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Original article

A new therapeutic strategy for gastroesophageal reflux disease resistant to conservative therapy and monotherapy in preterm neonates: a clinical trial

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Abstract

Background: Gastroesophageal reflux disease (GERD) is one of the most common problems in neonates. The main clinical manifestations of GERD are frequent regurgitation or vomiting associated with irritability, anorexia or feeding refusal, failure to thrive, Sandifer posturing, apnea, bradycardia and stridor in infants. Since the clinical manifestations of GERD are often non-specific in preterm infants, it has been described as the clinical syndrome responding to anti-reflux treatment.

Aims: To our knowledge, no clinical trial has compared the efficacy of histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) in preterm infants, nor has any study assessed the effect of adding a prokinetic agent to an acid suppressant and compared them together in these infants, so the present study was conducted.

Study design: This study was performed on 58 preterm newborns (mean age, 9.72 ± 6.78 days, 43.2% boys and birth weight of 1,571.9 ± 596.59 grams) with GERD resistant to conservative therapy and monotherapy hospitalized in neonatal wards and NICUs of Shariati and Bahrami Children Hospitals during 2014-2016. Neonates were randomly assigned to a double-blind trial with either oral metoclopramide plus omeprazole (group A) or oral metoclopramide plus ranitidine (group B). After one week and one month, their symptoms and signs were evaluated again. The response rate in each group was the primary outcome and the side effect of drugs in each group was the secondary outcome.

Results: Our study showed that both regimens were effective in the treatment of GERD resistant to conservative therapy and monotherapy in premature infants. The response rate of "omeprazole plus metoclopramide" was significantly higher than the response rate of "ranitidine plus metoclopramide" (91.37 ± 7.5 vs. 77.06 ± 3.38, respectively; p = 0.04) (primary outcome). There were no drug-related complications of drugs in both groups in our study (secondary outcome).

Conclusion: This study showed that combined therapy led to the response rate of > 70% in each group, but it was significantly higher in group A (> 90%). Both combination therapies led to higher response rate in comparison with conservative therapy and monotherapy used before intervention.

Keywords

Gastroesophageal reflux disease, preterm, ranitidine, omeprazole, metoclopramide, combined therapy.

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Introduction

Gastroesophageal reflux (GER) is a common phenomenon in otherwise healthy neonates, either term or preterm [1, 2]. It affects 70-85% of the infants in their first two months of life but resolves spontaneously in nearly all of them by one year of age [2].

On the other hand, gastroesophageal reflux disease (GERD), a term used when GER causes troublesome symptoms or results in complications, is reported in 9.8-10.7% of preterm infants [3]. The incidence reaches 22% in neonates born under 34 weeks' gestation [4]. The main clinical manifestations of GERD in infants are frequent regurgitation or vomiting associated with irritability, anorexia or feeding refusal, failure to thrive, Sandifer posturing, apnea, bradycardia and stridor [3-5].

Although GERD is common in preterm neonates, its diagnosis and treatment in this population is still a matter of debate [4-6]. Since the clinical manifestations of GERD in preterm infants are often non-specific, it has been described as a clinical syndrome responding to anti-reflux treatment [7]. GERD is empirically diagnosed and treated in the clinical practice based on the clinician's assessment of symptoms. Indications for testing include treatment failure, diagnostic uncertainty, and treating (or preventing) GERD complications [8]. A narrow body of controversial evidence supports treatment of GERD in preterm neonates [7-10]. It is advised to consider conservative strategies, including changes in the body position and feeding pattern, as the first-line treatment in neonates who experience troublesome symptoms without significant clinical complications [9, 11, 12].

For neonates who do not respond to conservative measures or experience complications, acid suppressants including histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have increasingly been used despite limited and controversial data on their efficacy and safety [13]. Two different pathophysiologic mechanisms have been described for GERD in preterm infants, including acid and nonacid reflux [14]. In this study, metoclopramide was added to each group to exert its effect on the lower esophageal sphincter and treat nonacid reflux. Metoclopramide and erythromycin are two prokinetics available in the USA [15] while the use of domperidone and cisapride is prohibited because of their cardiac adverse effects [16, 17]. On the other hand, the adverse effects of metoclopramide have been reported to occur only following overdose and long-term administration of the drug [18].

To our knowledge, no clinical trial has compared the efficacy of H2RAs and PPIs in preterm infants, nor has any study assessed the effect of adding a prokinetic agent to an acid suppressant in these infants, which was the reason why this study was conducted.

Patients and methods

This double-blind randomized controlled trial was conducted to compare the effectiveness of metoclopramide plus omeprazole with meto-

clopramide plus ranitidine for GERD in preterm infants.

Subjects

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 GERD were enrolled in this study. The number of participants was determined by a prospective power analysis, assuming a power of at least 90%, a 2-sided alpha of 0.05, and treatment response based on the studies by Omari et al. [19] and Kelly et al. [20].

Preterm neonates aged < 28 days who were born at 28-37 weeks' gestation and did not respond to conservative anti-GERD treatments (including postural change, reduction of the feeding volume, increased frequency of feedings, hypoallergenic formulas, and use of hypoallergenic regimens by mothers) and monotherapy were considered eligible.

Neonates were excluded if they had any significant underlying condition (e.g., major congenital abnormalities, gastrointestinal or neurological disorders) or diseases (e.g., sepsis, apnea of prematurity), required invasive or noninvasive ventilation or were administered any muscle relaxant or sedative medication.

Diagnosis

In our study, a diagnosis of GERD was made if there was regurgitation or vomiting associated with at least two other clinical GERD-related problems, such as apnea, failure to thrive, Sandifer syndrome, etc. Since pH monitoring is not available in many centers and is not safe in some clinical situations like apnea, GERD was diagnosed based on clinical manifestations by two neonatologists and an expert master nurse. The term "resistant to conservative therapy and monotherapy" was applied when the response rate was above 50% but below 70%, so all patients showed relative responses that did not satisfy the treatment team and parents. This definition and the high positive response to combination therapy also emphasized the diagnosis of GERD in each patient. Other diagnoses were ruled out based on the clinical manifestations of the patients; for example – if there were vomiting, apnea and failure to thrive – sepsis, intraventricular hemorrhage, etc. were ruled out by clinical examination, lab tests, brain sonography, etc. 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.

Feeding

Feeding started on the first day as follows:

1. in neonates 28-32 weeks / 1,000-1,500 g, 2 mL/kg breast milk was given every 2 hours via a nasogastric tube;
2. in neonates > 32 weeks / > 1,500 g, breastfeeding or bottle feeding started with a volume tolerated by the infant every 2-3 hours.

After the first day, the feeding volume was increased by 10-20 mL/kg/day to a maximum volume of 170-200 mL/kg/day according to the neonate's feeding tolerance. Feeding was stopped once the clinical problems became severe (for example recurrent apnea or vomiting) and re-started as soon as the infant regained feeding tolerance. The mode of feeding was continuous when a nasogastric tube was used. Apnea was considered a sign of GERD if it was associated with vomiting, regurgitation, or other clinical GERD-related manifestation like Sandifer syndrome. All patients received total parenteral nutrition (TPN) according to our NICU protocol. As far as they could tolerate feeding, TPN was tapered gradually.

All patients were breastfed except those who had a family history or other clinical presentations of allergies. These patients received hypoallergic formulas for 5-7 days until their mothers' breastmilk was free of cow's milk proteins after using a hypoallergic regimen.

Trial

The study protocol was approved by the research ethics committee of Tehran University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (IRCT: 2016030226876N1). Written informed consent was obtained from parents or guardians of all infants before enrollment.

The neonates who met the inclusion and exclusion criteria were randomly assigned (in blocks of two per site) to a double-blind clinical trial to receive omeprazole plus metoclopramide or ranitidine plus metoclopramide for a 30-day period. The random allocation sequence was generated by an independent statistician.

Patients in group A received oral omeprazole 0.5 mg/kg/dose twice daily plus metoclopramide 0.1 mg/kg/dose twice daily. Patients in group B received oral ranitidine 1 mg/kg/dose twice daily plus metoclopramide 0.1 mg/kg/dose twice daily. Before initiation of pharmacotherapy, a checklist including demographic data (age, gender, birth weight, and weight at presentation) and symptoms attributed to GERD was filled by a neonatologist (researcher). At the end of the first week, the patients were re-evaluated by the same neonatologist and post-treatment weight and symptoms were recorded. The patients were then re-evaluated after one month to assess further changes in the presenting symptoms.

Changes in the total number of GERD-related signs and symptoms from baseline to the end of treatment were considered as the primary outcome. Secondary outcomes were defined as complications in either group following oral administration of metoclopramide, ranitidine, and omeprazole.

Data analysis

The SPSS® for Windows version 21.0 was used for data analysis (SPSS Inc., Chicago, IL, USA). Descriptive data are reported as mean and standard deviation (SD) for numerical and number (percent) for categorical data. Post-treatment results were compared against baseline data using two-sided paired t-test for differences in the mean values and chi-square test and Fisher's exact test (two-sided) for differences in the percentage of response to treatment. A p-value of < 0.05 was considered significant.

Results

Fifty-eight preterm newborns (43.2% male, 56.8% female) with a mean age of 9.72 ± 6.78 days (range: 1-28 days) and a mean birth weight of 1,571.9 ± 596.59 g were studied. There was no significant difference in demographic data and baseline characteristics between the two groups (**Tab. 1**).

The most frequent gastrointestinal-related signs and symptoms were vomiting and Sandifer syndrome. The most frequent respiratory-related signs and symptoms were apnea and cyanosis. No case of hematemesis, anemia, coughing, seizure and stridor was reported (**Tab. 2**). The number of patients with baseline and post-treatment GERD-associated clinical manifestations, categorized by the treatment group, are presented in **Tab. 2**.

The response rate of all clinical manifestations in the "omeprazole plus metoclopramide" group was significant except for rumination and cyanosis (intra-group comparison).

In the ranitidine plus metoclopramide group, the response rate of irritability, cyanosis, and failure to thrive was not significant (intra-group comparison).

This study showed that both ranitidine plus metoclopramide and omeprazole plus metoclopramide were effective in reducing the frequency of GERD symptoms in premature neonates. The response rate in both groups was > 75%, but the response rate of the "omeprazole plus metoclopramide" group was significantly higher (91.37 ± 7.5 vs. 77.06 ± 3.38, respectively; p = 0.04). The response rate after one month was the same as the response rate after one week in both groups (**Tab. 2**).

Discussion

Despite the fact that GERD is a common condition in preterm infants, its therapeutic management remains controversial [7].

The main aims of GERD management in infants are to maintain symptomatic relief, provide

Table 1. Patients' characteristics in the two intervention groups.

Patients' characteristics	Omeprazole plus metoclopramide (n = 29)	Ranitidine plus metoclopramide (n = 29)	p-value
Gender			
Girls, n (%)	15 (51.7%)	18 (62.1%)	0.426
Boys, n (%)	14 (48.3%)	11 (37.9%)	
Age, mean ± SD, days at intervention	9.41 ± 7.54	10.03 ± 6.05	0.731
Birth weight, mean ± SD, g	1,567.04 ± 603.88	1,600.36 ± 591.28	0.322
Weight at presentation, mean ± SD, g	1,548.89 ± 624.93	1,558.04 ± 545.13	0.446
Gestational age at birth, mean ± SD, weeks	31.48 ± 3.08	31.93 ± 3.07	0.593
Corrected gestational age, mean ± SD, weeks at intervention	33 ± 3.46	33.54 ± 2.91	0.537

Table 2. GERD-related signs and symptoms before and one week after intervention.

Clinical manifestations	Omeprazole plus metoclopramide (n = 29)	Ranitidine plus metoclopramide (n = 29)	Inter-group p-value
Irritability, n (%)			
Pre-intervention	4 (13.8%)	3 (10.3%)	0.31
Post-intervention	0 (0%)	1 (3.4%)	
Response rate	100%	66.6%	
Intra-group p-value	0.001	0.103	
Weight-gain failure, n (%)			
Pre-intervention	3 (10.3%)	1 (3.4%)	0.56
Post-intervention	0 (0%)	1 (3.4%)	
Response rate	100%	0%	
Intra-group p-value	0.001	NA	
Regurgitation, n (%)			
Pre-intervention	5 (17.2%)	4 (13.8%)	0.313
Post-intervention	1 (3.4%)	0 (0%)	
Response rate	80%	100%	
Intra-group p-value	0.026	0.001	
Vomiting, n (%)			
Pre-intervention	16 (55.2%)	17 (58.6%)	0.553
Post-treatment	1 (3.4%)	2 (6.9%)	
Response rate	93.7%	88.2%	
Intra-group p-value	0.035	0.021	
Rumination, n (%)			
Pre-intervention	7 (24.1%)	3 (10.3%)	0.313
Post-intervention	1 (3.4%)	0 (0%)	
Response rate	85.7%	100%	
Intra-group p-value	0.07	0.001	
Sandifer position, n (%)			
Pre-intervention	11 (37.9%)	9 (31%)	0.754
Post-intervention	1 (3.4%)	1 (3.4%)	
Response rate	90.9%	88.8%	
Intra-group p-value	0.019	0.012	
Wheezing, n (%)			
Pre-intervention	1 (3.4%)	1 (3.4%)	NA
Post-intervention	0 (0%)	0 (0%)	
Response rate	100%	100%	
Intra-group p-value	0.0001	0.0001	
Apnea, n (%)			
Pre-intervention	13 (44.8%)	17 (58.6%)	0.15
Post-intervention	2 (6.9%)	0 (0%)	
Response rate	84.6%	100%	
Intra-group p-value	0.019	0.0001	
Cyanosis, n (%)			
Pre-intervention	8 (27.6%)	4 (13.8%)	0.053
Post-intervention	1 (3.4%)	2 (6.9%)	
Response rate	87.5%	50%	
Intra-group p-value	0.09	0.124	
Overall response rate, %, mean ± SD	91.37 ± 7.5	77.06 ± 3.38	0.04

Intra-group p-value means p-value between Pre and Post intervention in every group.
Inter-group p-value means p-value between two groups of intervention.
GERD: gastroesophageal reflux disease.

adequate growth, and prevent GERD-related complications and recurrence of symptoms [21]. In case of uncomplicated GERD, a stepwise therapeutic approach based on conservative strategies is strongly advised. However, when symptoms do not subside in spite of conservative measures, pharmacological therapy should be considered [22].

H2RAs and PPIs have been increasingly used as the main drugs in the management of pediatric GERD [23]. Recent guidelines suggest that a 4-week trial of a PPI or H2RA be considered for infants with a significant regurgitation associated with symptoms such as unexplained feeding problems, abnormal behavior, and unfavorable weight gain [24].

H2RAs act by binding competitively with histamine to the H2 receptors of the gastric wall to reduce the secretion of hydrochloric acid by the parietal cells and increase intragastric pH [20].

Ranitidine is the main H2RA used in NICUs [25]. Kuusela [26] showed that ranitidine at a dose of 0.5 mg/kg/q12h intravenously effectively kept gastric pH above 4 in critically ill preterm infants, whereas the optimal dose was 1.5 mg/kg/q8h intravenously in critically ill term infants. However, the chronic use of ranitidine is discouraged due to the frequent development of tachyphylaxis within 6 weeks [2, 21].

PPIs act as long-term blockers of the gastric proton pump, which catalyzes the final phase of the acid secretory process, hindering both basal and stimulated acid secretion by the parietal cells. The prescription of PPIs as therapeutic agents for the treatment of GERD in the pediatric population has largely increased over the last 10 years, in particular after the therapeutic failure of H2 blockers [27]. They are being increasingly used in neonatal units. Moore et al. [28] reported that omeprazole at a daily dose of 0.7 mg/kg results in an increase in the gastric pH, a significant decrease in acid GER frequency, and a decline in the esophageal acid exposure.

Despite the widespread use of acid suppressants in infants with GERD, the overall available evidence on the safety and efficacy of these medications in preterm infants is quite limited [25]. Most of these medications have been neither assessed nor approved for use in preterm infants.

In this study, we compared the efficacy of ranitidine plus metoclopramide with omeprazole plus metoclopramide in clinical improvement of GERD in preterm infants. According to a study by Omari et al. [19], the use of esomeprazole in preterm infants is associated with a significant decrease in the number of GERD-related symptoms, a remarkable reduction of the overall esophageal acid exposure, and a lower frequency of acid bolus reflux episodes whereas non-acid GER features are not affected. However, these results were not controlled for placebo effects; therefore, they should be confirmed in further placebo-controlled trials.

On the other hand, Orenstein et al. [29] assessed the efficacy of lansoprazole versus placebo in a large cohort of both term and symptomatic preterm infants and reported no advantage over placebo in the reduction of symptoms attributed to GERD (i.e., crying, regurgitation, feeding refusal, back arching, wheezing, and coughing). However, as the enrolled infants did not undergo pH-metry, the authors hypothesized a causal role of predominant nonacid reflux events, for which PPIs are ineffective.

Our study showed that both ranitidine plus metoclopramide and omeprazole plus metoclopramide were effective in reducing the frequency of GERD symptoms in premature neonates. The response rate in both groups was > 75%, but the response rate of the "omeprazole plus metoclopramide" group was significantly higher (91.37 ± 7.5 vs. 77.06 ± 3.38, respectively; $p = 0.04$).

Some studies [30-33] have reported a significant risk of infections associated with the use of both H2RAs and PPIs and necrotizing enterocolitis associated with H2RAs in very low birth weight preterm infants.

According to a systematic review and meta-analysis performed by Lau Moon Lin et al. [34], a total of 108 (57 prospective) studies involving 2,699 patients (2,745 metoclopramide courses) were surveyed. The most common adverse effects reported in children were extra-pyramidal symptoms, diarrhea, and sedation, which were reversible and of no long-term significance. Dysrhythmia, respiratory distress/arrest, neuroleptic malignant syndrome, and tardive dyskinesia occurred rarely.

On the other hand, according to the FDA Gastrointestinal Drugs Advisory Committee Meeting, the adverse effects of metoclopramide have been reported only with overdose and long-term administration of the drug [18]. Another meta-analysis of metoclopramide in children below 2 years with GERD confirmed a decrease

in GERD symptoms [35]. However, this effect comes at the cost of significant adverse effects, including drowsiness, restlessness, and extra-pyramidal reactions in 10-20% of the patients in our search and up to 34% of the patients in earlier studies [35].

We found no complications in either group following the use of oral ranitidine or omeprazole plus metoclopramide (secondary outcome) in the present study.

In conclusion, although both "omeprazole plus metoclopramide" and "ranitidine plus metoclopramide" were safe and highly effective in controlling reflux symptoms in GERD of premature infants in this study, the response rate of "omeprazole plus metoclopramide" was significantly higher. On the other hand, the combination of each acid suppressant with metoclopramide increased the response rate in comparison with monotherapy with an acid suppressant before intervention. It seems that the synergistic effect of an acid suppressant with metoclopramide on the lower esophageal sphincter increases the response rate in these patients. We suggest combined therapy in GERD of preterm neonates not responding to conservative treatments and monotherapy. This combined therapeutic regimen prevented mortality, morbidity, and surgery in these patients. We found no complications in these patients following combined therapy. We suggest similar studies to be undertaken in larger sample sizes in this age group to determine the efficacy of these combination therapies.

Highlights

The highlights of the paper are presented in **Tab. 3**.

Table 3. Highlights of the paper are presented.

- GERD is one of the most common problems in premature neonates.
- The therapeutic management of GERD in premature neonates is still a matter of debate.
- Two therapeutic regimens including "omeprazole plus metoclopramide" and "ranitidine plus metoclopramide" were compared in preterm neonates with GERD resistant to conservative therapy and monotherapy.
- Both combined regimens were effective in GERD of premature neonates.
- The response rate was significantly higher in "omeprazole plus metoclopramide" group.
- The combination of each acid suppressant with metoclopramide led to higher response rate in comparison with monotherapy before intervention.

GERD: gastroesophageal reflux disease.

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Conflict of interest

Authors mention that there is no conflict of interest in this study.

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