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# NEW INSIGHTS IN THE MANAGEMENT OF REFRACTORY NEONATAL GERD

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## ABSTRACT

***Gastroesophageal reflux disease (GERD) is one of the most common problems in neonates. The main goals of infantile GERD treatment are maintaining clinical recovery, sufficient growth, and preventing the recurrence rate and related problems. Acid-suppressive therapy including H2RAs and PPIs are the basic pharmacologic therapy for adult and pediatric GERD. PPIs are more effective than H2RAs in GERD treatment. Neonatal GERD remains a difficult entity to define and manage, and additional studies to aid in the clinical diagnosis and management are needed. Neonatal GERD refractory to conservative and monotherapy is a dilemma and performing trials to evaluate the effect of a PPI or a H2RA plus prokinetics in the management of these neonates is necessary to prevent considering invasive diagnostic procedures and early surgical treatment. we performed three different clinical trials to survey the efficacy and safety of combined therapy including an H2RA plus a prokinetic or a PPI plus a prokinetic in neonatal GERD refractory to conservative and monotherapy.***

**KEYWORDS:** ***Neonates, Gastroesophageal reflux disease, refractory, treatment***

## 1-INTRODUCTION

Neonatal Gastro-esophageal reflux (GER) is defined as a normal physiological retrograde passage of gastric contents into the esophagus occurring daily with or without regurgitation and/or vomiting in otherwise healthy neonates [1-3]. GER is most commonly observed in two-thirds of healthy infants during the first 4 months of life that declines gradually to reach one-third between 4 to 9 months of age and almost 4% after 1 year of age [3]. In apposite, gastro-esophageal reflux disease (GERD) refers to troublesome symptoms or conditions (e.g., frequent vomiting, poor weight gain, irritability and respiratory symptoms) which complicate the physiologic GER. The prevalence of GERD differs from 8.5% in Eastern Asia to 10-20% in Western Europe and North America [4,5]. The principal symptoms of neonatal GERD are GI troubles including frequent regurgitation or vomiting, anorexia, refusal or stopping feeding along with irritability, crying, inappropriate weight gain, retrocollis, and sleep disturbance. It may also present as respiratory problems including coughing, choking, wheezing, or upper respiratory tract symptoms [6]. Prematurity, neurological diseases, drugs (e.g., sedatives and muscle relaxants), positive family history of GERD, and gastrointestinal malformations increase the risk of GERD [7].

The main goals of infantile GERD treatment in are maintaining clinical recovery and sufficient growth, and preventing the recurrence rate and related problems [8].

## 2.TREATMENT

### 2.1. Conservative Therapy

In most cases of infantile GER, parental reassurance is the mainstay of treatment because of the benign and self-limiting nature of GER. In frequent and troublesome regurgitation (GERD); conservating therapy including thickening the formula or expressed breast milk with cereal, postural therapy, and lifestyle changes are recommended [4,7].

### 2.2. Pharmacotherapy

It should be considered in the treatment of more severe gastroesophageal reflux disease for patients who do not respond to conservative measures [5,7]. Acid-suppressive therapy including H2RAs and PPIs are the main pharmacologic therapy for adult and pediatric GERD [4,9,10]. Adult data suggest PPIs are more effective than H2RAs in reducing GERD symptoms. [9,11].Although there is a lack of published data for enhanced results and increasing worries about side effects, oral PPIs have been increasingly used in infantile (under one year of age) GERD

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[12-14]. A 4-week trial of a PPI or H2RA for infants with symptoms such as unexplained feeding difficulties, distressed behavior and unsuitable weight gain plus overt regurgitation has been suggested in recent guidelines [7]. There is no documentation that support the efficacy of acid-suppressant drugs for the treatment of symptoms in neonatal GERD. [15]. Neonatal GERD remains a difficult entity to define and manage, and additional studies to aid in the clinical diagnosis and management are needed [16]

PPIs induce inactivation of H+/K+-ATPase in the gastric parietal cells canaliculi and inhibition of gastric acid production. They also decline gastric secretion volume and facilitate gastric emptying [12,13]. The PPIs are superior over H2RAs because they have longer duration of action, fewer complications and higher inhibition of meal-induced acid secretion [5]. Moreover, the probability of tachyphylaxis may occur after repeated administration of H2RAs, leading to a decline in acid suppression [17].

As PPIs have international accredit due to fewer therapeutic interruptions and switches in the first four weeks of treatment [13,18]. The past viewpoint to the management of infantile GERD was a "step-up" protocol of acid suppression treatment in which ranitidine was the first line of prescription that was changed to PPIs if the symptoms persisted despite receiving high-dose ranitidine [19]. According to the recommendation of an updated review, pharmacotherapy is suggested for the treatment of severe GERD in children who are refractory to conservative therapy. In this regard, PPIs are favored over H2-receptor antagonists because of their superior efficacy [20]. Recent studies have shown that the symptoms of neonatal GERD are due to either acid reflux or nonacid reflux [21].

Among prokinetics, although metoclopramide may induce irritability, drowsiness, oculogyric crisis, dystonic reaction, apnea, and emesis in infants, these adverse reactions are only induced with prolonged or high-dose metoclopramide exposure [22]. Domperidone and cisapride are prohibited to be used in the USA because of inducing probable cardiac arrhythmia [23, 24]. Macrolides are among prokinetics and may also induce cardiac arrhythmia in long-term usage [25]. Metoclopramide may be a safe prokinetic if it is prescribed with a low-dose amount for a short duration. It was why we used metoclopramide in our studies.

2.3. Surgical intervention (typically fundoplication) is generally reserved for infants with severe GERD who have failed maximal medical management [15].

## 3.ALGORITHMIC APPROACH IN REFRACTORY NEONATAL GERD

The indication of diagnostic evaluation for further investigation includes:1-Symptoms that are nonresponsive or only partially responsive to a common dose of PPI administered properly for at least 4 to 8 weeks 2-Positive alarm symptoms (e.g., failure to thrive, bleeding, dysphagia) in all age groups and 3-Prescence of atypical symptoms for GERD (e. g., chest pain or extraesophageal symptoms, contrary to typical heartburn and/or regurgitation) in children and adults [3,26,27]. The diagnostic evaluation may include: upper digestive endoscopy, esophageal manometry, and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring) [3,26,27]. This analytical approach is a general recommendation and should not be regarded as a substitute for clinical experience or as a treaty appropriate for all patients [3].

There are still controversies about the management of neonatal GERD especially the patients with relative or no response to conservative and monotherapy.

## 4. NEW INSIGHTS INTO THE MANAGEMENT OF REFRACTORY NEONATAL GERD

According to our research in literature, PubMed, and Google Scholar; we found no clinical trial that has studied the efficacy and safety of combined therapy including an H2RA plus a prokinetic or a PPI plus a prokinetic in the treatment of neonatal GERD refractory to conservative and monotherapy, so we performed three different clinical trials to survey the efficacy and safety of combined therapy including an H2RA plus a prokinetic or a PPI plus a prokinetic in neonates [28-30].

## 5. CURRENT CLINICAL TRIALS WITH NEW INSIGHTS

As almost all parents of our patients were not satisfied with performing the mentioned invasive diagnostic procedures [upper digestive endoscopy, esophageal manometry, and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring)] for their neonates; instead of performing the mentioned invasive diagnostic procedures in unresponsive cases to conservative and monotherapy, we added metoclopramide to acid suppressant regimen in the treatment of GERD in these patients

The term "refractory to conservative therapy and monotherapy" was defined as a response rate of less than 50% in the first and third studies and 50% to 70% in the second study, so the patients with relative responses that did not satisfy the treatment team and parents before the combined intervention, participated in the study. Other diagnoses were ruled out in regard to the clinical manifestations and examination of the patients; lab tests; sonography, etc. The highly positive response to combination therapy emphasized the diagnosis of GERD in each patient too. The duration of conservative treatment and then monotherapy was about 3-7 days each, according to a careful balance of risk and benefits between the severity of clinical problems and the response rate. Our performed 3 clinical trials included:
1: In the first study, the response rate of GERD symptoms was less than 50% after conservative therapy and monotherapy in

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refractory cases of term infants, so we added metoclopramide to each group of receiving conservative therapy plus ranitidine or conservative therapy plus omeprazole.

In this study the response rate increased to 93.74% ± 7.28% in "omeprazole plus metoclopramide" group and 75.43% ± 23.24% in "ranitidine plus metoclopramide" group after one week and one month of intervention. There were no side effects in either group after one week and one month of intervention.

Generally, this study showed that combined therapy led to a response rate was > 70% in each group, but it was significantly higher in "omeprazole plus metoclopramide" group (> 90%). A combination of each acid suppressant with metoclopramide led to a higher response rate in comparison with monotherapy used before the intervention.

2: In the second study, the response rate of GERD symptoms was about 50% -70% after conservative therapy and monotherapy in refractory cases of preterm infants, so we added metoclopramide to each group of receiving conservative therapy plus ranitidine or conservative therapy plus omeprazole.

The response rate increased to %91.37 ± 7.5 in "omeprazole plus metoclopramide" group and to %77.06 ± 3.38 in "ranitidine plus metoclopramide" group after one week of intervention. There were no drug-related complications of drugs in both groups in our study.

Generally, this study showed that combined therapy led to the response rate of > 70% after one week of intervention in each group, but it was significantly higher in the PPI group (> 90%). Both combination therapies led to higher response rate in comparison with conservative therapy and monotherapy used before intervention.

3: In the third study, a diagnosis of GERD was made according to the last version of the I-GERQ-R clinical scoring that consists of 12 items. The total score items in the IGERQ-R range from 0 to 42 with a cut point > 15 scores [20]. In this study, we added metoclopramide to the regimen of ranitidine and lansoprazole group in refractory cases of GERD in term infants. In this study, the clinical response rate in "lansoprazole plus metoclopramide" increased and the score 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 "ranitidine plus metoclopramide" group as the score rate decreased to 9:3±4:57after one week and 4:5±4:12 score after one month of intervention. There were no drug adverse effects in either group during interventions.

In these three trials, the response rate was significant in each group after one week and one month of treatment. Adding metoclopramide to each acid suppressant led to a better response rate than monotherapy used before the new intervention. Generally, the results of these three trials suggest that combined treatment of both nonacid reflux (metoclopramide) and acid reflux (PPI or H2RA) is successful in refractory cases of GERD in neonates before performing complementary exams such as upper digestive endoscopy, esophageal manometry and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring). Combination therapy prevents unnecessary performance of invasive complementary exams, while it is safer and more cost-effective too.

## 6.CONCLUSION

The combination of each acid suppressant with metoclopramide led to a higher response rate in comparison with monotherapy used before intervention. This new regimen prevents considering invasive diagnostic procedures and early surgical treatment.

### Limitations

As far as our knowledge, there are no other trials that has studied and suggested pharmacologic combination therapy in neonates. Further studies with more participants and longer follow up are recommended to compare the effect of these combined therapy in refractory cases of neonatal GERD before surgical intervention.

### Compliance with Ethical Standards

### Acknowledgments

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### Disclosure of Conflict of Interest

The authors declare no conflict of interest.

### Statement of Informed Consent

Informed consent was obtained from all parents or guardians of infants who entered the studies. All three clinical trials were approved by the Research Ethics Committee of Tehran University of Medical Sciences. They were also registered in the Iranian Registry of Clinical Trails.

### Author's Contribution

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

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