Original Article

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Mesalazine vs. IBS-D: Examining its impact on patient symptoms & stool calprotectin levels: A randomized double-blind, placebo-controlled trial

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Abstract

Background: Irritable bowel syndrome (IBS) is the most common disorder of the gastrointestinal system. The study aimed to determine the effect of Mesalazine prescription on patients' symptoms and level of fecal calprotectin in patients with IBS with predominant diarrhea and high fecal calprotectin.

Methods: We conducted a double-blinded randomized clinical trial with 90 patients aged 18 to 45. These patients were selected from referrals to the gastroenterology clinic. They were evenly divided into two groups: the Mesalazine group, with an average age of 35.4, and the placebo group, with an average age of 36. The patients in both groups were then monitored for 8 weeks. There were no differences in the distribution of sexes between the two groups.

Results: In comparison between before and after Mesalazine therapy in our patients marked a statistically significant effect on the quality of life variables ($p<0.05$), patient's level of pain ($p<0.05$), abdominal distension ($p<0.05$), and calprotectin level ($p<0.05$) compared to before Mesalazine in patients studied, which showed the effectiveness of this treatment. However its effect on stool form was not significant ($P=0.11$).

Conclusion: Comparing the two groups after the intervention, the quality of life in patients treated with Mesalazine was significantly higher than in patients of the placebo group. The number of defecations in patients treated with Mesalazine was significantly lower than in patients of placebo groups. Abdominal distention and calprotectin levels were significantly lower in these patients than in patients of the placebo group.

Keywords: Abdominal pain; Calprotectin, Inflammatory cells, Irritable bowel syndrome, Mesalazine.

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Irritable bowel syndrome (IBS) stands out as one of the most prevalent functional disorders of the digestive system. This condition is characterized by persistent abdominal pain, fluctuations in bowel movements and, bloating, which plague up to 20% of the adult population, with a higher incidence recorded in women (1). To date, the identification of biomarkers that are specific to IBS still remains an elusive pursuit. Hence, the diagnosis of this condition primarily relies on the clinical symptoms presented by the patient and the implementation of the Rome diagnostic criteria. Despite extensive research in the field of IBS, the lack of reliable biomarkers has made it difficult to achieve more accurate and speedy diagnoses, and consequently, to deliver effective treatments for patients (2). The diagnostic criteria for identifying patients with IBS were established by the Rome IV criteria. The Rome IV criteria for IBS define it as recurrent abdominal pain that has been present for at least 6 months before diagnosis and is associated with two or more of the following, at least one day per week in the last 3 months: related to defecation, with a change in frequency of stool, with a change in form or appearance of stool (3).

To classify IBS, researchers have identified four distinct categories that are primarily based on the predominant type of bowel movement. These categories include IBS-D for cases where diarrhea is predominant, IBS-C for cases where constipation is predominant, and IBS-M for cases where there is a mixed state of both. Additionally, there is a subtype known as IBS-Unclassified which does not fit into any of these categories. By understanding and acknowledging these categories, medical professionals and researchers can better diagnose and treat this complex condition (4).

From a pathophysiological standpoint, IBS is a complex disorder with diverse yet interconnected factors. These include aberrant motor and sensory activity within the gastrointestinal tract, impairments in central nervous system functionality, and the presence of psychological afflictions, mucosal inflammation, elevated stress levels, genetic predispositions, dietary habits, and intraluminal factors such as deficient bile acid absorption mechanism. In conjunction, these factors contribute to the manifestation of IBS symptoms, thereby highlighting the multifaceted nature of this condition (5). We tailor our approach to treating the disease based on the unique clinical symptoms of each patient. Our regimen includes a combination of potent anti-diarrheal, anti-depressant, anti-spasm, and anti-flatulence drugs to alleviate discomfort and promote healing (6).

Exciting new research on patients with IBS has shed light on the presence of certain mucosal inflammatory indicators, particularly fecal calprotectin. This is particularly significant for individuals with IBS that have been preceded by an infection. Also, some studies suggest an increase in the level of mast cells in the pathophysiology of IBS patients (7). Calprotectin is a protein predominantly located in neutrophils. It plays a critical role in the inflammatory response by accumulating in the digestive system upon the activation of inflammation. Once there, its concentration in the stool corresponds to the severity of acute inflammatory conditions in the intestine. Therefore, measuring levels of calprotectin in stool can provide valuable insights into the diagnosis and management of inflammation in the gut (8). The measurement of calprotectin level has emerged as a valuable tool for examining mucosal inflammation in individuals diagnosed with inflammatory bowel diseases (IBD). A consensus among healthy adults suggests that 50 micrograms per gram is a reasonable upper limit (9).

This approach is not only useful in determining the absence or presence of IBD but also in identifying patients with IBS who would benefit from anti-inflammatory medication. In light of these findings, calprotectin level may serve as an effective biomarker for assessing inflammatory bowel conditions and directing appropriate therapeutic intervention (10). The occurrence of such inflammatory activities indicates that certain anti-inflammatory drugs that target the intestines could be an appropriate treatment option for IBS. Mesalazine (also known as 5-Aminosalicylic acid) is one such drug that has a notable anti-inflammatory impact and effectively works on specific types of immune mediators (11).

Some studies have confirmed the effect of Mesalazine on inhibiting mast cell infiltration and improving abdominal pain and diarrhea in IBS patients (12-14). While some studies showed that Mesalazine did not have a significant effect on reducing the level of mast cells and improving the symptoms of IBS patients (15, 16). As current treatment strategies for IBS only alleviate symptoms without addressing the underlying pathophysiology, and due to the limited and conflicting results of prior studies, this particular study aimed to investigate whether Mesalazine can improve clinical symptoms and calprotectin levels in patients with irritable bowel syndrome where diarrhea is the primary manifestation and calprotectin levels are elevated. To accomplish this, we analyzed stool samples.

Methods

Study design: This study is a double-blind randomized clinical trial, which was conducted on outpatients with IBS referred to gastroenterology clinics affiliated with Imam Reza Hospital, Tabriz University of Medical Sciences in 2021. The patients were diagnosed according to Rome IV criteria and their predominant symptoms were diarrhea, high fecal calprotectin level, and normal colonoscopy. The protocol for the research project has been approved by the Ethics Committee of the Tabriz University of Medical Sciences. All persons gave their informed consent prior to their inclusion in the study. All items of the Declaration of Helsinki have been observed in this study. No additional costs were imposed on patients. All patient information is collected and stored confidentially and will not be available to any real or legal person. The benefit of the patient and the correct treatment of the disease is a priority, and this study did not create a problem in that. Patients in need of medical treatment were included in the study and no threatening treatment was done. Also, during the study, patients could be excluded from the study.

The sample size was selected using G-power software with a confidence level of 95 and a power of 80%, and also taking into account the results of the study by Corinaldesi et al. (13). On the ROME IV criteria parameter of the number of stools per day, 35 people were selected for each

group, including Attrition (30%) was considered to be 45 people for each group. 90 patients referred to the gastroenterology clinic were selected based on the entry and exit criteria and written consent was obtained from the patients. The patients were divided into two Mesalazine group (45 people) and a placebo group (45 people) using the block randomization method. The patient and the researcher were kept unaware of which group they were in. This was done so that the safety and data monitoring committee could track whether the patient received a placebo or the actual drug (Mesalazine) while maintaining the integrity of the study. To ensure this, the drug and the placebo were packaged in identical boxes and delivered in separate envelopes by the committee. The researcher then randomly assigned the patients to the two groups by selecting an envelope, effectively keeping the assignment process unbiased. The two study groups were given either 500 mg Mesalazine tablets twice a day for 8 weeks, or a placebo twice a day for 8 weeks. Patients were instructed to keep a record of their medication intake on a provided table for assessment of intervention compliance throughout the study. Subsequently, a doctor assessed the patient's clinical symptoms. To assess the participants' health-related quality of life, we administered the Irritable Bowel Syndrome Quality of Life (IBS-QoL) questionnaire. The IBS-QoL comprises 34 items, each rated on a 5-point Likert scale from 0 to 4. The total scores range from 0 to 136. Higher scores indicate a better quality of life (17). The quality of patients' pain was assessed with a visual analog scale (VAS, 0-10) and grouped as 0-3=Mild, 4-5=Moderate, 6-8=Severe, 9-10=Very severe (18). The level of calprotectin was also analyzed by ELISA method with a laboratory kit (Calprest) in the stool sample and its normal value was considered below 50 mg per kg of stool (9).

Abdominal distention also was assessed by a graphic rating scale from 0 to 6. (0-1=mild, 2-3=moderate, 4-5=severe, and 6 very severe) (19). To evaluate the stool form of our study participants, we utilized the Bristol Stool Form Scale (BSFS), a widely accepted visual grading system that categorizes stool types from type 1 (hard lumps) to type 7 (watery diarrhea). This scale enabled us to assess the stool form of patients and record their stool type accordingly (20). Before and 8 weeks after the treatment, questionnaires related to patients' clinical symptoms and calprotectin levels were measured and completed. Patients visited the researcher in the hospital for follow-up appointments without experiencing any delays. The consumption of capsules was followed weekly and through phone calls. Also, patients could contact the researcher during the study if necessary.

Study patients: According to the Rome IV criteria, the selected patients had recurrent abdominal pain that lasted at least one day a week in the last 3 months with symptom onset at least 6 months before diagnosis and was accompanied by at least two of the following: 1) related to defecation, 2) change in stool frequency, 3) change in stool form. "Discomfort" is no longer required due to its non-specificity and recurrent abdominal pain. Confirmatory symptoms include a change in stool frequency, a change in stool shape, a change in stool pressure or urgency, mucus discharge, abdominal bloating, or distension. Inclusion criteria included the diagnosis of IBS-D according to the Rome IV criteria, age over 18 years and under 45 years, stool calprotectin level above 50 mg per kilogram of stool, and normal colonoscopy in the last 5 years. Exclusion criteria also include pregnancy and breastfeeding, any positive history of food or drug allergy, sensitivity to Mesalazine, recent history of taking probiotic compounds and lactulose in the last 3 months, history of taking anti-inflammatory drugs and antibiotics and mast cell stabilizing drugs in the previous 3 months, history of psychological diseases, celiac disease, IBD, normal stool calprotectin, diagnosis of other diseases with colonoscopy, evidence of organic disease in colonoscopy, history of major abdominal surgery (like small bowel resection, total colectomy, total proctocolectomy, etc) other than appendectomy and cholecystectomy.

Statistical analysis: SPSS Version 22 software was used for data analysis. The normality of the data was checked with the Kolmogorov-Smirnov test, and if the distribution of the data was normal, the t-test was performed, and if it was not normal, the Wilcoxon signed rank test was performed. Comparison between groups was done with ANOVA test and adjusted for confounding factors and initial values. Chi square test was also used to compare qualitative variables.

Results

In the examination of the two groups before the intervention, there was no statistically significant difference between the placebo and Mesalazine groups, which makes the comparison of the two groups appropriate. The average age of the two groups was selected close to each other, and there was no statistically significant difference between them in terms of gender (table 1). In the comparison before the intervention and after the intervention, there was no statistically significant difference in the placebo group, which indicates that the placebo has no effect on the patients in the variables examined (table 2).

In the comparison before and after the intervention in the group receiving Mesalazine, a significant difference was observed in QoL variables, pain, abdominal distension, and calprotectin after the intervention, which indicates the effectiveness of this drug in the treatment of the disease. However, there was no change in stool form before and after taking Mesalazine (table 3). In the comparison between the two groups after the intervention, the quality of life in the patients treated with Mesalazine was significantly higher than the placebo group. The number of bowel movements in patients treated with Mesalazine was significantly lower than in patients receiving a placebo. Abdominal distension and calprotectin levels in these patients were significantly lower than in those receiving placebo (table 4).

Table 1. Comparison between the two groups before the intervention

		Mesalazine group	Placebo group	P-value
Age (year)		35.40±8.19	36±7.30	N.S
Sex	**Female**	23 (51%)	25 (55.6%)	N.S
	Male	22 (48.9%)	20 (44.4%)	N.S
Duration of disease (year)		3.45±23.2	4.2±36.4	N.S
Calprotectin (mg/kg stool)		77.86±14.5	72.51±13.1	N.S
IBS-QoL		71.68±8.40	68.78±9.24	N.S
Stool form	**Soft blebs (Type 5 BSFS)**	19 (42%)	22 (48.9%)	N.S
	Mild diarrhea (Type 6 BSFS)	23 (51.1%)	22 (48.9%)	N.S
	Severe diarrhea (Type 7 BSFS)	3 (6.7%)	1 (2.2%)	N.S
Abdominal distention	**Mild**	7 (15.6)	18 (40)	N.S
	Moderate	20 (44.4)	12 (26.7)	N.S
	Severe	15 (33.3)	13 (28.9)	N.S
	Very severe	3 (6.7)	2 (4.4)	N.S
Frequency	**2-3 days/week**	4 (8.9)	5 (11.1)	N.S
	4-5 days/week	28 (62.2)	24 (53.3)	N.S
	More than 5 days/week	13 (28.9)	16 (35.6)	N.S
Pain	**Mild**	15 (33.3)	15 (33.3)	N.S
	Moderate	20 (44.4)	19 (42.2)	N.S
	Severe	9 (20)	8 (17.8)	N.S
	Very severe	1 (2.2)	3 (6.7)	N.S

IBS-QoL: Irritable Bowel Syndrome Quality of Life

Table 2. Comparison of the placebo group before and after the intervention

	Before intervention	After intervention	P-value
IBS QoL	68.78±9.24	67.69±9.55	0.11
Pain (VAS)	3.96±1.78	3.87±1.78	0.59
Frequency (days/week)	3.24±0.64	3.12±0.52	1.00
Abdominal distention (graphic rating scale)	3.96±1.88	4.09±1.75	0.44
Stool form (Bristol scale)	5.53±0.54	5.56±0.50	0.81
Calprotectin (mg/kg stool)	72.51±13.12	72.24±13.05	0.94

Table 3. Comparison of the group receiving Mesalazine before and after the intervention

	Before intervention	After intervention	P-value
IBS QoL	71.68±8.40	78.71±6.45	<0.05
Pain (VAS)	3.82±1.58	2.84±1.16	<0.05
Frequency (days/week)	3.20±0.58	2.42±0.54	<0.05
Abdominal distention (graphic rating scale)	4.62±1.64	2.98±1.75	<0.05
Stool form (Bristol scale)	5.64±0.60	5.22±0.42	0.11
Calprotectin (mg/kg stool)	77.86±14.15	68.95±14.54	<0.05

Table 4. Comparison between the two groups receiving Mesalazine and receiving placebo after the intervention

	Mesalazine	placebo	P-value
IBS QoL	78.71±6.45	67.69±9.55	<0.05
Pain (VAS)	2.84±1.16	3.87±1.78	<0.05
Frequency (days/week)	2.42±0.54	3.12±0.52	<0.05
Abdominal distention (graphic rating scale)	2.98±1.75	4.09±1.75	<0.05
Stool form (Bristol scale)	5.22±0.42	5.56±0.50	0.11
Calprotectin (mg/kg stool)	68.95±14.54	72.24±13.05	<0.05

IBS-QoL: Irritable Bowel Syndrome Quality of Life

Discussion

According to the results of this study, the use of Mesalazine among patients with IBS-D brought about several positive outcomes. It improved the patient's quality of life, reduced pain and the frequency of defecation, as well as abdominal distension. Moreover, it also decreased fecal calprotectin levels. The study's data confirms that there is not a noteworthy variance in the prevalence of the disease between males and females. Additionally, there was no significant age difference detected between the two groups; both cases and controls were similar in this aspect. Pain intensity was measured using a visual analog scale (0-10) both before and after Mesalazine treatment. Results indicate that the pain intensity was significantly reduced in the group treated with Mesalazine when compared to the placebo group. During the study's initial stages, all patients had defecation disorders like abdominal pain and distention. However, after the patients received Mesalazine treatment, the number of individuals in the group who still had defecation disorders significantly decreased.

Andrew et al's research also support these findings, revealing Mesalazine's effectiveness in improving abdominal pain in IBS patients, further corroborating the results of this study (12). Furthermore, Dorofeyev et al.'s study demonstrated that Mesalazine has an impact on the symptoms experienced by individuals with IBS-D, including their satisfaction with treatment and the duration of pain (14). In a study conducted by Corinaldesi et al., it was determined that the use of Mesalazine leads to a decrease in mast cell count, an improvement in quality of life, and a reduction in abdominal pain, bloating, and bowel movements (13).

The findings of Ghadir et al.'s study in 2017 indicate that Mesalazine did not result in a considerable reduction in mast cell levels nor did it improve the symptoms experienced by IBS-D patients. Rather, treatment with Mesalazine led to increased pain, bloating, and incomplete bowel movements, creating a contradiction with previous research. Regardless, the study did reveal that Mesalazine decreased the number of bowel movements, aligning with the results of the current investigation (15). In contrast to the present investigation, Lam et al.'s study did not demonstrate a significant impact of Mesalazine on the symptoms experienced by individuals with IBS-D (16). In another study, Tejera et al. showed that Mesalazine is ineffective in reducing IBS symptoms which does not confirm our findings (21). These differences may result from variations in study conditions, intervention durations, Mesalazine dosages, or demographic makeup of the statistical populations. Consequently, further studies should be done in various populations and with different

dosages and longer periods of treatment to evaluate the effect of Mesalazine. Overall, it can be concluded that Mesalazine has a positive impact on patients with IBS-D. Following the intervention, the group treated with Mesalazine reported a significantly higher quality of life and a lower frequency of defecation, abdominal distention, and calprotectin levels when compared to the placebo group. Based on our results, Mesalazine may be effective in some patients. To advocate for Mesalazine as a safe, low-risk anti-inflammatory treatment for individuals with IBS, future research will require a larger statistical population, higher doses of Mesalazine, and a longer treatment duration. Finally, it can be said that the administration of mesalazine is not currently recommended due to the contradictory effects reported.

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Ethics approval: This study was approved under the ethical approval code of IR.TBZMED.REC.1399.786 in Tabriz University of Medical Sciences and its related hospitals and it is registered in the Iranian Registry of Clinical Trials (IRCT) which publicly accessible at https://www.irct.ir/trial/53050. (IRCT20151106024901N5)

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