Mast cell stabilizers as a potential treatment for Irritable bowel syndrome: A randomized placebo-controlled clinical trial

*[1]Ebrahimi Daryani N., [2]Hashemian F., [3]Afkham M., [4]Habibollahi P., [5]Keramati M.R., [6]Fereshtehnejad S.M., [4]Bashashati M

[1] Professor of gastroenterology Tehran University of Medical Sciences, [2]Associate Professor of pharmacology of Azad University of Medical Sciences, [3]Pharmacologist, Azad University of Medical Sciences, [4]Gastroenterology Division, Imam Khomeini Hospital,, Tehran University of Medical Sciences, [5]Resident of Surgery, Iran University of Medical Sciences, [6]Medical student, Iran University of Medical Sciences. Tehran, Iran

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ABSTRACT

Objectives: Mast cells are believed to play a role in irritable bowel syndrome pathogenesis and symptom genesis due to their close neighborhood to gastrointestinal innervations. This study was designed to evaluate the efficacy of orally administered cromolyn for reduction of symptoms in patients with irritable bowel syndrome (IBS).

Material and Methods s: A randomized placebo-controlled double-blinded 6×6 weeks cross-over study was performed in a private gastrointestinal clinic. 10 patients were allocated to group A and 6 patients to group B. Patients in group A received 150 mg cromolyn divided in three equal doses for the first 6 weeks and placebo for the next 6 weeks but patients in group B received placebo for the first 6 weeks and cromolyn in the next 6 weeks. Weekly evaluation was performed and visual analogue scale was used to determine severity of symptoms.

Results: Sixteen patients completed the study. Mean age of the patients was 40.3 ± 10.9 years old [range: 24-57]. Eight patients had D-IBS (Diarrhea dominant) and other 8 had C-IBS (Constipation dominant). Both cromolyn sodium and the placebo decreased the severity of bloating (Freidman test, p 0.001 and 0.006 respectively). The severity of the main symptom (diarrhea or constipation) did not decrease in patients of group A and B who were treated with different sequences of the drug or placebo. The severity of pain decreased drastically after 6th week of treatment with cromolyn. Freidman test showed a significant difference between the pain levels of the former defined treatment spots (p 0.01, and 0.02 for patients in group A and B, respectively). No adverse drug reactions were observed during the study.

Conclusion: In conclusion, long term administration of cromolyn seems to be partially effective for treatment of abdominal pain in patients with IBS while main symptoms (diarrhea or constipation) might not decrease during this treatment.

Key words: Irritable bowel syndrome, Mast cells, Cromoly sodium

INTRODUCTION

Irritable Bowel Syndrome (IBS) as one of the most prevalent gastrointestinal motility disorders, is generally characterized by abdominal pain and distress allied with changed bowel habits including diarrhea, constipation or both (1, 2). IBS prevalence has been estimated 3-20%, where estimates in North America is 10- 15% (3-5).

IBS as a chronic and troublesome disorder often affects patient activity and quality of life and also places a considerable financial load on patients and the health care system(1). Moreover, the most presenting symptoms are preserved permanently (5, 6).

IBS usually does not coincide with any structural and biochemical abnormalities except minor levels of inflammation which is reported in post infections IBS (7). Although gastrointestinal infections, food hypersensitivity and psychosocial factors are suspected as triggers for IBS, the

Correspondence: naser@yahoo.com

pathophysiology of IBS is not well understood(1).IBS treatment is based on relief of symptoms and improving overall comforts (8). According to close immediacy of mast cells to mucosal innervations and increased number of mast cells in colonic and ileal mucosa of IBS patients, mast cells are thought to play a role in IBS pathophysiology (9-11). Additionally mast cell activation has been shown to cause visceral hypersensitivity and abnormal gut motor function due to augmented excitability of enteric and primary afferent neurons (12-15).

Orally administered sodium cromoglycate has been reported to decline the gastrointestinal permeability (16) and to stop symptoms due to unfavorable reactions to foods and additives of food products (17). Some studies declare that cromoglycate has of recognized efficacy in IBS with dominant diarrheal features but only a limited number of trials have evaluated this compound (18, 19) and the real effect of cromoglycate is steel controversial. The aim of this study was to evaluate the therapeutic effect of mast cell stabilizers in relieving symptoms of patients with IBS.

MATERIAL AND METHODS

A double-blinded cross-over randomized placebo-controlled clinical trial was performed in a private gastrointestinal clinic in Tehran, Iran during the spring of 2007. The trial was conducted in accordance with the declaration of Helsinki and subsequent revisions and approved by ethics committee at Tehran University of Medical Sciences. Twenty patients (14 women, 6 men) with IBS diagnosis were recruited into the trial. IBS diagnosis was made upon ROME criteria II regarding their clinical history, a normal clinical examination, serum biochemical profile and serum thyroid hormones [(T_3, T_4 and thyroid stimulating hormone (TSH)]. Organic gastrointestinal disorders were excluded by means of stool and urine analyses for bacteria, blood sedimentation rate, and serum and urine amylase, occult blood in the stools, rectoscopy, sigmoidoscopy, and abdominal ultrasonography. Patients were excluded if they were pregnant or during lactation. Additionally, patients with history of cardiac, hepatic, renal failure or chronic treatment with steroids were also excluded. Lactose tolerance tests were performed to exclude lactase deficiency. Psychiatric disorders were excluded using General Health Questionnaire-28 (GHQ-28) and psychiatric evaluation.

Prior of entering to this trial, patients were fully informed of the conduct and consequences of the study and signed a consent form.

The patients were randomly assigned into two groups. The trial design was a 6×6 weeks cross-over study, during which they were all consulted to consider the appropriate regimen. Ten patients in group A received oral cromolyn for the first 6 weeks and placebo for the next 6 weeks but the patients in group B received placebo for the first 6 weeks and oral cromolyn for the next 6 weeks. Each treatment period was lasted for 6 weeks and the two periods were not separated by wash-out period.

Active treatment consisted of oral cromolyn 150 mg daily divided in three equal doses 30 minutes before each main meal. Pure Cromolyn powder was purchased from Cambrex Co. (Italy). Cromolyn capsules contained cromolyn power (50 mg), corn starch (40 mg), avicell (56 mg), magnesium stearate (2 mg), and PVP (2 mg). Placebo capsules contained the same ingredients except 50 mg cromolyn sodium and had of corn starch instead of cromolyn powder. Patients were told to open capsules before use and dissolve the contents in a glass of warm water. Patients were asked to use no other drugs during the trial.

Patients underwent weekly evaluation by a physician who was blind about the group which patients were allocated. Capsules for the next week were given to the patients at the end of each visit. The total number of visits for each patient throughout the study was thirteen. During each visit patients were asked to fill a form in which using visual analogue scale changes in main symptoms (diarrhea or constipation), bloating and abdominal pain were recorded. Patients were asked in each visit for the side effects such as coughing, itching, face swalloing, difficult swelling, bad taste, burning sensation in the eyes, throat irritation and etc. In addition to the main variables which were evaluated in each visit, their demographic characteristics including sex, age, body mass index (BMI), smoking and the severity of their symptoms during the last three months prior to their first visit using visual analogue scale- were also recorded.

Statistical analysis

The severity of different symptoms were presented as mean± SD. Freidman test was used in order to compare symptoms severity within last 3 months before trial as initial severity, and 6 and 12 weeks after beginning of the trial as the end points of treatment sequences. In the cases of

significant difference with Freidman test, Wilcoxon ranks test was employed to find out the spot (6th or 12th weeks) which was different from initial severity.

RESULTS

General findings

Twenty patients were involved in the study. Four patients discontinued the follow-up examinations and finally 10 patients (8 women, 2 men) were recruited in group A, and 6 patients (4 women, 2 men) were studied in group B. After all, sixteen patients completed the study. Mean age of the patients was 40.30 ± 10.90 years [range: 24-57]. Eight patients had D-IBS (diarrhea dominant) and other 8 had C-IBS (constipation dominant). In group A that were treated by cromolyn sodium and then with placebo 6 patients had diarrhea and 4 patients had constipation. In group B which were treated with the reverse trend (first placebo and then cromolyn sodium) 2 patients had diarrhea and 4 patients had constipation (Table 1).

Effect of different treatments on the severity of main symptom

The severity of the main symptom (diarrhea or constipation) did not decrease in patients of group A and B who were treated with different sequences of the drug or placebo (Figure 1). By separation of patients according to their main symptom again there was no statistical change in the severity of the main symptom during the treatment trend (data not shown).

Effect of different treatments on the severity of abdominal pain

Mean pain level within last 3 months and 1 year was 5.30±2.90 and 4.50±3.00 respectively. There was no significant difference between mean pain level among D-IBS and C-IBS patients (Mann-Whiteny U, P>0.45).

The pain severity drastically decreased after 6th week of treatment with cromolyn. Freidman test showed a significant difference between the pain levels of the former defined treatment spots (P-values 0.01 and 0.02 for patients who were treated first with cromolyn (group A) and who were treated first with placebo (group B) respectively. Wilcoxon ranks test confirmed that the difference was due to the decrease in pain level after using cromolyn rather than placebo (Figure 2).

To assess the effect of cromolyn sodium on pain severity among D-IBS patients, the treatment trend in 6 patients with diarrhea and 4 patients with constipation who were treated in group A was analyzed (Figure 3). According to Freidman test a statistical difference was detected in initial severity, severity at 6th week, and severity at 12th week (P-values 0.03, and 0.004 for patients with diarrhea and constipation respectively). Again, Wilcoxon ranks test confirmed that the difference was due to the decrease in pain level after using cromolyn.

Effect of different treatments on the severity of bloating

Both cromolyn sodium and placebo decreased the severity of bloating (Freidman test, P-values 0.001 and 0.006, respectively), therefore decrease in severity of bloating can not be considered as the effect of cromolyn sodium (Figure 4).

DISCUSSION

The appropriate treatment for IBS remains controversial. While this disorder is known as an unimportant, unpleasant condition, there is growing evidence that IBS is an actual disease that noticeably reduces the patients' quality of life though deserves serious attention. Several pharmacologic and non pharmacologic approaches are used as current treatments to decrease severity of symptoms in IBS.

Anticholinergic or antispasmodic drugs, opoid deviates, laxatives, antidepressants, and serotonin (5-HT) receptor modulating agents (20) are among the most common drug therapies available for IBS. Restricted dietary have not shown to be beneficial in IBS but few studies have reported that increased ingestion of fibers through constipation, modest fat ingestion, or avoidance of turmoil foods is useful for IBS (21). Since psychological events may disturb IBS patients, some gain benefits from psychotherapy though it is mentioned as another treatment option (21). Cromolyn sodium is a well-studied mast cell stabilizer that is effective in the treatment of allergic disorders and systemic mastocytosis (22, 23). The drug has no direct anti-inflammatory or antihistaminic effects. It has been demonstrated to protect mast cells against antigen-antibody reactions and block liberators of anaphylaxis such as histamine. Mast cells are disseminated throughout the gastrointestinal tracts in all tissue layers. In lamina propria, 2-3% of the cells and in submocusal layer 1% of the cells are mast cells (24). In the field of research numerous diverse observations such as increase in number of mast cells and increase in concentrations of substance P in colonic mucosa (27), increase in levels of tryptase and histamine in mast cells near (<5μm) the nerve fibers of colonic mucosa(28, 29)

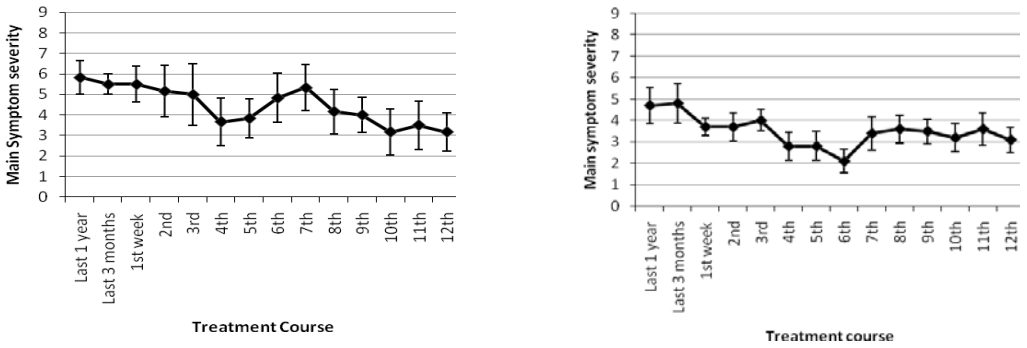

Figure 1. Effect of Treatment regimen on the severity of main symptom (diarrhea or constipation) in patients who received cromolyn at first 6 weeks, then placebo for another 6 week period (10 patients) (A) and patients treated with placebo at first 6 weeks, then cromolyn for another 6 week period (6 patients) (B). No significant decrease in main symptom severity was observed during treatment with cromolyn. Data is presented as Mean±SEM.

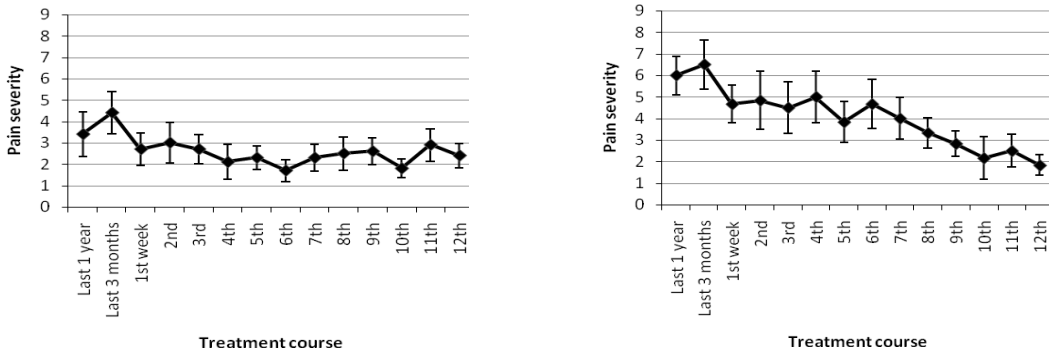

Figure 2. Effect of Treatment regimen on the severity of pain in patients who received cromolyn at first 6 weeks, then placebo for another 6 week period (10 patients) (A) and patients treated with placebo at first 6 weeks, then cromolyn for another 6 week period (6 patients) (B). Significant difference was observed between previous pain levels of defined treatment spots (Friedman test, P-values 0.01, and 0.02 for patients in group A and B, respectively). Data is presented as Mean±SEM.

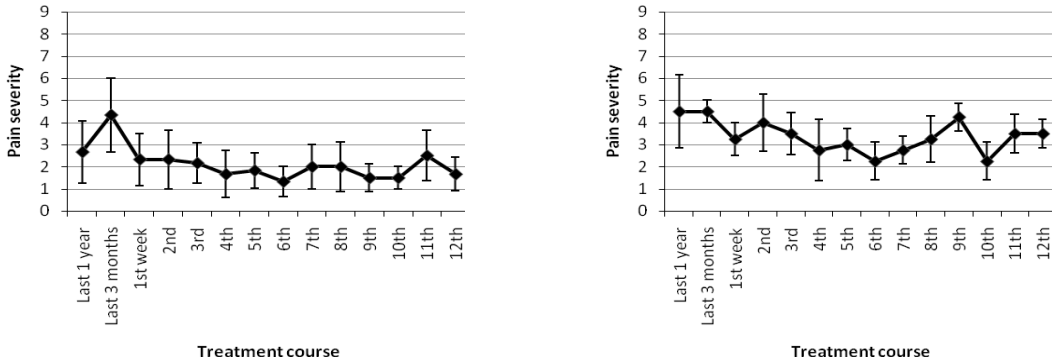

Figure 3. Effect of Treatment regimen on the severity of pain according to the main symptom in patients who received cromolyn for 1st 6 weeks, then placebo for another 6 week period. (A) Patients with diarrhea as the main symptom(6 patients) and (B) with constipation (4 patients). Statistical difference was observed between initial severity, severity at 6 th week, and severity at 12 th week (Friedman test, P-values 0.03, and 0.004 for patients with diarrhea and constipation respectively) that was confirmed using Wilcoxon ranks test. Data is presented as Mean±SEM.

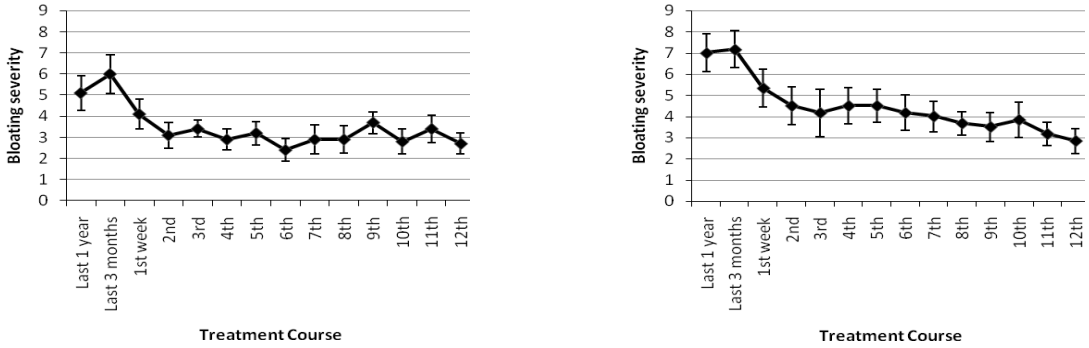

Figure 4. Effect of Treatment regimen on the severity of bloating in patients who received cromolyn at first 6 weeks, then placebo for another 6 week period (10 patients) (A) and patients treated with placebo at first 6 weeks, then cromolyn for another 6 week period (6 patients) (B). Significant decrease in bloating severity was observed during treatment with both cromolyn and placebo (Freidman test, p 0.001 and 0.006, respectively). Data is presented as Mean±SEM.

Table 1. Baseline characteristics of the patients in two groups of study (all the values are presented as mean±SD)

Variable	Group A	Group B	P-value
	Cromolyn+Placebo *(n=10)*	Placebo+Cromolyn *(n=6)*	
Main symptom			
Diarrhea	6(60%)	2(33.3%)	0.61
Constipation	4(40%)	4(66.7%)	
Main symptom severity			
Within last 1 year	4.70(±2.63)	5.83(±2.04)	0.31
Within last 3 months	4.80(±2.90)	5.50(±1.22)	0.26
Abdominal pain severity			
Within last 1 year	3.40(±3.34)	6.00(±2.19)	0.12
Within last 3 months	4.40(±3.13)	6.50(±2.81)	0.31
Bloating severity			
Within last 1 year	5.10(±2.60)	7.00(±2.19)	0.18
Within last 3 months	6.00(±2.87)	7.17(±2.14)	0.56

as well as correlation between the number of activated mast cells and severity of abdominal pain (28, 29), led to the hypothesis that straight mast cell–nerve interactions might have a role in creation of symptoms and also pathophysiology of the IBS.

Results of this study demonstrated a significant decrease in the severity of pain after 6th week of treatment with Cromolyn compared to placebo in both treatment groups. These results were in accordance with the previous findings, mentioned above. The number of activated mast cells closely correlates with the severity of abdominal pain in patients with IBS and other reports raised the idea of functional association between mast cells and the intestinal nervous system though cromolyn as mast cell stabilizer might decrease the pain in IBS which was in harmony with results of this study (29). In the present investigation a significant reduction in the severity of bloating was observed during 6 weeks of active treatment with cromolyn in both groups. It is worthwhile to notice that in active-placebo group, there was still statistically significant reduction in the severity of bloating, even after discontinuation of cromolyn treatment, which demonstrated the placebo effect. The placebo response rate in IBS patients showed a discrepancy in randomized controlled trials from 40% to 70% (32, 33). This placebo response can persevere for up to 1 year based on recent preliminary trial evidence and did not, as anticipated, diminish after 1 or 2 months (49). As symptoms are distorted by cognitive processing and IBS is a fluctuating disease, a high placebo

response would be expected although the persistence of the response is unexplained.

Some studies have declared that cromoglycate is effective in diarrhea-predominant IBS (18, 19). In this study, any improvement in main symptoms, except abdominal pain which decreased significantly among patients could not be detected. The conflicting results obtained by earlier studies may be explained by the lower dosage and shorter treatment period of this study. Bolin et al. carried out a study on patients with persistent diarrhea and declared that oral cromolyn could improve diarrhea in these patients, but their results could not be compared to results of this study because they used higher doses (34). According to what explained above, it seems that cromolyn might help to decrease diarrhea in these patients but higher doses are needed as we could not detect any improvement among our patients compared to the placebo. Another study on the patients with IBS due to food intolerance showed improvement in the symptoms significantly but the study was focused on food tolerance as patients were allowed to use irritable foods during treatment (35).

It has been shown that cromolyn is well tolerated, with low incidences of side effects. The most common side effects are bad taste, burning sensation in the eyes, and throat irritation. Rare but more serious adverse effects include anaphylaxis and bronchospasm. Orally administered cromolyn has a very low bioavailability of 1% and is excreted unchanged in the urine. A dose adjustment for renal failure was made, based upon the manufacturer's recommendation. However, there are no data on dose-response and dose-toxic effects in patients with end-stage renal disease (ESRD) (22, 23). However, no side effect was reported in patients who underwent cromolyn treatment in this study.

CONCLUSION

In conclusion, long term, high dose treatment with cromolyn seems to be partially effective for treatment of abdominal pain in patients with IBS while main symptoms (diarrhea or constipation) may not decrease during treatment period. Bloating also decreased in these patients but it can not be attributed to cromlyn since same results were obtained in those receiving placebo.

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