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The Effect of Mesalazine on Pain Management in Patients with Diarrhea-Predominant Irritable Bowel Syndrome

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ABSTRACT

Background and Objective: Irritable bowel syndrome is one of the common gastrointestinal complaints that is often resistant to standard treatment. Since mesalazine reduces abdominal pain and diarrhea through its anti-inflammatory effects, this study was conducted to investigate the effect of mesalazine on pain management in patients with diarrhea-predominant irritable bowel syndrome (IBS-D).

Methods: This case-control study was conducted among 100 patients diagnosed with diarrhea-predominant irritable bowel syndrome referred to Ayatollah Rouhani Hospital in Babol. Patients were randomly divided into two groups of 50, receiving standard treatment (amitriptyline 25 mg) and a group that received mesalazine at a dose of 500 mg for 4 weeks three times a day in addition to standard treatment. Subjects were examined and compared in terms of pain intensity and frequency of discharge and recovery.

Findings: The intensity of pain after treatment in the case group was lower than before treatment (4.66±2.29 vs. 7.80±2.01) (p=0.004). Out of 50 patients, 38 people (76.0%) in the case group and only 20 people (40%) in the control group recovered (p<0.001). In the case group, the number of bowel movements after treatment (2.20±0.92) was significantly less than before (4.92±0.92) (p<0.001). In the control group, the number of bowel movements showed a statistically significant difference before and after treatment (5.22±1.07 vs. 2.50±1.19) (p<0.001).

Conclusion: Based on the results of this study, mesalazine is significantly effective in reducing the intensity of pain caused by irritable bowel syndrome. However, there was no difference in the number of excretions.

Keywords: *Mesalazine, Amitriptyline, Irritable Bowel Syndrome, Diarrhea, Abdominal Pain*.

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Introduction

Irritable Bowel Syndrome (IBS) is the most common dysfunction of the digestive system, which is associated with abdominal pain and is associated with changes in bowel habits and excretion disorders. Irritable bowel syndrome causes a significant decrease in the quality of life in people with this disease (1). Patients often believe that stress aggravates their symptoms, but there is a weak correlation between stress and symptoms (2). This disease is the cause of 12% of referrals to gastroenterology specialists (3). This syndrome can directly and indirectly cause an increase in health care costs, and this figure is estimated to be around 30 million dollars in the United States (4). In the conducted surveys, the prevalence of irritable bowel syndrome in North America is 10-15% and in Europe it is about 11.5% (5). However, its prevalence is very different in different countries. Based on population studies conducted in Iran, the prevalence of irritable bowel syndrome has been reported from 3.5 to 5.8%. But the disease seems to be higher in certain groups of people. In a study conducted on medical students, the prevalence of irritable bowel syndrome was reported to be 18.5% (6, 7). In a study by Khoshkrood-Mansoori et al., the prevalence of irritable bowel syndrome was estimated to be about 1.1% and the prevalence in women was 2.2 times higher than men (8).

It has been shown that the number of mast cells increases in patients with diarrhea-predominant irritable bowel syndrome (IBS-D), and eventually leads to abdominal pain. Anxiety and chronic stress increase the number of activated mast cells throughout the intestine in patients with irritable bowel syndrome. Treatment with mesalazine may reduce the number of mast cells due to its anti-inflammatory effects, and therefore reduce abdominal pain and diarrhea (9). Treatment with mesalazine reduces abdominal pain and diarrhea through its anti-inflammatory effects, which increases intestinal permeability and sensitivity due to the reduction in the number of mast cells and the subsequent release of their mediators. Mesalazine can reduce mucosal immune response both by inhibiting other inflammatory pathways and directly inhibiting mast cell pathways (10).

Mesalazine is the active form of sulfasalazine drug, which belongs to salicylates and is used in the treatment of Crohn's disease and ulcerative colitis. The main mechanism of the drug is unclear. It probably inhibits the cyclooxygenase enzyme and reduces the synthesis of prostaglandins in the intestine. Nevertheless, it seems to regulate the chemical response to inflammatory mediators, especially leukotrienes, and to inhibit TNF, and on the other hand, it also has antimicrobial properties. This drug has very few complications and can be considered as a suitable drug for patients with irritable bowel syndrome (11).

Several clinical trials (11, 12) and randomized controlled trials (13, 14) were conducted on the effect of mesalazine in people with IBS-D. All studies, except for a study by Corinaldesi et al., were conducted on patients with IBS-D, and a significant decrease in the number of mast cells and a general decrease in inflammatory cells were observed in patients with irritable bowel syndrome (13). In a study by Ghadir et al., mesalazine had no effect on the number of mast cells and the severity of symptoms in people with IBS-D (15). In a study by Barbara et al., mesalazine had no superiority over placebo. However, in some subgroups of irritable bowel syndrome, the response and benefits of treatment with mesalazine were observed (16). The treatment of irritable bowel syndrome requires a multi-component approach. In fact, irritable bowel syndrome is a chronic disease that has no known definitive treatment, so the goal of treatment should be based on eliminating the symptoms and identifying the patient's concerns (17).

The mechanism and pathogenesis of diarrhea-predominant irritable bowel syndrome are not fully understood and various drug classifications such as antispasmodics, dopamine antagonists, 5-HT3 antagonists, sedatives and probiotics, diet and lifestyle changes have been used as treatment for the

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symptoms of the disease (18). In some studies, they refer to the effects of psychological factors such as depression, stress, anxiety on the cause of occurrence or the effect on the onset of the disease. But in no research, these factors have been mentioned as risk factors for irritable bowel syndrome. Nevertheless, psychological factors play an important role in increasing the severity of abdominal symptoms in patients (19).

In the study of Corinaldesi et al., mesalazine significantly reduced immune cells compared to the control group and improved the patient's general condition. But it had no effect on abdominal pain, bloating and bowel habits. No serious drug side effects were observed in this study. In this study, it was concluded that mesalazine is an effective method to reduce infiltration of mast cells and may improve general health in patients with irritable bowel syndrome. These results indicate that immune mechanisms should be potential therapeutic targets in irritable bowel syndrome (13). One of the causes of the pathophysiology of irritable bowel syndrome that researchers have recently focused on is the inflammatory processes and the activation of the immune mechanism that can explain it. Because irritable syndrome is often resistant to standard treatment (20). Therefore, inflammatory processes in the colon mucosa can be one of the most promising targets for treatment in patients with irritable bowel syndrome. Few studies have evaluated the therapeutic effect of mesalazine, which is an intestinal anti-inflammatory drug, in the treatment of irritable bowel syndrome (21).

According to the studies, contradictory results of the effects of mesalazine on pain control in patients with irritable bowel syndrome have been observed, which makes this study even more necessary. The aim of this study is to compare the effect of mesalazine and standard treatment (amitriptyline) on pain management in patients with diarrhea-predominant irritable bowel syndrome.

Methods

After being approved by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1398.176 and after the estimation of the sample size, this case-control study was conducted on 100 patients diagnosed with IBS-D referring to Rouhani Hospital in Babol. After obtaining written consent, subjects were randomly divided into two groups of 50 people. Men and non-pregnant women over 18 years of age who were diagnosed with irritable bowel syndrome based on Rome III criteria, not having hard and lumpy stools (types 1 and 2), no history of inflammatory bowel disease, no history of type 1 or 2 diabetes, no history of breastfeeding, and no history of hepatitis B or C and AIDS, as well as no history of painkiller use were included in the study. In case of non-cooperation for taking medicine during the study, change of diarrhea to constipation, possible complication or sensitivity to taking medicine, detection of a specific disease during the study, subjects were excluded from the study.

The first group includes patients receiving standard treatment (amitriptyline 25 mg) and the second group includes patients who, in addition to standard treatment, received mesalazine at a dose of 500 mg for 4 weeks and three times a day. The primary outcome of the study was to examine the response rate of patients based on abdominal pain related to irritable bowel syndrome and the number of bowel movements during 4 weeks. Abdominal pain response is defined as a 30% improvement in pain compared to the beginning of the week (3). Abdominal pain was evaluated using a Visual Analogue Scale (VAS) (0 equals no pain, 10 equals the worst possible pain) (22). Patients' response to the number of bowel movements was defined as a decrease of more than or equal to 50% of the number of days of the week compared to the beginning of the week. Patients who had response to abdominal pain and frequency of defecation for at least 2 weeks out of 4 weeks were defined as response to treatment. In order to more accurately evaluate and analyze the effect

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of mesalazine on pain management in patients with diarrhea-predominant irritable bowel syndrome, the age of the patients was divided into two categories; less than or equal to 30 and more than 30 years.

The data were collected using the patient information file as well as clinical data provided by the doctor and the patient's own information and analyzed using SPSS V.22 and Mann-Whitney, Chi-square, Wilcoxon and T-test tests. $P<0.05$ was considered significant.

Results

In this study, out of 123 patients diagnosed with diarrhea-predominant irritable bowel syndrome during the years 2016 to 2019 who referred to Rohani Babol Hospital, 23 patients were excluded from the study due to lack of meeting the inclusion criteria, and 100 patients were subjected to final examination. The mean age of the patients was 31.08±6.38 years, with a minimum age of 18 and a maximum of 40 years. There were no significant differences between the two groups of patients in terms of demographic characteristics (Table 1).

There was no statistically significant difference in the intensity of pain and the number of bowel movements in the patients before the treatment in the two groups. The intensity of pain after treatment was significantly lower in the case group than in the control group (4.66±2.29 vs. 6.04±2.15) (p=0.004). Comparing the number of bowel movements after treatment, the mean number of bowel movements was 2.20±0.92 in the case group and 2.50±1.19 in the control group. The number of bowel movements was lower in the case group, but the difference between the two groups was not statistically significant (Table 2).

Table 1. Demographic characteristics of patients in general and its comparison between the two groups

Variables	Total Number(%)	Control group Number(%)	Case group Number(%)	p-value
Gender				
male	40(40)	19(38)	21(42)	0.68
female	60(60)	31(62)	29(58)	
Age (years)				
less than or equal to 30	49(49)	21(42)	28(56)	0.16
more than 30	51(51)	29(58)	22(44)	

Table 2. Comparison of pain intensity and number of bowel movements before and after treatment in patients in general and its comparison between two groups

	Intensity of pain Mean±SD	Number of excretions (frequency) Mean±SD
Before treatment		
Total	7.83±1.93	5.07±1
Control group	7.86±1.87	5.22±1.07
Case group	7.80±2.01	4.92±0.92
p-value	0.98	0.12
After treatment		
Total	5.35±2.32	2.35±1.07
Control group	6.04±2.15	2.50±1.19
Case group	4.66±2.29	2.20±0.92
p-value	0.004	0.27

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In the examination of the treatment response between the two groups, it was found that in the case group, out of 50 patients, 38 people (76%) had improvement, and in the control group, only 20 people (40%) responded to the treatment and there was a significant difference between two groups (p<0.001) (Figure 1). The intensity of pain before and after treatment in the control group (receiving amitriptyline) showed a significant difference (7.86±1.87 vs. 6.04±2.15) (p<0.001). The number of bowel movements before and after treatment in the control group (receiving amitriptyline) was also statistically significant (5.22±1.07 vs. 2.50±1.19) (p<0.001).

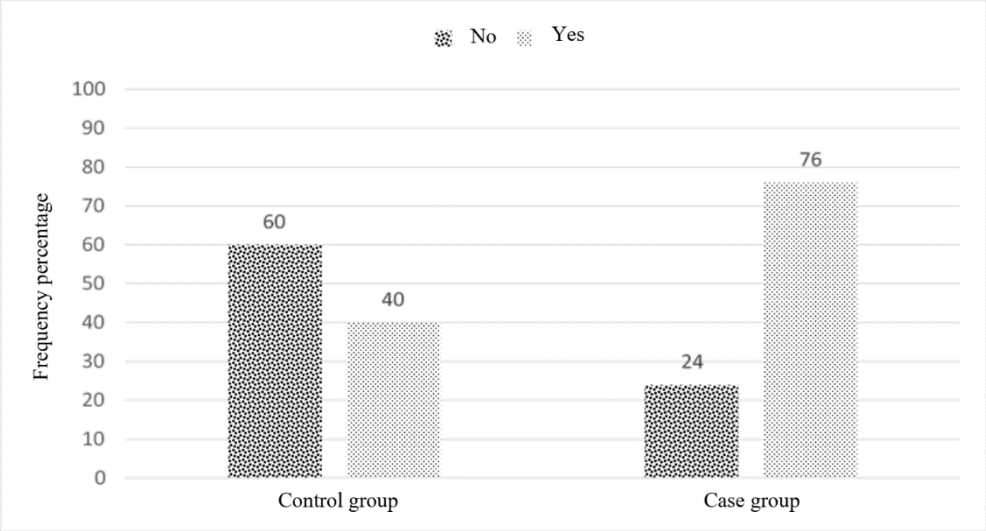


Figure 1. Comparison of response to treatment between case and control groups

In the comparison of pain intensity before and after treatment in the case group (receiving amitriptyline plus mesalazine), pain intensity was significantly lower than before treatment (p<0.001). Comparing the number of bowel movements before and after treatment in the case group (amitriptyline plus mesalazine), the number of bowel movements after treatment was significantly lower than the control group (p<0.001) (Table 3).

Table 3. Comparison of pain intensity and number of bowel movements before and after treatment in the case group

Variables	Before treatment Mean±SD	After treatment Mean±SD	p-value*
Intensity of pain	7.80±2.01	4.66±2.29	<0.001
Number of excretions (frequency)	4.92±0.92	2.20±0.92	<0.001

*Using the Wilcoxon test

Discussion

In this study, patients with irritable bowel syndrome who used mesalazine improved significantly compared to the control group. In the study of Vahedi et al., mesalazine significantly reduced pain intensity compared to nortriptyline. They reported that mesalazine as an anti-inflammatory is very effective in the treatment of diarrhea-predominant irritable bowel syndrome in patients without psychological disorders

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(23). The results of the above study are in line with our findings. Mesalazine, with its anti-inflammatory effects, may be helpful in reducing abdominal pain. Guilarte et al. demonstrated that there is a relationship between stress and irritable bowel syndrome, which can stimulate mast cells, and the number of mast cells increases significantly in affected patients (9). It seems that mesalazine with anti-inflammatory effects can reduce the number of mast cells and subsequently reduce abdominal pain and diarrhea (24). In a study similar to the results of the present study, Barbara et al. stated that all symptoms such as abdominal pain in the patients of the mesalazine group significantly improved more than the patients in the control group. In general, they concluded that in some subgroups of irritable bowel syndrome, the response and benefits of treatment with mesalazine were noticeable (16).

In the study of Andrews et al., it was shown that 67% of patients had a significant reduction in abdominal pain and increased satisfaction with bowel function and defecation (11), which is similar to the present study. Mesalazine probably reduces pain by reducing intestinal bacteria. Bafutto et al. also mentioned in their study that mesalazine can be effective in the treatment of symptoms caused by irritable bowel syndrome (12) and this finding is in line with the results of the present study.

Dorofeyev et al. reported that mesalazine is effective in reducing the severity of symptoms of irritable bowel syndrome and significantly reduces the intensity and duration of pain (25). Ghadir et al. conducted a study and concluded that the use of mesalazine does not reduce the symptoms of the disease such as abdominal pain, bloating, fecal urgency and frequency of defecation. They reported that mesalazine had no effect on the severity of symptoms in people with IBS-D (15). The result of the above study is not consistent with the present study.

This finding is inconsistent with the hypothesis that immune mechanisms are potential therapeutic targets in irritable bowel syndrome. It seems that the effects of mesalazine should be investigated in more studies and on different races and geographical locations. In the study of Tuteja et al., the frequency of defecation, consistency of stool, fecal urgency, severity of abdominal pain, severity of bloating, general symptoms and quality of life in the mesalazine group were not significantly different from the control group. In this study, it was concluded that mesalazine does not provide any significant improvement in quality of life and disease symptoms in people with irritable bowel syndrome following intestinal infection (gastroenteritis) (14).

In the study of Corinaldesi et al., mesalazine significantly improved the general condition of patients, but had no effect on abdominal pain, bloating, and bowel habits. No serious drug side effects were observed in this study. This study concluded that mesalazine is an effective method of reducing infiltration of mast cells and may improve general health in patients with irritable bowel syndrome (13). These results suggest that immune mechanisms should be potential therapeutic targets in irritable bowel syndrome.

In another opposing study, Lam et al. reported that mesalazine could not improve abdominal pain, bowel habits and bowel movements, stool consistency, and ultimately patient satisfaction (26). The results obtained in Lam's study are in conflict with the findings of the present study. The reason for this difference could be the difference in the duration of mesalazine use and the follow-up period of the patients. Because its pathophysiology is unknown, the treatment of irritable bowel syndrome is not always a single treatment, and several treatments are used based on the patient's symptoms.

Based on the results of this study, mesalazine is significantly effective in reducing the intensity of pain caused by irritable bowel syndrome. However, no difference was observed in the number of bowel movements with mesalazine.

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