, Tehran University of Medical Sciences, Bahrami Children Hospital, Tehran, Iran

ABSTRACT: Gastroesophageal reflux (GER) is a common physiologic process in infants that often resolves with growth and maturation, while gastroesophageal reflux disease (GERD) is a serious and common referral disease in infants and neonates. The first-line treatment for both GER and GERD is conservative therapy. H2RAs and PPIs are the two basic pharmacologic agents in the treatment of GERD in pediatrics and adults. The efficacy of PPIs is higher than that of H2RAs in GERD treatment. There are controversies in the pharmacologic treatment of neonatal GERD, and performing more clinical trials to survey the effect of PPIs and H2RAs and compare them with each other is necessary in this age group. We conducted three different clinical trials to compare the efficacy and safety of ranitidine with omeprazole or lansoprazole in refractory neonatal GERD.

KEYWORDS: Neonates, Gastroesophageal reflux disease, Pharmacologic, Treatment, Comparing

1. INTRODUCTION

GER involves the retrograde passage of gastric contents into the esophagus and pharynx with or without regurgitation and/or vomiting [1-4]. GER is a common physiologic process in infants that often resolves with growth and maturation [1]. It occurs in 60–70% of healthy infants during the first 4 months of life and often resolves with maturation by 12-14 months of age [4, 5]. When GER becomes bothersome and is accompanied by other symptoms such as frequent vomiting, failure to thrive, severe arching, irritability, poor oral feeding, signs of esophagitis or hematemesis, or respiratory symptoms, it is defined as GERD [6]. The prevalence of GERD changes from 8.5% to 10-20% from Eastern Asia to Western Europe and North America [7, 8]. The hazards that increase the occurrence rate of GERD include prematurity, neurologic upsets, some drugs like sedatives and muscle relaxants, a positive history of GERD in the family, and gastrointestinal abnormalities [9]. The main aims of infantile GERD treatment are preserving the clinical response, promoting suitable growth, and preventing recurrence and complications [10].

2. TREATMENT

2.1. Parental reassurance

As the nature of GER is benign and self-limiting, parental reassurance is the mainstay of treatment for infantile GER.

2.2. Conservative therapy

The first-line treatment in both GER and GERD is conservative therapy, including lifestyle changes (not wearing tight clothes, changing diapers before feeding, prohibiting the use of drugs that increase the occurrence rate of GER, feeding slowly in patients with nasogastric tubes, and avoiding passive smoking), in addition to anti-GER diet (low volume and more divided feeding, thickened formula, or thickening of expressed breast milk with cereal), and position guidelines [9, 11].

2.3. Pharmacotherapy

Pharmacotherapy is not recommended for physiologic GER unless GERD is evident. It is recommended when more severe GERD is refractory to conservative therapy [9]. The first-line medication is acid suppression therapy [12, 13].

2.3.1. Acid-suppressants

PPIs and H2 receptor antagonists increase gastric pH and inhibit acid reflux, which can induce injuries in the esophageal mucosa. [12, 13]. PPIs inactivate H+/K+-ATPase in the gastric parietal cells' canaliculi and inhibit gastric acid production, reduce the volume of gastric secretion, and make gastric emptying easier [14]. As PPIs have a longer duration of action, fewer side effects, and a higher prohibition of meal-induced acid secretion, they are superior to H2RAs [15, 16]. PPIs are preferred to H2RAs in reducing GERD

symptoms in adults [17]. Despite the lack of published data about the efficacy of acid suppressants and increasing worries about their complications, oral PPIs have been increasingly used in infantile (under one year of age) GERD [18, 19]. In recent guidelines, a 4-week trial of a PPI or H2RA for infants with symptoms such as unexplained feeding difficulties, bizarre behavior, and unsuitable weight gain, along with significant regurgitation, has been suggested [9]. There is no documented data that supports the efficacy of acid-suppressants in the treatment of neonatal GERD [20]. Neonatal GERD is still difficult trouble to define and manage, and more studies are needed for clinical diagnosis and management [21].

PPIs have fewer therapeutic discontinuations and diversions in the first month of management. [18]. A "step-up" protocol of acid suppression usage was the past viewpoint of infantile GERD therapy, in which ranitidine was administered as the first acid suppressant. If there was no response despite the prescription of high-dose ranitidine, it was switched to PPIs [22]. An updated review has recommended pharmacotherapy for the treatment of severe pediatric GERD refractory to conservative therapy, and PPIs have been advised over H2-receptor antagonists because of their higher efficacy [23]. Recent studies have found that either acid reflux or nonacid reflux may induce the clinical features of neonatal GERD [24].

2.3.2. Prokinetics

These drugs are another group of pharmacologic agents used in the treatment of GERD. Metoclopramide is among the prokinetics. Whenever it is received for a prolonged period of time or in a high dose, the side effects, including irritability, drowsiness, oculogyric crisis, dystonic reaction, apnea, and emesis in infants may appear [25]. Domperidone and cisapride are prohibited from being used in the USA because they induce probable cardiac arrhythmia [26, 27]. Macrolides are among the prokinetics and may also induce cardiac arrhythmia in long-term treatment [28]. It seems that metoclopramide can be a safe prokinetic if it is administered in a low-dose quota over a short period of time. It is the reason why we prescribed metoclopramide in our trials.

2.4. Surgical intervention

Fundoplication is generally advised for infants with severe GERD who are refractory to maximal medical therapy [16].

3. THE COMPARISON OF THE SAFETY AND EFFICACY OF PPIS WITH H2RAS IN NEONATAL GERD

According to our research in the literature, PubMed, and Google Scholar, few clinical trials have compared the efficacy and safety of PPIs with H2RAs in pediatric GERD and very few in neonatal GERD.

4. CURRENT CLINICAL TRIALS COMPARING THE SAFETY AND EFFICACY OF PPIS WITH H2RAS IN NEONATAL GERD

We performed three clinical trials and administered H2RAs and PPIs in neonatal GERD. We also compared the safety and efficacy of H2Ras with PPIs in these patients. In our studies, other diagnoses were ruled out regarding the clinical manifestations and examination of the patients, lab tests, sonography, etc. The highly positive response to our interventions emphasized the diagnosis of GERD in each patient too. Each patient had already been managed by conservative therapy or conservative therapy plus monotherapy for three to five days, according to a balance of danger and advantages between the intensity of clinical symptoms and the cure rate. The patients with the diagnosis of protein milk allergy were excluded from our studies. The clinical trials performed included [29-31]:

1.In our first double-blind trial study, 116 term neonates (mean age 10.53 ± 8.17 days; girls 50.9%) who were diagnosed with refractory GERD in the neonatal ward of Bahrami Children's Hospital (during 2013- 2015) were randomly administered either "oral ranitidine plus metoclopramide" or "oral omeprazole plus metoclopramide". The Research Ethics Committee of Tehran University of Medical Sciences accepted the protocol of this survey (IR. TUMS.1393.110 code). The informed consent form was filled out by the parents or guardians of the participants before the intervention. The response rate was 75.43 ± 23.24% in the "ranitidine plus metoclopramide" group versus 93.74 ± 7.28% in the "omeprazole plus metoclopramide" group after one week and one month of intervention. There were no side effects in either group after one week or one month of intervention.

This clinical trial showed that therapy with "ranitidine or omeprazole plus metoclopramide" led to a response rate of > 70%, but it was remarkably better (> 90) in the "omeprazole plus metoclopramide" group [29].

2. In our second randomized double-blind clinical trial, fifty-eight preterm neonates hospitalized in neonatal wards and neonatal intensive care units (NICUs) of Bahrami Children's Hospital and Shariati Hospital (during 2014-2016) with a clinical diagnosis of refractory GERD, were randomly administered either "oral ranitidine plus metoclopramide "or "oral omeprazole plus metoclopramide". The Research Ethics Committee of Tehran University of Medical Science approved the protocol of this survey (IR.TUMS.REC.1395.2766), and the Iranian Registry of Clinical Trials accepted the registry of this clinical trial (IRCT2016030226876N1). Consent was obtained from the parents or guardians of participants before the intervention. The response rate was 77.06 ± 3.38 % in the "ranitidine plus metoclopramide" group versus 91.37 ± 7.5% in the "omeprazole plus metoclopramide" group after one week of intervention. We found no drug-related side effects in either group in this trial.

This clinical trial showed that therapy with the "ranitidine or omeprazole plus metoclopramide" led to a response rate of >70% after one week of intervention in each group, but the response rate was remarkably better (> 90%) in the "omeprazole plus metoclopramide" group [30].

3.In our third randomized double-blind clinical trial, 120 term neonates (mean age 10:91 ± 7:17 days; girls 54.63%) with the diagnosis of refractory GERD to conservative and monotherapy admitted to Bahrami Children Hospital (during 2017-2019) were randomly administered "ranitidine plus metoclopramide" or "lansoprazole plus metoclopramide". The Research Ethics Committee of Tehran University of Medical Science accepted the protocol of this study (IR.TUMS.MEDICINE.REC.1396.3714), and the Iranian Registry of Clinical Trials approved the registry of this clinical trial (RCT20160827029535N3). The parents or guardians of all infants filled out the written informed consent form before the study. The diagnosis of GERD was established due to the I-GERQ-R clinical scoring, which consists of twelve items. The range of total scoring in the final version of the IGERQ-R is from 0 to 42, with a cut point of > 15 scores [20]. We gathered the alterations in symptoms and signs after one week and one month of intervention. In the end, fifty-four neonates in each group completed the study, and their data were analyzed. In this study, the clinical response rate increased in "lansoprazole plus metoclopramide" group and the scoring rate decreased to 7.44 ± 3.86 score after one week, and 2.41 ± 3.06 score after one month of intervention. The clinical response rate also increased in the "ranitidine plus metoclopramide" group as the scoring rate decreased to 9.3±4.57 after one week and 4.5±4.12 score after one month of intervention. We did not find any drug-related adverse effects in either group during interventions.

This clinical trial showed that therapy with "ranitidine or lansoprazole plus metoclopramide" led to a response rate of >50% and >70% in each group after one week and one month of intervention, respectively, but it was significantly higher in the PPI group (lansoprazole) (88:47 ± 13:18%) [31].

5. CONCLUSIONS

Generally, in all three trials, the response rate was significant in both groups of H2RA and PPIs after one week and one month of intervention, but it was significantly higher in the PPIs group. The first and second studies showed that omeprazole induced a significantly higher response rate in comparison with ranitidine in the treatment of GERD in preterm and term neonates. In the third study, lansoprazole also had a higher response rate in comparison with the H2RA group, which was significant in the treatment of GERD in term neonates.

LIMITATIONS

As far as our knowledge, few clinical trials have administered H2Ras or PPIs in neonatal GERD. There are also very few clinical trials that have compared the efficacy and safety of PPIs with H2RAs in neonatal GERD. Further studies with more participants and longer follow-ups are recommended to administer PPIs or H2RAs to this age group and compare the effects of these agents with each other, and their side effects.

INNOVATIONS AND BREAKTHROUGHS

The novelty of this study includes:

1. Administering of H2RAs and PPIs in neonatal GERD.
2. Comparing the safety and efficacy of H2Ras with PPIs in neonatal GERD.

LIST OF ABBREVIATIONS

Gastroesophageal Reflux (GER); Gastroesophageal Reflux Disease (GERD)

DATA AVAILABILITY

The points of documents used to assist the results of this study are available upon the rational request from the corresponding author.

DISCLOSURE OF CONFLICT OF INTEREST

The authors proclaim that there was no conflict of interest.

FUNDING STATEMENT

The authors mention that no funding was received from commercial institutions to conduct this study.

STATEMENT OF INFORMED CONSENT

Before conducting the mentioned trials, the parents or guardians of neonates filled out the informed consent form. Our three clinical trials were approved by the Research Ethics Committee of the Tehran University of Medical Sciences and were registered in the Iranian Registry of Clinical Trails.

AUTHOR'S CONTRIBUTION

Peymaneh Alizadeh Taheri created the idea, gathered the data, and wrote and revised the manuscript.

ACKNOWLEDGMENTS

The Author wishes to thank the Research Development Center of Bahrami Children's Hospital and the personnel of the Neonatal Clinic and Neonatal Ward of Bahrami Children's Hospital, and Shariati Hospital.

REFERENCES

1) Nelson SP, Chen EH, Syniar GM, and 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(6): 569-72. DOI: 10.1001/archpedi.1997.02170430035007.
2) Hegar B, Dewanti NR, Kadim M, Alatas S, Firmansyah A, and Vandenplas Y. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009; 98(7): 1189-1193. DOI: 10.1111/j.1651-2227.2009.01306. x.
3) Ciciora SL, and Woodley FW. Optimizing the use of medications and other therapies in infant gastroesophageal reflux. Paediatr Drugs. 2018; 20 (6): 523–537. DOI: 10.1007/s40272-018-0311-3.
4) Rosen R, Y. Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines. J Pediatr Gastroenterol Nutr. 2018;66(3):516–554. DOI: 10.1097/MPG.0000000000001889.
5) Campanozzi A, Boccia G, Pensabene L, Panetta F, Marseglia A, Strisciuglio P,et al. Prevalence and natural history of gastroesophageal reflux: A pediatric prospective survey. Pediatrics 2009;123(3):779-83. DOI: 10.1542/peds.2007-3569.
6) Orenstein SR. Symptoms and reflux in infants: Infant gastroesophageal reflux questionnaire revised (I-GERQ-R)–utility for symptom tracking and diagnosis.Curr Gastroenterol Rep 2010;12(6):431-6. DOI: 10.1007/s11894-010-0140-1.
7) Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: A systematic review. J Neurogastroenterol Motil. 2011;17(1):14-27. DOI: 10.5056/jnm.2011.17.1.14.
8) Dent J, El-Serag HB, Wallander MA, and Johansson S. Epidemiology of gastro-esophageal reflux disease: A systematic review. Gut. 2005; 54 (5):710-17. DOI: 10.1136/gut.2004.051821.
9) National Collaborating Centre for Women's and Children's Health. Gastro-esophageal reflux disease: Recognition, diagnosis and management in children and young people. National Institute for Health and Care Excellence (NICE). London (UK): Clinical Guidelines. 2015. Bookshelf ID: NBK293624
10) Ferreira CT, de Carvalho E, Sdepanian VL, de Morais MB, Vieira MC, and Silva LR. Gastroesophageal reflux disease: exaggerations, evidence and clinical practice. J Pediatr (Rio J). 2013;90(2):105- 18. http://dx.DOI.org/10.1016/j.jped.2013.05.009
11) van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, and Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: A systematic review. Pediatrics. 2011;127(5):925–935. DOI: 10.1542/peds.2010-2719.
12) Winter HS. Management of gastroesophageal reflux disease in children and adolescents. In: Post TW, ed. UpToDate. Waltham, MA. Accessed on April 1, 2019.
13) Mattos ÂZ, Marchese GM, Fonseca BB, Kupski C, and Machado MB. Antisecretory treatment for pediatric gastroesophageal reflux disease - a systematic review. Arq Gastroenterol. 2017;54(4):271–280. DOI.org/10.1590/s0004-2803.201700000-42.
14) Ward RM, Kearns GL. Proton pump inhibitors in pediatrics. Mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. Pediatr Drugs. 2013;15(2):119-131. DOI: 10.1007/s40272-013-0012-x.
15) Nelson SP, Kothari S, Wu EQ, Beaulieu N, McHale JM, and Dabbous OH. Pediatric gastroesophageal reflux disease and acid-related conditions: Trends in incidence of diagnosis and acid suppression therapy. J Med Econ. 2009; 12(4):348–355. DOI: 10.3111/13696990903378680.
16) Lightdale JR, and Gremse DA. Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal Reflux. Management guidance for the pediatrician. J Pediatrics. 2013;131(5): e1684-1695. DOI: 10.1542/peds.2013-0421.

17) Chiba N, De Gara CJ, Wilkinson JM, and Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis. Gastroenterol. 1997;112(6):1798–1810. DOI: 10.1053/gast. 1997.v112.pm9178669.
18) Barron JJ, Tan H, Spalding J, Bakst AW, and Singer J. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr. 2007;4: 421–427. DOI: 10.1097/MPG.0b013e31812e0149.
19) Zhou Y , Xu L , Wushouer H , Yu A , Xu Z, Chen C, et al. Acid suppression use among infants in one tertiary children's hospital in China, 2015-2018: A retrospective observational study. Front Pediatr. 2021; 21(9):679203. DOI: 10.3389/fped.2021.679203. eCollection 2021.
20) Murthy P, Dosani A, and Lodha A. Acid suppression in neonates: Friend or Foe? 2019.Indian Pediatr. 56(15):541-546.
21) Chabra S, and Peeples ES. Assessment and management of gastroesophageal reflux in the newborn. Pediatr Ann. 2020;49(2): e77–e81. DOI: 10.3928/19382359-20200121-02.
22) Hassall E. Step-up and step-down approaches to the treatment of gastroesophageal reflux disease in children. Curr Gastroenterol Rep. 2008; 10(3): 324–331. DOI: 10.1007/s11894-008-0063-2.
23) Leung AKC, and Hon KL: Gastroesophageal reflux in children: An updated review. Drugs Context.2019; 8: 1-12. DOI: 10.7573/dic.212591. eCollection 2019.
24) Orenstein SR. Infant GERD. Symptoms, reflux episodes & reflux disease, acid & non-acid reflux- implications for treatment with PPIs. Curr Gastroenterol. Rep. 2013;15(11):353. DOI: 10.1007/s11894-013-0353-1.
25) US Food and Drug Administration: Metoclopramide-containing drugs. November 2013, http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety Alerts for Human Medical Products/ucm106942.htm, date of publication: 2009, last access: November 7, 2013.
26) Djeddi D, Kongolo G, Lefaix C, Mounard J, and Léké A: Effect of domperidone on QT interval in neonates. J Pediatr. 2008; 153(5): 663–666. DOI: 10.1016/j.jpeds.2008.05.013.
27) Zamora SA, Belli DC, Ferrazzini G, and Friedli B. Effects of cisapride on ventricular depolarization-repolarization and arrhythmia markers in infants. Neonatol. 2001; 80(1) :30–34. DOI: 10.1159/000047116.
28) Albert RK, Schuller JL, and COPD Clinical Research Network. Macrolide antibiotics and the risk of cardiac arrhythmias. Am J Respir Crit Care Med.2014;189(10): 1173–1180. DOI: 10.1164/rccm.201402-0385CI.
29) Taheri PA, Mahdianzadeh F, Shariat M, and Sadeghi M. Combined therapy in gastroesophageal reflux disease of term neonates, refractory to conservative therapy and monotherapy: A clinical trial. JPNIM.2018;79(2): e070201.
30) Sajjadian N, Akhavan Z, Taheri PA, and Shariat M. A new therapeutic strategy for gastroesophageal reflux disease refractory to conservative therapy and monotherapy in preterm neonates: A clinical trial. JPNIM. 2019;8(1): e080125.
31) Taheri PA, Validad E, and Eftekhari K. The safety and efficacy of lansoprazole plus metoclopramide among neonates with gastroesophageal reflux disease refractory to conservative therapy and monotherapy: A clinical trial.2021: Int J Pediatr.2021. Article ID 3208495, 9 pages https://DOI.org/10.1155/2021/3208495.