

# Comparison of Hypoallergenic Diet vs. Ranitidine in Treatment of Gastroesophageal Reflux Disease of Infants: A Randomized Clinical Trial

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## Abstract

**Background:** Gastroesophageal reflux disease (GERD) is defined as “troublesome symptoms or complications of GER”, and is a multifactorial disorder. This study aimed to compare the treatment outcomes of hypoallergenic diet vs. ranitidine on symptoms of gastroesophageal reflux disease (GERD) in infants.

**Methods:** In this randomized clinical trial, 50 patients aged less than 1 year, who were suspected to have GERD on the basis of I-GERQ-R, were enrolled. They were randomly allocated to two groups of equal number, one group received ranitidine and the other hypoallergenic diet for 2 weeks. The frequency of GERD symptoms, including irritability, vomiting, anorexia, respiratory symptoms and arching, were compared between the two groups before and after the trial.

**Results:** After a two-week trial, the frequency of vomiting and respiratory symptoms decreased significantly in both groups ( $P < 0.05$ ). The frequency of vomiting decreased in 19 (76%) and 19 (76%) of infants in ranitidine and hypoallergenic diet groups, respectively ( $P = 0.05$  between groups). Moreover, the respiratory symptoms improved significantly in both groups ( $P < 0.05$ ). The frequency of irritability did not decrease significantly in any of the groups ( $P = 0.18$ ).

**Conclusions:** The current findings suggest that the hypoallergenic diet might have significant effect on GERD symptoms; these effects are comparable with those of ranitidine. Considering the possibility of cow's milk protein allergy in this group of patients, we recommend that the treatment of GERD in pediatric population be initiated with hypoallergenic diet and in case of not achieving significant effect, pharmacological treatment be added and applied as a combination therapy.

**Keywords:** Gastroesophageal Reflux Disease, Ranitidine, Food Allergy

## 1. Background

Gastroesophageal reflux (GER) is defined as the passive movement of gastric contents into the esophagus with or without regurgitation or vomiting. It is a common disorder of infancy, which can affect 50% of infants aged less than 3 months (1). Episodes of regurgitation peaks at about 4 months of age and resolves without treatment in 95% of infants by 1 year of age (1, 2).

GER disease (GERD) is defined as “troublesome symptoms or complications of GER” including failure to thrive, feeding or sleeping problems, chronic respiratory disorders, irritability, hematemesis, apnea, and life-threatening events (3). GERD is a multifactorial disease and its pathophysiology is not clearly understood yet. Decreased lower esophageal sphincter (LES) tone is the most important cause of GERD (4). The role of other factors such as food allergy and cow milk allergy (CMA) have also been suggested in this regard (5).

Though the symptoms of food allergy overlap with GERD and the conditions could co-exist in 42% - 58% of infants and children, there are evidences showing that not only GER can be associated with CMA, but CMA itself can also induce GER (5, 6). The findings of studies that have investigated the association of CMA and GERD are controversial (7-9). However, the underlying mechanisms remain unclear (9). The goals of GERD management are to alleviate symptoms, to decrease frequency and duration of reflux episodes, to prevent complications and to improve normal growth. A stepwise approach, including lifestyle modifications, pharmacotherapy and surgical procedures, is considered in this regard (10, 11). Results of a systematic review on pharmacological treatment of GERD indicated that moderate evidences exist regarding the effectiveness of proton pump inhibitors (PPIs) or  $H_2$  antagonists. This review recommended designing further randomized clinical trials for different treatment approaches to GERD (12).

Considering the possible role of food allergy in the

pathogenesis of GERD, it is suggested that as an initial step for treatment of GERD, considering a hypoallergenic diet would be helpful for making an appropriate treatment design.

Given the worldwide increasing prevalence rate of GERD, presence of few randomized controlled trials for the management of GERD in infants (9) specially on the effectiveness of hypoallergenic diet in comparison with other commonly used pharmacological treatments, in the current study, we aimed to compare the treatment outcomes of hypoallergenic diet vs. ranitidine, the first choice treatment of GERD, based on symptoms improvement in affected infants.

## 2. Methods

This randomized clinical trial was conducted from May 2014 to January 2015 in Isfahan, Iran. Infants with suspected GERD aged less than 1 year were included in the study. Children and infants with vomiting or regurgitation plus one of the symptoms irritability at night, respiratory signs and symptoms (including apnea, hoarseness and wheeze) or insufficient weight gain were considered as suspected cases of GERD (13).

They were randomly selected from children and infants referred to the pediatrics clinics affiliated to IUMS or outpatient general pediatric or pediatric gastroenterology clinics in Isfahan city. GERD was diagnosed on the basis of I-GERQ-R (score of  $> 7$ ) (14).

Patients with other causes of vomiting including, anatomic GI abnormalities and anomalies of central nervous system, as well as metabolic, infectious, renal and other systemic diseases were excluded. Anemic patients were also excluded from study because they needed additional work-up. In addition, patients with severe respiratory complications such as apnea, cyanosis and respiratory distress that needed urgent medical managements were also excluded.

The study protocol was approved by the pediatrics review board and regional ethics committee of Isfahan University of Medical Sciences (IUMS) (research project number 393605). The trial was also registered in the Iranian registry of clinical trials under the code No. IRCT2015042714882N3. Written informed consent was obtained from the parents of participants.

Selected patients were randomly allocated in two groups of candidates for ranitidine or hypoallergenic diet in equal numbers. Patients in the ranitidine group received ranitidine (Alhavi company, Iran) with a dose of 6 mg/kg daily in two divided doses (drug.com). In the hypoallergenic diet group, mothers of breast fed infants were recommended to take hypoallergenic diet, and those who

fed formula to feed hypoallergenic (hydrolyzed protein or amino acid based formula). After initiation of complementary foods at 6 months of age, the parents were educated for preparing and using hypoallergenic food for both breast and formula fed groups. Hypoallergenic diet was defined as a diet free of milk and dairy products, cow's meat, peanut, fish, and soy. The intervention lasted 2 weeks. The study period was set for two weeks because our goal was to investigate the effect of the intervention, not the impact of the passage of time on GERD.

Symptoms of GERD, including irritability, vomiting, anorexia, regurgitation, respiratory symptoms and arching in selected patients were evaluated and recorded by a pediatrician at baseline and after the intervention to determine the outcome of the intervention. The findings were compared between ranitidine and hypoallergenic diet groups.

### 2.1. Statistical Analysis

Statistical analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA) and Student's t-test and Chi-square test. P value of less than 0.05 was considered as statistically significant.

## 3. Results

In this trial, from 53 initially enrolled infants with GERD, 50 patients were selected and allocated to the ranitidine ( $n = 25$ ) and hypoallergenic diet group ( $n = 25$ ). Baseline characteristics are presented in Table 1. No significant difference existed for age and weight between the two groups ( $P = 0.97$  and  $P = 0.1$ , respectively).

The frequency of different symptoms of GERD in the two studied groups is presented in Table 2. At baseline, there was no significant difference between studied groups with regard to vomiting or severe regurgitation episodes, respiratory symptoms and refusal of feeding episodes, but arching and irritability were more frequent in the group receiving ranitidine.

The frequency of GERD symptoms before and after trial in ranitidine and hypoallergenic diet group is presented in Table 3. After a two-week trial, the frequency of vomiting and respiratory symptoms decreased significantly in both groups ( $P < 0.05$ ).

Significant improvement in the symptoms was observed for vomiting in both ranitidine and hypoallergenic groups ( $P = 0.01$ ). Changes of irritability were not seen in any of the groups ( $P = 0.18$ ,  $P = 0.19$ ). Likewise, after the trial, the feeding refusal, anorexia, and arching did not change in any of the two groups ( $P > 0.5$ ).

**Table 1.** Baseline Characteristics in Ranitidine and Hypoallergenic Diet Groups (N = 25)<sup>a</sup>

Variables	Ranitidine Group	Hypoallergenic Diet Group	P Value
Age, mo*	2.8 (2.5)	3.4 (1.8)	0.97
Birth weight, kg*	2.7 (0.7)	3.0 (0.5)	0.06
Weight at study, kg*	5.0 (1.6)	5.5 (1.2)	0.10

<sup>a</sup>Values are expressed as mean (SD).**Table 2.** Baseline frequency of Different Symptoms of GERD in Ranitidine and Hypoallergenic Diet Groups (N = 25)<sup>a</sup>

Variables	Ranitidine Group	Hypoallergenic Diet Group	P Value
<b>Symptoms of GERD</b>			
-Irritability <sup>b</sup>	23 (84)	18 (72)	0.06
-Vomiting <sup>c</sup>	25 (100)	25 (100)	1.00
-Arching <sup>b</sup>	16 (64)	9 (36)	0.04
-Respiratory symptoms <sup>c</sup>	16 (64)	12 (48)	0.13
-Refusal of feeding <sup>c</sup>	4 (16)	2 (8)	0.33

<sup>a</sup>Values are expressed as No. (%).<sup>b</sup>Duration/week.<sup>c</sup>Episodes/week.**Table 3.** Frequency (No. %) of GERD Symptoms Before and After Trial in Ranitidine and Hypoallergenic Diet Groups (N = 25)<sup>a</sup>

Symptoms	Ranitidine Group			Hypoallergenic Diet Group		
	Baseline	After 2 Weeks Intervention	P Value	Baseline	After 2 Weeks Intervention	P Value
-Irritability <sup>b</sup>	23 (92)	21 (84) <sup>c</sup>	0.19	18 (72)	15 (60) <sup>c</sup>	0.18
-Vomiting <sup>d</sup>	25 (100)	19 (76)	0.01	25 (100)	19 (76)	0.01
-Respiratory symptoms <sup>d</sup>	16 (64)	8 (60)	0.01	12 (48)	6 (40)	0.04
-Arching <sup>b</sup>	16 (64)	17 (68) <sup>c</sup>	0.51	9 (36)	8 (32) <sup>c</sup>	0.51
-Refusal of feeding <sup>d</sup>	4 (16)	3 (12)	0.51	2 (8)	3 (9)	0.51

<sup>a</sup>Values are expressed as No. (%).<sup>b</sup>Duration/week.<sup>c</sup>P < 0.05 between groups after 2 weeks intervention.<sup>d</sup>Episodes/week.

#### 4. Discussion

In this trial, we have compared the effectiveness of hypoallergenic diet vs. pharmacological treatment with ranitidine in GERD infants. Our results indicated that both treatment methods had beneficial effects on some of GERD symptoms, including vomiting and respiratory symptoms. Of special concern was the improvement in the frequency of vomiting, i.e. the most persistent symptom of GERD, in both groups. Therefore, in our study hypoallergenic diet had significant effect on GERD symptoms.

The prevalence of food allergy has been reported to be more than 10% in infants and young children. In this re-

gard, CMA is the most common type of food hypersensitivity with a prevalence rate of 2% - 3% (15, 16).

Given the similarity of symptoms related to GERD and food allergy and evidences supporting the causal relationship between the two conditions, the consensus of the North American society for pediatric gastroenterology, hepatology, and nutrition (NASPGHAN) and the European society for pediatric gastroenterology, hepatology, and nutrition (ESPGHAN) on GERD have recommended to use a 2- to 4-week therapeutic trial of maternal strict cow milk protein elimination diet for breast fed infants, as well as an extensively hydrolyzed protein or amino acid formula for formula fed infants (17). Because of reported adverse

effects of anti-acid medications and prokinetics, some researchers have recommended dietary regimen and positioning as the first treatment for GERD (18). Ferreira and colleagues have indicated that the possibility of GERD occurrence due to CMA would be decreased by mentioned restricted diet without using unnecessary medications (19).

There are several studies on hypoallergenic diet for infants with GERD, but clinical trials in the form of comparison of this diet with other pharmacologic agents used for GERD are scarce.

Hill et al. investigated 19 infants with vomiting and irritability; nine of them had esophagitis resistant to medical treatment but showed improved symptoms after receiving 2 weeks of maternal hypoallergenic regimen (20).

Nielsen and colleagues have investigated the causative relationship between GERD and CMA, among 42 children with severe GERD. They demonstrated that 10 of 18 patients with GERD diagnosed by endoscopy and pH-metry had cow milk hypersensitivity. This group of patients had a significantly higher reflux index compared to children with a primary GERD (21). Atarod et al. have shown that 10% of children with CMA had concomitant GERD; and after weeks of restricted diet, both allergic manifestations and GERD subsided in the studied population (22).

Farahmand and colleagues have reported that one third of their studied pediatric cases of GERD had CMA. They evaluated the effectiveness of cow milk elimination among patients with refractory GERD, who did not respond properly to omeprazole. Their results showed that a 4-week elimination diet had significant effect on GERD symptoms. They suggested that CMA could aggravate GERD symptoms by dysmotility of the gastrointestinal tract. They also demonstrated that CMA could explain refractoriness of GERD to recommended pharmacologic treatment as well (23).

In the current trial, both ranitidine and hypoallergenic diet had similar beneficial effects on GERD, especially on its vomiting and respiratory symptoms.

After the two-week trial, the frequency of arching was higher in the ranitidine group. This is because even at baseline the frequency of arching was higher in ranitidine than hypoallergenic group, thus it can be concluded that both treatments had similar effects. The frequency of irritability did not change after intervention in any of the groups, perhaps a longer period of time is needed after improvement of vomiting or regurgitation and reduction of esophageal acid exposure, to reduce inflammation, leading to decreased irritability. This suggestion may be also true for other complications of longstanding GERD, including arching, feeding refusal, and anorexia. However it should be confirmed in future investigations.

According to the findings of the current trial, we rec-

ommend some practical approaches to better management of the disease in affected infants. In patients with partially improved outcome with ranitidine or hypoallergenic diet, a combination therapy is recommended. Given the association between GERD and CMA, it is recommended to use hypoallergenic diet for 2 weeks as the first therapeutic approach, and a trial of ranitidine added to therapy regimen in patients with inappropriate response. Moreover, for infants with inappropriate outcome by using ranitidine, a two-week trial of hypoallergenic regimen is also essential before changing the anti-reflux medication.

There is a possibility that H<sub>2</sub>-blockers could accelerate residual tissue inflammation by reducing acidity, so, it seems that even in infants with reduction of signs and symptoms on hypoallergenic regimen, especially in severe cases, addition of a short period of H<sub>2</sub>-blocker is also needed to complete the treatment. However, it is also recommended to evaluate the effectiveness of the combination use of the two above-mentioned treatment methods for future interventional studies. Subjects with GER due to CMA show a typical pH-monitoring pattern, characterized by a progressive, slow decrement of esophageal pH between meals (24). It should be noted that eliminated diet may have negative effects on growth and development of children if it is not used properly and according to a proper guideline (25).

The limitations of our study were the small sample size, the short duration of intervention and not using other diagnostic methods such as endoscopy, pH-metry and monometry. In addition, we did not evaluate the outcome of mothers' training regarding utilizing hypoallergenic diet and correct implementation of the diet by them.

#### 4.1. Conclusion

The findings of the current study indicate that hypoallergenic diet has the same effect as ranitidine in improving GERD symptoms. Therefore, because of the high prevalence of CMA in this age group and its similar symptoms with GERD, it can be suggested that the treatment of GERD in pediatric population be initiated with hypoallergenic diet and in case of not satisfactory response, pharmacological treatment be added as combination therapy. For achieving more conclusive results, further studies with larger sample size and longer duration of follow up are recommended.

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