doi:10.22100/ijhs.v3i1.194
Original Article

IJHS 2017;3(1):26-29
ijhs.shmu.ac.ir

IJHS
International Journal of Health Studies

The effect of Mesalazine and Nortriptyline on Patients with Irritable Bowel Syndrome with Diarrhea: A Randomized Clinical Trail

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Received: 6 December 2016
Accepted: 23 April 2017

Abstract

Background: *The objective of this randomized trial was to compare the effects of mesalazine and nortriptyline on relief of abdominal pain, discomfort, abnormal bowel habits and quality of life in patients with diarrhea-predominant irritable bowel syndrome (IBS-D).*

Methods: *In this triple blinded, randomized clinical trial, 44 patients with irritable bowel syndrome with diarrhea were randomly assigned to receive mesalazine (500 mg tablet orally, twice a day) or nortriptyline (10 mg tablet orally, once daily). IBS-D was diagnosed according to the Rome Ⅲ criteria. Before allocation, all patients completed the Beck questionnaire for screening for depression, and the informed consent form.*

Results: *Change score for abdominal pain severity was significantly higher for mesalazine than for nortriptyline (208.5±80.9 V.s 146.8±105.6) and change score for days with pain was not significantly different between two arms (3.9±2.8 V.s 2.8±3.0). The results show that the change score of satisfaction with bowel habits (56.2±20.2 V.s 37.5±24.9) and quality of life (42.0±26.7 V.s 26.3±18.6) in the mesalazine-treated group is greater than in the nortriptyline group.*

Conclusions: *This study showed that mesalazine, as an anti-inflammatory agent for treatment of IBS-D in patients without psychological disorders, is more effective than nortriptyline.*

Keywords: Mesalazine, Nortriptyline, Irritable bowel syndrome, Abdominal pain.
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Please cite this paper as: Vahedi H, Mousavi SA, Gholamzadeh SH, Khosravi A. The effect of mesalazine and nortriptyline on patients with irritable bowel syndrome with diarrhea: a randomized clinical trail. Int J Health Stud 2017;3(1):26-29.

Introduction

Irritable bowel syndrome (IBS) is the most common disorder among functional gastrointestinal disorders, affecting 10–20% of adults and adolescents in USA, 8.6% in Singapore, and 14% in Pakistan.[1,2] IBS is a functional bowel complaint in which abdominal pain is associated with defecation or change in bowel habit.[2] Approximately 20% of persons in the developed world have IBS symptoms at some time in their lives.[3] IBS is common in western Europe and North America, and many aspects of its epidemiology, risk factors, and natural history have been described in these regions.[4] Women are at slightly higher risk for IBS than men.[5] IBS decreases the patient's quality of life through repeated waxing and waning of symptoms over a long period.[6] Despite intensive research over the past two decades, the etiology of IBS remains poorly understood, thus leading to limited effective treatments for patients with these disorders.[1] At present, no effective and optimal treatment has been determined.[7]

IBS with diarrhea (IBS-D) as a subtype accounts for 23.4% of patients with IBS.[8] The mechanism and pathogenesis of IBS-D are not completely understood and different drug categories (antispasmodic, Dopamine antagonist, 5-HT3 antagonist, sedatives and probiotics), diet and life style modification have been used as symptomatic therapies.[9] Although psychological factors such as depression, stress and anxiety have not been shown to cause or influence the onset of IBS, psychological factors play a role in the persistence and perceived severity of abdominal symptoms.[2] Evidence suggests there is a relation between IBS and stress that can motivate the mast cells, and in IBS-D patients mast cell numbers have been shown to increase.[10] We hypothesize that treatment with mesalazine, through its anti-inflammatory effects, will reduce the number of mast cells and consequently reduce abdominal pain and diarrhea.[11] The Corinaldesi trial that had the goal of assessing the effect of mesalazine on mucosal immune cells in 20 patients with IBS indicated a decrease in mast cell numbers, a reduction in inflammatory cells and an improvement in general well-being.[12] In a review of the study protocol trial shown in a multicenter trial, 108 participants with diarrhea-predominant IBS randomized for intervention group with 12-week course of 2 g mesalazine granules twice a day; the control group was a blinded placebo granule formulation.[11] In another recent study, the effects of mesalazine alone, a combined therapy of mesalazine with lyophilised Saccharomyces boulardii (Sb) or alone on symptoms of IBS-D patients were assessed. In this study, improvement in the symptom score was greater with mesalazine alone or combined with Sb compared with Sb treatment alone.[13]

The objective of this randomized trial was to compare the effects of mesalazine and nortriptyline on patients with diarrhea-predominant irritable bowel syndrome (IBS-D) in relieving abdominal pain, discomfort and abnormal bowel habits and stool frequency recorded daily.

Materials and Methods

A triple blind, randomized clinical trial was conducted in the gastrointestinal clinic of Imam Hossein Hospital in Shahroud, northeast of Iran. This study was conducted from January 2013 to March 2014. In this study, 44 patients with IBS with diarrhea were randomly assigned to receive mesalazine or nortriptyline (Figure 1). IBS-D was diagnosed

according to the Rome Ⅲ criteria (mainly including abdominal pain, diarrhea and without any organic alteration).[14] Random allocation was based on the order of entry; eligible patients received envelopes that included codes and based on these codes they were randomly assigned into mesalazine or nortriptyline groups based on a four block design.

Patients were eligible for enrollment if they were aged between 18 and 65 years. Before allocation, all patients completed the Beck questionnaire for screening for depression. The main exclusion criteria were the use of analgesic drugs, pregnant or breastfeeding women, patients with major depressive disorder according to DSM-IV-TR and Beck Depression Inventory, gastrointestinal bleeding, presence of any finding of organic disorders in the lab tests, or organic disorders in the colonoscopies of high-risk patients, use of illicit drugs, and presence of mixed and constipation-predominant IBS. All patients provided informed consent. This study was approved by the institutional review board of Shahroud University of Medical Sciences (code: 9104) and was registered with the Iranian Registry of Clinical Trial (IRCT ID: IRCT201506171647N4).

Patients who met the inclusion criteria were recruited and randomized in two groups to receive mesalazine (500 mg tablet orally, twice a day) as intervention, and nortriptyline (10 mg tablet orally, once daily) for the control group for 8 weeks. Randomization was performed by a computer-generated table in blocks of 4. All patients and investigators and data analyzers, except for the study coordinator, remained blinded to the randomization process until study completion.

After filling in the informed consent forms, patients were referred to a particular pharmacy where a pharmacy technical assistant delivered drugs to them free of charge, in similar but sealed boxes with specific codes and with no labels.

The baseline (week 0) stool form, stool frequency, and visual analog scale score (from 0 to 100) for symptoms associated with IBS were recorded using IBS Severity Scoring system (IBS, SSS).

The IBS, SSS (15) had two parts: i) IBS severity score, and ii) other therapeutic features. Main outcome measure variables were measured with the (IBS,SSS) (15), which contains five 100 point scales (range: not pain (0), not very severe (25), quite severe (50), severe (75) and very severe (100)), that assess the severity of abdominal pain, frequency of abdominal pain expressed as the number of days that you get the pain over the preceding 10 days, dissatisfaction with bowel habits, interference with quality of life, and abdominal distension (bloating, swollen, or thigh tummy). The combination of these 5 scales led to a total possible score of 500 as overall IBS severity score. In part 2, for all patients other clinical signs consisting of incomplete evacuation, mucus in stools, site of pain, and stool frequency recorded daily were measured and compared between groups at the baseline and 8 weeks after the intervention. How IBS affected and interfered with quality of life in general was assessed with a line scale range from 0 to 100 (‘Not at all’ till ‘completely’).

Data were analyzed using SPSS software. Continuous variables were analyzed using Student’s t tests and categorical variables were analyzed using Chi-square tests or Fisher’s exact tests when 20% of expected frequencies were less than or equal to 5. To evaluate the change in symptom scores over time and to compare scores between the groups, we used change scores between before and after the investigation with t test. Results were considered statistically significant when p values were <0.05.

Results

Figure 1 shows the study flow chart. Among subjects screened for diarrhea-predominant IBS, 44 were eligible for the study. Of these, 22 were assigned to receive mesalazine and the other 22 to receive nortriptyline. Four patients dropped out and 40 patients with IBS-D in arm A and B completed the study. These patients were included in the intention-to-treat analysis. Demographic and baseline characteristics of the 40 participants are shown in Table 1. Patients in the two groups were balanced in demographic characteristics. No statistical difference was observed between the mean abdominal pain scores for the two groups. The mean baseline involving days with pain was comparable between the two groups.

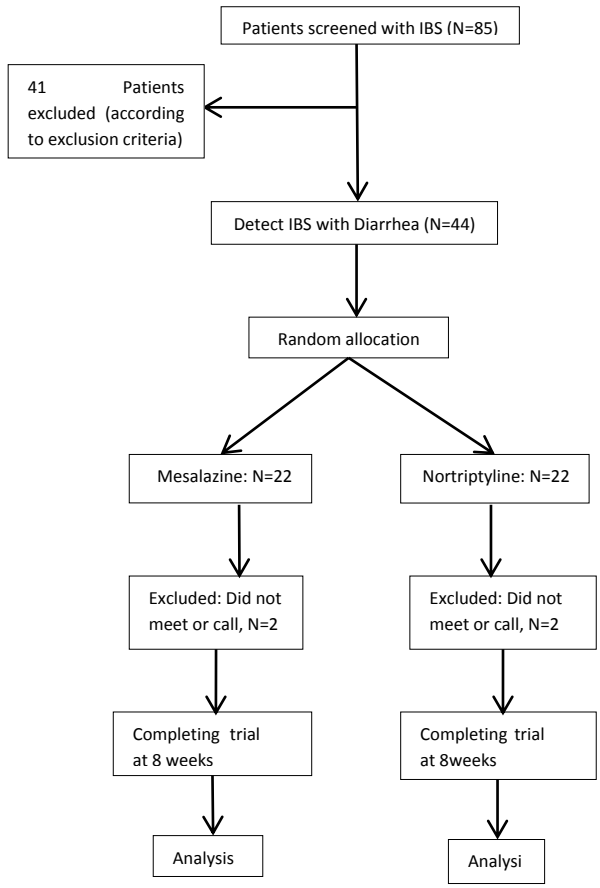

Figure 1. Chart of trial

Table 1. Demographic and baseline characteristics of the study participants with irritable bowel syndrome

	Mesalazine (N=20)	Nortriptyline (N=20)	P V
Sex			
- Male	14(70.0)	12(60.0)	0.507
- female	6(30.0)	8(40.0)	
Age (mean±sd)	36.9±7.2	37.2±12.3	0.9
BMI(mean±sd)	24.9±3.8	24.0±3.3	0.44
Abdominal pain score (mean±sd)	48.8±19.0	46.8±22.1	0.76
Mean involved days with pain (mean±sd)	5.4±3.0	4.8±2.9	0.69

Table 2. Comparison of mean differences of IBS- Severity Scoring system before and after intervention in the study participants with irritable bowel syndrome

	Mean difference (before and after change score)		
	Mesalazine (N=20)	Nortriptyline (N=20)	P.V
Abdominal pain score	37.5±18.7	27.2±21.6	0.047
Involved days with pain over the preceding 10 days	3.9±2.8	2.8±3.0	0.20
Abdominal distension score	33.2±27.7	28.2±28.2	0.57
Satisfaction with bowel habits	56.2±20.2	37.5±24.9	0.007
Interference with quality of life	42.0±26.7	26.3±18.6	0.047
Overall IBS severity score	208.5±80.9	146.8±105.6	0.045
Opening of bowels per day	3.9±3.2	2.0±1.5	0.019

According to the results in Table 2, a higher change score in abdominal pain of mesalazine-treated patients than in nortriptyline-treated patients indicated a significant relief in pain for mesalazine rather than for nortriptyline. The frequency of patients with an abdominal pain severity score of <25 (not very severe) for mesalazine and nortriptyline groups was 20 (100%) and 19 (95%), respectively. The pain component of the questionnaire incorporated both severity and duration. The latter was assessed by asking the patient to recall the occurrence of pain over the preceding 10 days. The change score for days involved with pain was not significantly different between the two groups. There was no significant change score in abdominal distension scores between the two groups. The frequency of patients with abdominal distension score of <25 (not very severe) after the treatment was for 19 (95%) for the mesalazine group and 17 (80%) for the nortriptyline group. The results of Table 2 show that the change score for satisfaction with a visit to toilet and quality of life in mesalazine-treated group is greater than in nortriptyline group. Summation of five 100 point scores, described as IBS severity score, resulted in a significant change in the overall IBS severity score in both groups with predominance of mesalazine group.

Comparison between number of visits to toilet per day (opening of bowels) in the two groups before and after the intervention showed a significant reduction (4.7±1.5 vs. 2.7±1.3 for the nortriptyline group, and 5.9±3.3 vs. 2.0±1.3 for mesalazine group). In contrast, mesalazine had a significantly better effect on number of opening of bowel/day between the two groups (P=0.019).

The results of this study show that use of mesalazine in contrast to nortriptyline did not have a better effect on mucus passage, straining on defecation and incomplete evacuation feeling after defecation (Table 3); however, the intervention in the two groups reduced the symptoms of IBS-D. No serious drug-related adverse events were reported during the study.

Table 3. Comparison of the other IBS symptoms after intervention

	Mesalazine (N=20)	Nortriptyline (N=20)	P.V*
Mucus passage (%)	1(5)	3(15)	0.72
Stool urgency (%)	1(5)	7(35)	0.018
Straining on defecation (%)	2(10)	7(35)	0.058
Feeling of incomplete evacuation after defecation (%)	1(5)	2(20)	0.151
*Fisher exact test			

Discussion

The etiology of IBS is unknown. However, it has been demonstrated that mental stress and psychological distress are correlated with development of IBS.[16] Due to the varied range of symptoms in patients with IBS, existing pharmacological treatments are largely targeted at symptom relief. Available therapies remain unsatisfactory and provide only symptomatic relief at best for many patients with IBS. Clinical trials have shown that IBS patients without a depressive disorder can benefit from low-dose tricyclic antidepressants (TCA) therapy.[17] TCA agents appear to normalize gastrointestinal (GI) motility and reduce visceral pain.[18,19] In this study, we hypothesized that mesalazine treatment, through its anti-inflammatory effects, will reduce the number of mast cells and thereby reduce abdominal pain and diarrhea.

The results of this study indicate that the use of mesalazine and nortriptyline has a positive effect on reducing IBS-D severity score over an 8- week interval. In contract, the improvement of the symptom score was greater with mesalazine compared with nortriptyline-treated patients. In a randomized trial on 360 patients with varying subtypes of IBS, treatment of IBS patients with mesalazine significantly reduced intensity and duration of pain in all subtypes of IBS.[20] Andrews et al. showed that mesalazine treatment is associated with a decrease in fecal bacteria abundance. In this study the patients responded favorably to mesalazine, with significant decrease in days with discomfort and increases in bowel movement

satisfaction.[21] Corinaldesi and et al. assessed the effect of mesalazine compared with placebo on mucosal immune cells in 20 patients with IBS. They showed that mesalazine considerably reduced immune cells compared with placebo, and mesalazine significantly increased general well-being (P=0.038), but had no significant effects on abdominal pain, bloating or bowel habits[12] unlike in our study. In a study in Iran, the researchers assessed the effect of amitriptyline (10 mg for 2 months) compared with placebo in treating of IBS-D. They showed that the amitriptyline group had greater reduction in the incidence of loose stool and feeling of incomplete defecation.[22]

Our results showed that other symptoms of IBS-D such as mucus passage, straining on defecation and feeling of incomplete evacuation in both treatment groups improved after 8 weeks of treatment period. However, there were no advantages for mesalazine compared with nortriptyline.

In this triple blinded, randomized clinical trial, treatment with mesalazine and nortriptyline significantly relieved abdominal pain and discomfort, decreased stool frequency and increased quality of life in patients with diarrhea-predominant IBS (IBS-D). Mesalazine in contrast to nortriptyline had a better effect on abdominal pain severity, quality of life and satisfaction with bowel habit. Therefore we recommend mesalazine as an anti-inflammatory agent for treatment of IBS-D in patients without psychological disorders.

Acknowledgement

The authors would like to thank all patients who kindly participated in this study. They also thank Shahroud University of Medical Sciences (Iran) for their support.

Conflict of Interest

The authors declared that they have no conflict of interest.

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