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The Efficacy of Baclofen to Treat Gastroesophageal Reflux disease in Children Aged 6 Months to 12 Years: A Clinical Trial Study

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Abstract

Background

Gastroesophageal Reflux is a physiological phenomenon, which occurs in infants, children, and normal adults. Various studies have shown that Baclofen is a potent inhibitor of lower esophageal sphincter and has beneficial effects in adult reflux disease. We aimed to evaluate the Baclofen effect in pediatric Gastroesophageal disease.

Materials and Methods: Children 6 months to 12 years old, with Gastroesophageal reflux disease were enrolled in this Clinical trial study. Patients referred to Taleghani Children's Center in Gorgan, Golestan province, Iran from May to August 2019. Patients were randomly divided into two intervention group and control group. The controls received only proton pump inhibitor 1 mg per kg treatment, and intervention group received proton pump inhibitor (PPI) plus baclofen 0.25 mg per kg two times per day. Patient data including age, gender, family history, growth status, reflux symptoms, previous drug treatment history, and symptoms in two groups, were compared.

Results: Fifty-four patients in the baclofen treatment group and 58 patients in the non-baclofen treatment group were included. The mean age of the patients was 6.61± 3.55 years. The most common symptoms of all patients were abdominal pain (73.2%), nausea (73.2%), regurgitation (64.3%), and dental erosion (55.4%). The rate of recovery was significantly related to gender, with 69.9% of patients having moderate to full recovery ($p = 0.017$). Weight gain in baclofen treated group was significantly higher.

Conclusion: The results suggest that baclofen along with routine Gastroesophageal reflux treatments in children can help reduce or improve symptoms of the disease. Due to limited studies, further studies are needed to confirm the positive effect of this drug with higher sample size.

Key Words: Baclofen, Children, Gastroesophageal reflux, Proton pump inhibitor.

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1- INTRODUCTION

Gastroesophageal Reflux (GER) is a physiological phenomenon and occurs in infants, children, and normal adults. Gastroesophageal reflux happens when stomach contents come back up into the esophagus causing heartburn, which is usually episodic attacks and does not cause symptoms or damage to the esophagus. However, Gastroesophageal reflux disease (GERD) is a more serious and long lasting form of GER and may prevent an infant from feeding. GERD happens when it is associated with signs and symptoms or complications caused by it. The severity and rate of symptoms and complications of GERD are different and variable in children depending on the age of patients (1). Physiologic reflux is usually seen in infancy, especially in the first 6 months in many infants and, in most cases, it improves spontaneously in the second half of the first year with the start of feeding solid foods. Thus, there is no need for diagnostic and therapeutic measures (1, 2).

Unlike physiologic reflux, pathologic reflux causes the histological changes in the esophagus, the occurrence of clinical symptoms and side effects, such as esophageal stricture and respiratory distress. Moreover, dissimilar to the physiologic reflux, pathologic reflux occurs in all age groups. Gastroesophageal reflux is very common in infants so that it is the most common cause of non-biliary vomiting in infancy. Currently, gastroesophageal reflux is the most common disorder of the esophagus and one of the most common gastrointestinal diseases in infants. The data available in pediatrics indicate a high prevalence and cost of gastroesophageal reflux. Supportive care and changes in lifestyle are the basis of treatment for gastroesophageal reflux (3). Five main classes of drugs have been currently used in the treatment of gastroesophageal reflux, including surface-covering drugs (e.g. sucralfate), antacids, histamine-type-2 receptor antagonists (H2RAs), proton pump inhibitors (PPI), and prokinetics (4). Transient lower esophageal sphincter relaxations (TLESRs) are the major cause of gastroesophageal reflux in the normal population and most patients with GERD. It has been demonstrated in various studies that baclofen β-(4-chlorophenyl)-γ-aminobutyric acid (β-(4-chlorophenyl)-GABA), which is a GABA-B receptor agonist, is a potent inhibitor of lower esophageal sphincter (LES) in normal subjects (5). The exact mechanism of the effect of baclofen is not entirely clear, but it seems to be a GABA agonist in the nervous system. This drug is an active spasmolytic and acts as a GABA agonist on GABA B receptors (6). Activation of the receptors in the brain by baclofen leads to hyperpolarization, which is probably caused by increased potassium ion transport (7). It is proposed that this hyperpolarization, by reducing calcium infiltration, possibly helps the presynaptic inhibitory action to reduce the release of excitatory chemical vectors in the brain and spinal cord (7-9).

One of the other applications of baclofen is to control the attacks of gastroesophageal reflux after meals as well as to accelerate gastric emptying(10). GABA B receptors have an inhibitory effect on vagal afferent terminals in the posterior medulla, which inhibit the release of neurotransmitters of the nucleus of the vagus. GABA B receptors also exist on gastric mechanical receptors (9). Studies conducted on the effect of baclofen on gastroesophageal reflux have often been done in adults. In a study carried out in Italy on thirteen normal individuals to study the control role of GABA agonist drugs in transient lower esophageal sphincter relaxation, the benefits of these drugs in this area among healthy people, especially after feeding became apparent (11). In other studies performed in the US and the Netherlands,

it was found that baclofen not only inhibited non-acid reflux but also inhibited acid reflux after eating (5). Because investigations in this area, especially in the pediatric population, are relatively limited and GER is one of the most common problems, we decided to design and implement this study aimed at investigating the effect of baclofen in the treatment of gastroesophageal reflux disease in children.

2- MATERIALS AND METHODS

2-1. Study design and population

This is a clinical trial study conducted on children with gastroesophageal reflux disease having an age range from 6 months to 12 years referred to Gastroenterology Clinic in Educational Center of Taleghani hospital, Gorgan, Iran, from May to August 2019. These children were referred to the gastroenterology clinic by the parents, or because of no response to treatments by other physicians. The data related to patients including age, gender, family history of gastroesophageal reflux, growth status, reflux symptoms, a history of previous drug therapy, dose of medication use, and symptoms examined were recorded in a checklist.

2-2. Method

According to the previous study (12), and considering a 95% confidence interval (CI), and test power of 80%, the sample size and sampling method for this study were determined to be at least 49 patients in each group. Considering a 20% probability of sample loss and adding this value, the sample size was determined to be 62 patients in each group. Convenience sampling was performed according to the estimated sample size for the study.

2-3. Inclusion and exclusion criteria

Inclusion criteria consisted of all children aged 6 months to 12 years with GERD, who had at least two of the following five symptoms for at least one month: vomiting immediately after feeding, the persistence of reflux symptoms despite other treatments, restlessness after feeding for one to three hours, apnea and respiratory distress after feeding, no weight gain or weight gain of less than 500 grams, or weight loss during the last month and refusal to feed. Exclusion criteria included patients less than 6 months and more than 12 years, patients taking baclofen for reasons other than GERD, patients with a history of anti-reflux surgery, patients with endoscopic evidence of Helicobacter pylori gastritis or eosinophilic esophagitis, patients with evidence of gastroparesis radiography and lack of parental consent to participate in the study.

2-4. Intervention

Participants in the study were divided into two treatment groups, which were allocated randomly: control group, who received proton pump inhibitor (PPI) treatment and intervention group who received PPI + baclofen treatment. After justifying and obtaining written consent from parents, baclofen, 0.25 mg per kg of body weight divided into two daily doses for 1 month and omeprazole 1mg per kg were administered to intervention group. Controls only were treated with omeprazole during this period. Consequences and results were evaluated before treatment, one week after treatment, and two weeks after treatment, and the fourth week in terms of the efficacy of the medication on the clinical symptoms of the patients. The symptoms evaluated included abdominal pain, nausea, retrosternal pain, weight loss, poor appetite, dyspepsia, regurgitation, coughing and wheezing, dental erosion, halitosis, crying and restlessness, cough during feeding, apnea, and respiratory distress after feeding, which was conducted based on records of patients and question of the parents efficacy, and response to treatment were defined based on improvement in the

initial symptoms reported by parents during follow-up visits to the center.

2-5. Ethical consideration

This single-blinded clinical trial study (TCTR20200415001), was approved and received permission from the Regional Ethics Committee at Gorgan University of Medical Sciences. (ID Ethics IR.GOUMS.REC.1398.261), and then written informed consent was obtained from all parents to enter the study.

2-6. Data Analyses

The results were recorded in short term (one week after treatment), and long term (2 weeks and 1 month after treatment). After coding and entering into SPSS software version 20.0, the data were analyzed. To compare the groups with each other, the Chi-square test ($\chi 2$) was used. In addition, in the case of normality of data, an independent t-test was used for quantitative data, otherwise, the Mann-Whitney test was used. The normality of the data was investigated using Kolmogorov-Smirnov and Shapiro Wilk tests. Moreover, the significance level was considered 0.05 in this study.

3- RESULTS

In this study, 62 patients in each group of control and intervention were enrolled. Eight cases in the treatment group with baclofen and four cases in the control group were excluded due to lack of follow-up, lack of medication, and incomplete records of patients. Finally, 54 patients were in the baclofen and the proton pump inhibitor (PPI) treatment group and 58 in the control group. The mean age of the patients was 6.61 years with a standard deviation of 3.55, the lowest age was 9 months and the highest age was12 years, respectively. During the study, no side effects of baclofen were observed. The frequency distribution of gender among patients in the two groups under study was examined; 27 cases (50%) in the baclofen treatment group and 20 cases (34.5%) in the non-baclofen treatment group were male, which was not statistically significant (p=0.096) (**Table.1**).

The frequency distribution of previous treatment history and drug use in the two groups under study were investigated; 29 cases (53.7%) in the baclofen treatment group and 26 cases (44.8%) in the non-baclofen treatment group had a history of previous treatment and drug use, which was not statistically significant (p=0.348). The frequency distribution of positive family history of reflux among patients in the two groups under study was examined; 24 cases (44.4%) in the baclofen treatment group and 20 cases (34.5%) in the non-baclofen treatment group had a positive family history of reflux, which was not statistically significant (p = 0.281) (**Table.2**).

The symptoms of patients in order of prevalence were abdominal pain (73.2%), nausea (73.2%), regurgitation (64.3%), dental erosion (55.4%) and bad breath (halitosis) (53.6%) (**Table.3**). The frequency distribution of improvement rate among patients in the two groups under study was examined; 46 (85.2%) cases in the baclofen treatment group and 32 cases (55.2%) in the non-baclofen treatment group had moderate and full remission (**Figure.1**).

Table-1: Sex distribution of control and intervention groups (n=112).

Study groups		Gender			P-value
		Boy	Girl	Total	
Baclofen and PPI	Number	27	27	54	0.096
	Percent	50.0%	50.0%	100.0%	
Control (only PPI)	Number	20	38	58	
	Percent	34.5%	65.5%	100.0%	
Total	Number	47	65	112	
	Percent	42.0%	58.0%	100.0%	

PPI: Proton pump inhibitor.

Table-2: Frequency of reflux history in family in patients and control groups (n=112).

Study groups		Familial history of GER			P-value
		Not present	Present	Total	
Baclofen and PPI	Number	30	24	54	0.281
	Percent	55.6%	44.4%	100.0%	
Control (only PPI)	Number	38	20	58	
	Percent	65.5%	34.5%	100.0%	
Total	Number	68	44	112	
	Percent	60.7%	39.3%	100.0%	

PPI: Proton pump inhibitor, GER: Gastroesophageal reflux.

Table-3: Symptoms and presentations in control and intervention groups (n=112).

Presentations	Number	Percentage
Abdominal pain	82	73.2
Nausea	82	73.2
Retrosternal pain	40	35.7
Weight loss	16	14.3
Loss of appetite	54	48.2
Dyspepsia	26	23.2
Regurgitation	72	64.3
Cough	42	37.5
Wheezing	8	7.1
Dental erosion	62	55.4
Halitosis	60	53.6
Irritability and crying	6	5.4
Cough during feeding	18	16.1
Apnea and respiratory distress	0	0

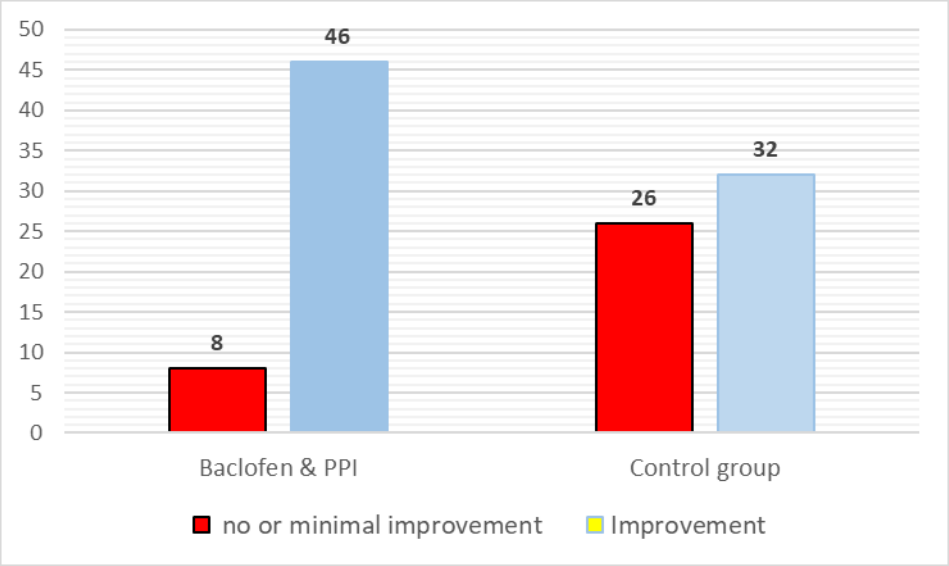

Fig.1: Frequency of improvement in intervention and control groups (n=112).
PPI: Proton pump inhibitor.

Among the patients treated with baclofen, the improvement rate was evaluated based on the variables of gender, positive family history of reflux (**Table.4**), previous treatment history (**Table.5**), and drug use, and age of the patients (**Table.6**). There was a significant relationship between the improvement rate and gender. This means that 69.9% of patients with moderate and complete improvement were male (p=0.017). Interval visit follow-up is presented in **Table.7**. Furthermore, the improvement rate was associated with the age of the patients. This means that 69.6% of patients with moderate and complete improvement were less than and equal to 7 years old (p=0.016). The mean, standard deviation, minimum and maximum age, weight before treatment, weight 1 month after the treatment, and weight changes during one month were evaluated; the only weight gain in baclofen-treated group (0.1704 kg) was significantly higher than in non-baclofen-treated group (0.0069 kg) (p=0.0001).

Table-4: Response to treatment based on positive family history of GERD.

Response		Familial history of GER			P-value
		Not present	Present	Total	
No improvement	Number	2	6	8	0.326
	Percent	25.0%	75.0%	100.0%	
Full recovery or acceptable response	Number	20	26	46	
	Percent	43.5%	56.5%	100.0%	
Total	Number	22	32	54	
	Percent	40.7%	59.3%	100.0%	

GERD: Gastroesophageal reflux disease.

Table-5: Improvement in GERD (Baclofen group) based on positive history of treatment and medication.

Improvement		Previous treatment and medication			P-value
		Not present	Present	Total	
No or minimal improvement	Number	2	6	8	0.756
	Percentage	25.0%	75.0%	100.0%	
Full recovery or acceptable response	Number	14	32	46	
	Percentage	30.4%	69.6%	100.0%	
Total	Number	16	38	54	
	Percentage	29.6%	70.4%	100.0%	

GERD: Gastroesophageal reflux disease.

Table-6: Frequency of improvement in baclofen group based on age (n=54).

Improvement		Age, year			P-value
		≤ 7	>7	Total	
No or minimal improvement	Number	2	6	8	0.016
	Percentage	25.0%	75.0%	100.0%	
Full recovery or acceptable response	Number	32	14	46	
	Percentage	69.6%	30.4%	100.0%	
Total	Number	34	20	54	
	Percentage	63.0%	37.0%	100.0%	

Table-7: Improvement follow- up intervals.

Improvement		Follow- up intervals (week)				P-value
		Two	Four	All follow-up	Total	
No improvement	Number	0	0	8	8	0.193
	Percentage	0.0%	0.0%	100.0%	100.0%	
Full recovery or acceptable response	Number	10	4	32	46	
	Percentage	21.7%	8.7%	69.6%	100.0%	
Total	Number	10	4	40	54	
	Percentage	18.5%	7.4%	74.1%	100.0%	

4- DISCUSSION

The aim of this study was to evaluate the effect of baclofen on Gastroesophageal reflux in children. The results are promising in favor of the positive effect of baclofen on reflux. Reflux treatment with anti-acid drugs reduces the complications of the disease and prevents esophagitis but resolves obvious or hidden reflux. Baclofen medication has no anti-acid effect but lowers the reflux process. In our study, baclofen influences the symptoms and problems associated with esophagitis, and according to similar studies, it may be considered as an effective drug in the treatment. In a meta-analysis study by Li et al. in 2014, the effect of baclofen treatment on GERD was examined. In this research, the randomized controlled studies published before November 2013 were systematically collected from various databases including Cochrane that were randomized controlled trials, and analysis of all eligible studies was conducted. Nine studies consisting of 283 patients with GERD and healthy people were identified (13). Comparative analysis of the data supported the conclusion that baclofen could reduce the frequency of reflux per patient, the length of any period of occurrence, and the amount of sphincter control. No serious side effects or mortality were reported, and there were no significant differences in the side effects

between baclofen and placebo. The studies listed have largely confirmed the results of our study, but there are very few trial studies mostly with a limited sample size. However, our study has a larger sample size, which is one of the strengths of this study that increases the generalizability of its results. In the review study carried out by Clarke et al. in 2018, the role of baclofen treatment in GERD was examined. In this study, it has been stated that baclofen causes a reduction in reflux and esophageal sphincter pressure, but a careful study on the specific role of baclofen in the treatment of GERD has never been published. Although the essential pathogenesis of reflux in infants is transient lower esophageal sphincter relaxations (TLESRs), other important factors such as diaphragm pressure and tonicity of the abdominal muscles, and even gastrointestinal spasms, can also cause reflux. Hence, internal sphincter pressure reduction caused by baclofen by reducing spasms in the points listed may be in the balance, which can improve reflux (14). In the study conducted by Lee et al., 20 patients with gastroesophageal acid reflux were selected, and the amount of 40 mg of baclofen and placebo were separately administered to the two groups for 4 weeks. Then, their esophageal pH was evaluated at 0, 4, 8, and 12 hours after a meal. Finally, it became clear that baclofen has a significant role in reducing gastroesophageal reflux attacks in patients with gastroesophageal reflux (13). Lee et al. in a recent study have indicated that baclofen decreases the frequency and onset of secondary peristalsis and increases the sensitivity of the esophagus to capsaicin-induced stimulation. This could be justified on the fact that, despite the effect of baclofen on the lower esophageal sphincter, its positive effect occurs more as well. In a study conducted by Vadlamudi et al. in 2013, the effect of baclofen treatment on GERD of children was evaluated. In this study, the medical records of 1 to 18-year-old patients treated with baclofen were retrospectively examined as to whether GERD symptoms had been relieved or if they persisted. Short-term response (at the first clinic visit) and long-term clinical response (12 months) were evaluated. 53 patients were evaluated in the final analysis. The mean duration of disease was 1.5 years, and the mean age was 6.1 years. All patients, at the beginning of the addition of baclofen, used PPI once daily (53%) or twice daily (47%). Thirty-five (66%) patients experienced a reduction in clinical symptoms at the first visit. In the remaining 18 cases, baclofen was stopped due to a lack of response (n = 15) or side effects (n = 3). 27 patients continued treatment and were evaluated for long-term response. Among them, 22 patients (81%) had a sustained response to baclofen in 12 months (12). This study is in line with our study. However, in our study, complications were not reported in both groups concerning any of the drugs.

The symptoms of patients in our study were examined, the most common of which were abdominal pain (73.2%), nausea and vomiting (73.2%), regurgitation (64.3%), dental erosion (55.4%), and halitosis (53.6%), respectively. In other similar studies, abdominal pain and vomiting were the most common symptoms of reflux among children in this study. In our study, it was found that baclofen had a significant impact on reducing vomiting and regurgitation. One of the critical findings in this study was the presence of crying and restlessness that could be caused by pain. Pain is a major symptom of esophagitis, which manifests as a crying in small infants. The continuity and relationship of pain are not fully associated with endoscopic manifestations or even histologic esophagitis (15). Forty-six cases (85.2%) in the group treated with baclofen and 32 cases (55.2%) in the non-baclofen treatment group had moderate and

complete improvement, which was statistically significant. However, the sample size and long-term follow-up were higher in our study, and this will enhance the power of our results. In this study, the improvement rate had a significant relationship with gender. This means that 69.9% of patients with moderate and complete improvement were male. In addition, the improvement rate was associated with the age of the patients. A better response at an early age may be due to developing the digestive and nervous system and a better response of the nervous system to baclofen. Essentially, the reflux process with growth improves in children, one of the reasons for this is the physical growth and the increasing length of the esophagus, as well as the balance of nutrition and type of feeding with the size of the stomach, but there is no difference in the case of gender in other studies, and further investigations are required. In our study, weight gain in the group treated with baclofen was significantly higher than the non-baclofen-treated group. In other cases, no significant difference was observed between the two groups. In the study conducted by Khodadad et al., the efficacy of baclofen to treat GERD in infants was examined. This clinical trial study was performed on 30 infants with GER. After selecting the cases in terms of the specified indicators and completing the questionnaire, the amount of 0.25 per kilogram of body weight was administered in two divided doses of oral baclofen for 3 months. Then, their symptoms were evaluated weekly and monthly (16). Of the 30 patients selected, 17 patients were male and 13 patients were female. The mean age of the participants was 7.1 months. The most common symptoms included vomiting (100%), weight gain disorder (93%), crying and restlessness (63%), cough (53%), apnea (6.7%), respectively. A significant difference in mean weight gain was observed at one month before treatment and the how many months after treatment (p=0.0001). Moreover, a significant change occurred in nutrition status, improvement of vomiting and crying and restlessness in the months before and after treatment (p = 0.001). This study also confirmed the results of our study concerning the weight gain of patients in the baclofen-treated group. However, the difference between the two studies was that our study, in addition to infants, included patients up to the age of 12 years, which is one of the strengths of the current study. In a meta-analysis performed by Li et al., no serious side effects of the administration of baclofen were observed. Although this study (13), and another study (16) have demonstrated the positive effect of baclofen to control gastroesophageal reflux, for the widespread application of this drug in treating infants and children and examining its complications, the need to carry out further research is recommended. In most previous studies conducted, esophageal pH has also been measured (9). However, due to the low age of patients and the limitations of resources, investigation of esophageal pH has not been performed in our study, which is considered as one of the limitations of this study. Failure to do manometry was also another limitation of the study. Indeed, use of baclofen in cerebral palsy (CP) patients in recent literature is recommended and it seems in these patients it would be more useful (17).

5- CONCLUSION

The results of this study revealed that complementary treatment of baclofen along with routine gastroesophageal reflux treatments in children can contribute to reduce or improve symptoms of the disease. However, given the limited number of studies in this area, it is necessary that further investigations to demonstrate the positive effect of this medication with a larger sample size are done.

6- CONFLICT OF INTEREST: None.

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