Original Article

Investigation the Effectiveness of Duloxetine in Quality of Life and Symptoms of Patients with Irritable Bowel Syndrome

Razieh Salehian, Marjan Mokhtare[1], Atefeh Ghanbari Jolfaei, Rouhallah Noorian

Department of Psychiatry, Iran University of Medical Sciences, Rasoul- E-Akram Hospital, [1]Department of Internal Medicine, School of Medicine Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran

Abstract

Background: Selective norepinephrine-serotonin receptor inhibitors (SNRIs) such as duloxetine have already shown beneficial effects on symptoms in irritable bowel syndrome (IBS) patients. The purpose of the present investigation was to assess the efficacy of duloxetine in the symptom and quality of life improvement in diarrhea predominant-IBS (IBS-D) patients. **Materials and Methods:** IN a randomized, double-blind and placebo-controlled study, sixty patients diagnosed with IBS-D (ROM-IV criteria), referred to the gastrointestinal clinic of Rasoul-e-Akram Hospital of Iran university of medical sciences, randomly assigned in the treatment groups, group A: patients who received 135 mg mebeverine tablet twice a day combined with 30 mg duloxetine capsule per day and group B, who received the same regimen, except for placebo capsule once per day instead of duloxetine for twelve weeks. The assessment was performed using the IBS severity index, and IBS quality of life questionnaire (IBS-QOF) at baseline, and weeks 4, 8, and 12 after beginning the treatment. Drug adverse effects and compliance to treatment were evaluated every 2 weeks after starting the treatment. **Results:** Sixty patients completed the trial. The duloxetine group showed significantly greater improvement on the IBS symptoms ($P < 0.001$), and the IBS-QOF ($P < 0.001$) in comparison to the placebo group at the endpoint. **Conclusions:** This study showed that adding duloxetine to mebeverine is safe with good efficacy on symptoms and QOL improvement in IBS-D patients. Besides, this study showed that 12 weeks' treatment duration is significantly more effective than 4 weeks' treatment, and drug adverse effects are more prominently seen in the first 2 weeks of treatment.

Keywords: *Duloxetine, Irritable Bowel syndrome, mebeverine, quality of life*

Introduction

Irritable Bowel Syndrome is one of the most common gastrointestinal dysfunctions affecting 5 to 20 percent of the world population[1], and its prevalence in Iran is 1.1 to 25 percent. More than 25% of these patients account for the patients visiting gastroenterologists. It causes significant impairment in the individuals' performance and incurs a lot of costs on the patient and the health system.[2] The exact etiology for this syndrome is not clear, but such factors as gut-brain axis problems, disorders related to bowel movements, pain sensitivity, infections, neurotransmitters, genetic factors, and food allergies have been reported as the factors involving in this disorder.[3,4] Serotonin is one of the most important neurotransmitters involved in this disease; 95% of the body's serotonin is found in the gastrointestinal tract, which is involved in the onset of peristaltic bowel movements, secretory reflexes, and visceral sensory perception.[5] 50-90% of patients with irritable bowel syndrome have psychiatric disorders, such as mood disorders and anxiety, so the use of psychotropic drugs in many patients can help improve their symptoms.[6]

Various treatments have been used so far for this syndrome, none of which has been able to completely improve the symptoms. Treatments are pharmacologic or non-pharmacologic. Pharmacologic approaches consist of the following: synthetic peripheral-opioid receptor agonists, antidiarrheal agents, antispasmodic agents, antidepressants, serotonin 5-HT3 antagonists, the non-absorbable antibiotic rifaximin, probiotics, bile acid sequestrated medicine, and/or supplementary medicines.[6] Indeed, antispasmodic agents have been commonly used worldwide for IBS-D treatment. Antidepressant agents, however, are more commonly used in the United States.[7]

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Address for correspondence:
Dr. Rouhallah Noorian, Department of Psychiatry, Iran University of Medical Sciences, Rasoul-e-Akram Hospital, Tehran, Iran.
E-mail: shahradnoorian2020@yahoo.com

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Given the high comorbidity of this syndrome with mood and anxiety disorders, one of the effective treatments for the syndrome and comorbid symptoms can be anti-depressants.[8,9] Various types of antidepressants, including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), have been used to treat the disease. Several studies have been conducted on the efficacy of these drugs which have different results. Some investigations showed the efficacy of tricyclic antidepressants such as amitriptyline, nortriptyline, and desipramine on various symptoms of irritable bowel syndrome, but their side effects in many cases are not tolerated by patients. SSRIs such as fluoxetine, citalopram, and paroxetine which have also been evaluated in various studies, revealed different results.[10-12]

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), which has been approved in the United States and Europe for the treatment of the major depressive disorder, generalized anxiety disorder, peripheral neuropathy in patients with diabetes and fibromyalgia, but it has not been approved for the treatment of irritable bowel syndrome.[13,14] In an open-label study on the duloxetine impact on symptoms of irritable bowel syndrome, duloxetine resulted in significant improvement in the severity of pain, the severity of illness, quality of life, anxiety, and disability at work and life, but this study was conducted on small sample size.[15] Considering the high prevalence of irritable bowel syndrome and its functional disorder associated with considerable costs for the individual and health system, paying attention to its treatment is crucially important. For this reason, the present study has investigated the effectiveness of duloxetine on the quality of life and symptoms of patients with irritable bowel syndrome.

Materials and Methods

Current research is applied research in terms of purpose, and it is a randomized double-blind placebo control study (RCT) in terms of the data collection method. This research has been approved by the ethics committee of Iran University of Medical Sciences with Number of IR.IUMS.REC.1397.947 and registered on the website to register clinical experiments performed in Iran at http://www.irct.ir: IRCT20200928048862N1. Research statistical population included patients referring to the gastrointestinal clinic of Rasoul-e-Akram Hospital whom Irritable Bowel Syndrome (IBS) was diagnosed based on Room-IV Criteria for Irritable Bowel Syndrome (IBS-D), and there was no suspicion of anxiety or depressive disorder based on the Hospital Anxiety and Depression Scale (HADS). Room-IV criteria include recurrent abdominal pain for at least one day per week and a minimum duration of one month, with at least two of the other factors associated with fecal excretion along with changes in fecal frequency and shape.

After completing the required examinations and submitting the required tests, when the diagnosis of irritable bowel syndrome based on Room IV criteria was made, all patients informed about the study and before completing the questionnaires, informed consent form was taken from the patient Then a psychiatrist interviewed the subjects for assessment regarding the criteria of the study and requested them to complete Hospital Anxiety and Depression Scale (HADS) questionnaires and informed consent from. The exclusion criteria included psychotic patients, bipolar patients, patients with obsessive-compulsive disorder, drug abuse in the past 6 months, dementia, recent suicidal thoughts, using the psychotropic drug in the last 2 weeks, pregnancy and breast-feeding, age under 18 and over 65, presence of risky symptoms such as gastrointestinal bleeding, persistent vomiting, persistent abdominal pain, unexplained weight loss, Crohn's disease, celiac disease, colon cancer, seizures, hypertension, closed-angle glaucoma, and untreated thyroid disease. Suspicion of anxiety or depressive disorder based on the Hospital Rating Scale (Score more than 10) was considered another exclusion criterion. The patients above 50 years old must have negative colonoscopy over the last three years.

The patients with each of these symptoms were excluded and finally, 60 patients with irritable bowel syndrome and the scores below 11 for Hospital Anxiety and Depression Scale (HADS), were selected.

The questionnaires of the IBS Severity Index and quality of life in IBS (IBS-QOF) were completed by all patients. Then they were randomly divided into two groups (n = 30) by the clinic secretary (the patients and researchers were not aware of it) [Figure 1]. One group was treated with tablet mebeverine 135mg twice daily plus a placebo, and the same dose of mebeverine along with 30 mg capsule duloxetine was prescribed for the other group. Both drugs were from Tadbir Kalay Jam Company. During the weeks of 4, 8, and 12, IBS Severity Index, and IBS-QOF were completed for the patients, and the required data were collected. The clinical interview and the questionnaires below were used for data collection:

A. Irritable Bowel Syndrome Severity Index (IBSSI):

It includes 5 items that examine IBS symptoms including pain, stooling disorder, flatulence, the effect of illness on daily activities, and extra-intestinal symptoms with IBS-SI (IBS Severity Index). The mean score of each part is a maximum of 100, and the total score of the questionnaire is a maximum of 500. Mild, moderate, and severe cases are represented by the scores of 75 to 175, 175 to 300, and above 300, respectively. Although none of the IBS symptom severity measurement tools has been fully validated, the above-mentioned tool is currently reported to be the best tool in most similar studies.[16]

B. Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire:

This questionnaire was designed originally by Huhen, with 30 items in 9 areas. This tool was later modified by Patrick

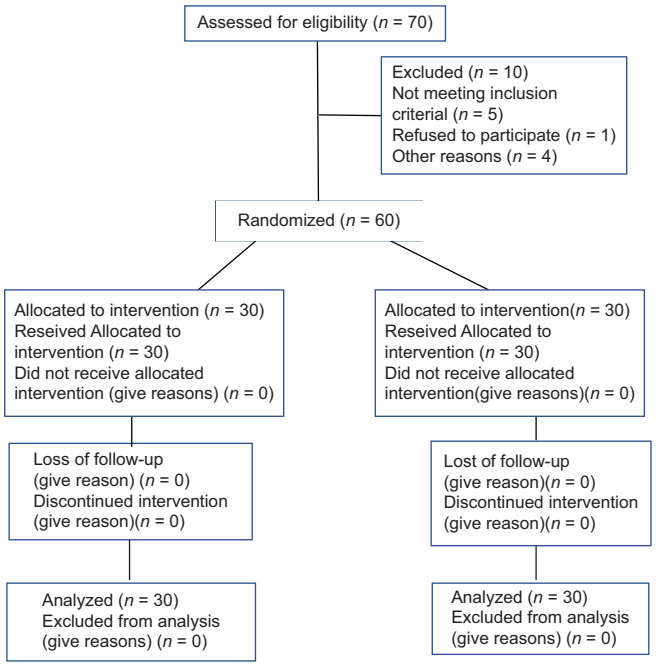

Figure 1: Flow diagram of subject progress through the phases of a randomized trial

et al. (2000), and included 34 items with a five-point Likert scale in 8 areas so follows Dysphoria, Interference with activity, Body image, Health worry, Food avoidance, Social reaction, Sexual and Relationship.[17] The score ranges between 0 and 100, and the time duration for its implementation by the patient was 10 minutes. The higher scores in this tool denote the worse quality of life. This tool has been examined in England, France, and Italy based on their culture. The Persian version of this questionnaire showed that it has good reliability (Cronbach's alpha as 0.95, ranging from 0.65 to 0.90) and validity with eight principal components.[18,19]

C. Hospital Anxiety and Depression Rating Scale (HADS):

This questionnaire consists of 14 items in two parts, 7 of which measure anxiety, and the other 7 items measure depression. Each item has 4 options. A score of 0-3 is assigned for each of these options. Scoring is such that score 3 indicates a high presence of anxiety or depression and a score of zero implies the minimum presence of anxiety or depression, the sum of scores on each of the two scales of anxiety or depression is in the range of 0-21. Scores 11-21 in each of the two scales are considered as the clinically suspected to disorder, scores 8 to 10 as the interstitial and abnormal, and scores 0 to 7 are considered healthy. Kaviyani validated the questionnaire with 0.70 alpha in the depression subscale, and 0.85 alpha in the anxiety subscale and examined reliability through test-retest in the depression subscale (r = 0.77 P <.001) and the anxiety subscale (r = 0.81, P <.001)[20].

The sample size of the study was calculated according to the sample size formula with the maximum type I error of 5% and type II error of 20% and the probability of difference detection of 17.36. The sample size was calculated for each group as 25, and it was considered as 30 in each group considering the probability of sample loss.

Data were entered into SPSS software and scores of quality of life and severity of disorder were reported by the mean and SD. Nominal variables were reported by obvious frequency and numerical variables were reported by mean and SD. The normal distribution of variables was analyzed by the Kolmogorov-Smirnov test. Using the Chi-square test or Fisher's exact test for the nominal data, mean comparison tests such as independent t-test or ANOVA were performed for quantitative data of the nominal data.

Results

Baseline characteristics

From a total of seventy patients screened for this study, 60 patients had the study criteria and were randomly assigned to this trial of mebeverine plus duloxetine and mebeverine plus placebo with 30 patients in each group. All 60 patients (30 in each group) completed the trial. The baseline characteristic of the patients is summarized in Table 1. There was no significant difference in baseline Irritable Bowel Syndrome Severity Index (IBSSI) and Irritable Bowel Syndrome Quality of Life (IBS-QOL) scores between the two groups of patients.

Irritable Bowel Syndrome Severity Index (IBSSI)

Baseline total score didn't differ significantly between the two groups [MD: (95%CI) =0.9 (-8.2 to 10), t (40) =0.201, P = 0.84]. Repeated measures ANOVA indicated a significant effect for time-treatment interaction [Greenhouse-Geisser: F (2.324, 92.957) =11.980, P < 0.001]. By week 12, patients in the duloxetine group experienced significantly greater reduction in their IBSSI score than the placebo group [MD: (95%CI) =-15.81 (-22.3 to -9.4), t (40)=-4.972, P < 0.001] [Table 2].

Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire

Baseline positive subscale score didn't differ significantly between the two groups [MD: (95%CI) =-0.6 (-4.3 to 3.1), t (40) =-0.312, P < 0.001]. Repeated measure ANOVA showed a significant effect for time-treatment interaction [Greenhouse-Geisser: F (2.549, 101.95) =10.678, P < 0.001]). By week 12, patients in the duloxetine group experienced significantly greater reduction in their IBS-QOL score than the placebo group [MD: (95%CI) =-14.6 (-16.5 to 8.4), t (40) =-3.641, P < 0.001] [Table 2].

Adverse effects

In comparison to drug side effects in two groups, some side effects were recognized throughout the study. Applying the fisher's exact test, the frequency of side effects didn't differ significantly between the duloxetine and the placebo group [Table 3].

Discussion

The results of this study showed that duloxetine improves patient's quality of life and severity of irritable bowel syndrome. Duloxetine is used in the treatment of some mood and neurological disorders and chronic pain conditions such as migraine headaches, diabetic neuropathy, and fibromyalgia. Similarly, antidepressants are effective in treating symptoms of IBS and other functional gastrointestinal disorders. Patients who have taken antidepressants for their IBS symptoms have reported significant improvement in their abdominal pain and reduction in other IBS symptoms, such as diarrhea, constipation, bloating, nausea, or urgency.[21]

Several studies examined the efficacy of tricyclic antidepressants (TCAs) on the IBS symptoms. Foorotan *et al*. compared the effects of fluoxetine, amitriptyline, and nortriptyline on IBS symptoms, and reported that all three drugs improve abdominal pain, bloating, and functional performance. Amitriptyline and nortriptyline decrease the rate of stool excretion in both IBS groups (with diarrhea or constipation predominance), whereas fluoxetine can improve gastrointestinal motility in people with IBS constipation.[15] In the study by Vahedi *et al*., it was shown that amitriptyline improves IBS symptoms more than placebo.[22] In a randomized controlled study by Rajagopalan *et al*., Amitriptyline caused higher improvement in the general symptoms and feeling of well-being and reduction of abdominal pain compared to placebo.[17] In another study, desipramine improved abdominal pain, stool frequency, diarrhea, and less depression than placebo.[18] In a study investigated the effect of doxepin on symptoms of irritable bowel syndrome, doxepin improved the patient's symptoms.[19] The side effects of TCAs such as drowsiness, dry mouth, constipation, and orthostatic hypotension in many cases are not tolerated by patients and can result in drug withdrawal.

In addition to TCAs, some studies were conducted to evaluate the efficacy of SSRIs or SNRIs on the IBS symptoms. SSRIs revealed different results and have been discontinued in most cases due to their sexual side effects.[13-15] For example, it has been shown that citalopram has no superiority over placebo in controlling IBS symptoms.[20]

Recently, several studies explored the duloxetine add-on effect on IBS symptoms. Kaplan A *et al*., conducted a 12-week, open-label trial of duloxetine in 13 subjects with irritable bowel syndrome and comorbid generalized anxiety disorder, and examined the efficacy of duloxetine in improvement in symptoms and quality of life in patients with both conditions by using the Hamilton Anxiety Rating Scale, IBS Quality of Life (IBS-QOL) Scale, and IBS Symptom Severity Scale (IBS-SSS). This study revealed a significant reduction in both symptoms of anxiety and IBS components including IBS-SSS and IBS-QOL improvements.[23]

Lewis-Fernández R *et al*., in an open-label, 12-week trial explored efficacy, tolerability, and time to onset of action of duloxetine in comorbid irritable bowel syndrome (based on meeting Rome III criteria) and Major Depressive Disorder (IBS-MDD), and assessed both the rate of change of the gastrointestinal symptoms and the depression. The results showed that duloxetine has led

Table 1: Demographic characteristics of the patients

Variables	Placebo (*n*=30), *n* (%)	Duloxetine (*n*=30), *n* (%)
Age, mean±SD (years)	42.4±7.8	41.4±5.9
Marital status		
Single	10 (72)	13 (80)
Married	20 (28)	17 (20)
Divorced	-	-
Level of education		
Illiterate	1 (4.7)	-
Primary school	15 (71.4)	17 (85.7)
High school diploma	14 (19)	13 (14.2)
University degree		

SD: Standard deviation

Table 2: Changes from baseline in the irritable bowel syndrome quality of life and irritable bowel syndrome severity index

Variable	*t* (40)	*P*	Effect size (Cohen's *d*)
IBSSI			
Duloxetine	−4.972	<0.001	−1.3
Placebo			
IBS-QOL			
Duloxetine	−3.641	<0.001	−1.2
Placebo			

IBSSI: Irritable bowel syndrome severity index, IBS-QOL: Irritable bowel syndrome quality of life

Table 3: Frequency of the side effects in the two study groups

Side effect	Placebo (%)	Duloxetine (%)
Asthenia	23.8	14.2
Constipation	9.5	19
Diarrhea	9.5	23.8
Dizziness	23.8	28.5
Insomnia	14.2	19
Headache	23.8	28.5
Other	4.7	9.5

to significant improvement in gastrointestinal symptoms and MDD symptoms. Similar to our study, they observed that IBS symptoms improved gradually. This trial like the previous study had some limitations including the lack of placebo control, modest sample size and restriction to patients with comorbid psychiatric disorders (GAD or MDD).[24]

Regarding the IBS symptoms, factors such as mood and anxiety disorders should be considered, so the use of psychotropic drugs in many patients can help improve their symptoms.[25] Brennan *et al*. conducted an open-label 12-week trial of duloxetine 60 mg daily in patients with IBS. The subjects were 15 and they had not a concurrent major depressive disorder. Abdominal pain, IBS symptoms, Clinical Global Impression-Severity, Hamilton Anxiety Rating Scale, IBS Quality-of-Life Scale, and Sheehan Disability Scale were considered as the outcome measures. From 14 patients who completed at least one post-baseline evaluation, 8 completed the study. Duloxetine in this trial was associated with significant improvement in pain, loose stool, the severity of illness, work and family disability, quality of life, and anxiety. In that small, open-label study, duloxetine appeared to be effective for many features of IBS, but its adverse effects, most notably constipation, limited its use. Similar to our study, the researchers excluded individuals with concurrent major depression.[14]

The results of the current study indicate that duloxetine as an add-on to mebeverine has a significant beneficial effect on the symptoms of IBS. Since the current study excluded individuals with the suspicion of a concurrent major depressive or anxiety disorder, it appears that duloxetine may have beneficial effect on IBS independently of its psychotropic effects.

Conclusively, it is desired that duloxetine, as a selective serotonin-norepinephrine receptor inhibitor (SNRI) be able to provide patients with the benefits of serotonin and norepinephrine in the brain without potential peripheral adverse effects. The results of this study should be interpreted with consideration of its limitations. Small sample size, restriction to IBS-D, and short observation period are the major limitations of this study. These results may be confirmed in more prolonged trials with larger sample sizes to ensure study power. Also, it should be mentioned that the IBS symptom scale is limited to assessing behavioral problems; therefore, patient function improvement had not measured.

In conclusion, this double-blind, placebo-controlled clinical trial revealed duloxetine as a tolerable adjunct to mebeverine with improvement in IBS-D symptoms. Additional studies with long-term follow-up periods seem to be essential to reinforce clinical use of adjuvant duloxetine in IBS patients.

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Conflicts of interest

There are no conflicts of interest.

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