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Potential Benefit of Fluoxetine Adjuvant Therapy to Mebeverine in Patient with Irritable Bowel Syndrome

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Abstract

Background: Irritable bowel syndrome is an important form of functional bowel disease. Mebeverine is a well-known antispasmodic that has been successfully used for many years to treat IBS. The preference for utilizing selective serotonin reuptake inhibitors is frequently significant because psychological issues are associated with the etiology of IBS.

Objectives: The study aimed to examine the effect of adding Fluoxetine as adjuvant therapy to Mebeverine on symptoms of irritable bowel syndrome.

Materials and Methods: This study examined the effects of fluoxetine 20 mg capsule and Mebeverine 135 mg tablet on IBS symptoms. A total of 44 patients were recruited into the study. Twenty-one patients were given 135 mg of Mebeverine twice daily before meals by the doctor, and twenty-three patients were given 20 mg of fluoxetine once daily at bedtime in addition to 135 mg of Mebeverine twice daily before meals for two weeks.

Results: After two weeks of treatment with Mebeverine and fluoxetine there was a highly significant drop in the proportion of patients who reported substantial abdominal pain, and significant urgency ($P < 0.01$), which was absent in the group receiving Mebeverine ($P>0.05$) only. Both study groups had highly significant reductions in flatulence and stomach bloating within the first two weeks of treatment ($P < 0.01$).

Conclusion: The findings revealed a highly significant and substantial decline in the abdominal pain, abdominal bloating, flatulence and substantial urgency in the group receiving both drugs (Mebeverine and fluoxetine) which result in more relief of irritable bowel symptoms in those patients.

Keywords: Irritable Bowel Syndrome; Mebeverine; Fluoxetine; Abdominal Pain; Flatulence

1. Introduction

Irritable bowel syndrome (IBS) is believed to be one important form of functional bowel disease. Which affects 50% of all gastrointestinal consultations (1). A symptom-based diagnosis of IBS is typically regarded as accurate if any alarming symptoms, such as anemia, weight loss, and a family history of colon cancer, have been ruled out (2). Patients with IBS may experience a decreased quality of life and level of productivity due to the burden of the condition (3). Mebeverine is a well-known antispasmodic that has been successfully used for many years to treat IBS(4). The preference for utilizing selective serotonin reuptake inhibitors (SSRIs) in pain and constipation-predominant IBS results from the fact that current treatments for constipation-predominant IBS are not ideal (4–6), and are frequently significant because psychological issues are associated with the etiology of IBS. Currently, it is anticipated that fluoxetine would be effective

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in treating IBS(7). The study aimed to examine the effect of adding Fluoxetine as adjuvant therapy to Mebeverine on symptoms of irritable bowel syndrome

2. Materials and Method

2.1. Study design

Randomized cross-sectional study examined the effects of fluoxetine 20 mg capsule and Mebeverine 135 mg tablet on IBS symptoms.

2.2. Patients

A total of 44 patients (22 male, 22 female) were recruited into the study with IBS diagnosed by physician according to Rome 3 criteria (7) between January 2022 to May 2022 and followed up for two weeks.

Group 1 was included twenty-one patients were given 135 mg of Mebeverine twice daily at 20 minutes before meals by the doctor, and group 2 was included twenty-three patients were given 20 mg of fluoxetine once daily at bedtime in addition to 135 mg of Mebeverine twice daily at 20 minutes before meals for two weeks.

Another four patients; one on Mebeverine alone withdrew from the research because of the development of a rash, three on Mebeverine with fluoxetine withdrew from the research (two of them leave the treatment due to anorexia and the other leave the treatment due to gastroesophageal reflux disease). After two weeks, the symptoms and side effects were evaluated.

This study recruited adult patients from community-based gastroenterology clinic.

The patients invited to participate in the study after explaining the aim of the study. Written informed consent was obtained from all patients of the study. Information regarding their identity obtained during the study has been strictly kept confidential.

2.3. Inclusion criteria

- IBS was definitively diagnosed by clinical diagnosis or by Rome III criteria.
- Age above 18 years old.

Patients who failed to meet these requirements or who refused to complete the questionnaire were not included in the analysis.

Age, gender, marital status, employment status, sense of bloating, consistency of stool, number of bowel movements per week, duration of symptoms, presence of urgency or incomplete evacuation, and lastly, whether or not there has been a change in bowel habits are all information that is gathered directly from the patients.

Symptoms monitored during study period include abdominal pain which scored from 1(none) to 5(very sever) and gastrointestinal symptoms that involve abdominal bloating, flatulence, urgency, and the feeling of incomplete evacuation which also scored according to self-rated scale (which derived from the validated Gastrointestinal Symptom Rating Scale (GSRS) from 0 (no discomfort at all) to 6 (very sever discomfort).

Patients with significant IBS syndrome are who have ≥ 4 points in abdominal pain, abdominal bloating and flatulence (7). After two weeks the symptoms were either relieved or unchanged.

2.4. Statistics

For statistical analysis, Minitab 16.1 (2010) was employed. Data presented as percentages, integers, and (mean SD). Independent t-test was used to test between groups; chi square test of association was used. Result of analysis considered not significant if ($P > 0.05$), *significant if ($P < 0.05$), and **highly significant if ($P < 0.01$).

3. Results

The following characteristics did not significantly differ across research groups: mean age, gender, marital status, education level, employment status, IBS subtypes, symptom durations, and number of bowel movements per week ($p \geq$

0.05). Mean age in group 1 was (35.90 ± 12.70) years, while it was slightly higher in group 2 (42.96±15.44). 50% of participants in each group were female, with slightly more males in group 2 than in group 1. (54.5 % compared to 45.5 % in group1). In both study groups, the majority of the patients were unmarried (66.67 % in group1 and 78.26% in group 2). Regarding educational attainment, a greater proportion of patients in both groups had a B.Sc (33.3 % in group 1 and 43.5 % in group2). In both groups, the constipation subtype predominated (47.6 %in group 1 and 69.6 % in group 2), whereas the mixed subtype came in second in both groups (38 % in group 1 and 17 % in group2). More than 80% of patients in both groups had IBS symptoms that had persisted for more than a year (85.7 % in group 1 and 82.6% %in group2). The majority of the study participants have at least one bowel movement every day (47.6% in group 1 and 60.9 % in group 2) [table 1].

Table 1 Demographic and disease characteristics of study groups patients

Variables	**Mebeverine group Group 1**		**Fluoxetine +Mebeverine group Group 2**		**P value**
Mean age ±SD(years)	**35 ± 12.70**		**42.96 ± 15.44**		**0.104^{NS} ©**
	No	**%**	**No**	**%**	
Gender					
-Male	10	45.50	12	54.50	0.09^{Ns}®
-Female	11	50.50	11	50.50	
Marital status					
-Married	7	33.30	5	21.74	0.388 N.S
-Previously married	0	0.00	0	0.00	
-Never married	14	66.67	18	78.26	
Education					
-Less than high school	4	19.00	6	26.10	0.450 N.S
-High school graduate	6	28.60	6	26.10	
-College graduate	7	33.30	10	43.50	
-Advanced degree	4	19.00	1	4.30	
Employment					
-employed	12	57.10	11	47.80	0.488 N.S
-not working	8	38.10	11	47.80	
-disabled	0	0.00	4.20		
-student	4.80		0	0.00	
IBS subtypes					
-Diarrhea	3	14.30	3	13.00	0.268 N.S
-Constipation	10	47.60	16	69.60	
-Mixed	8	38.10	4	17.40	
Duration of symptoms:					
-6 months-1 year	3	14.30	4	17.40	0.778^{NS}
-1> year	18	85.7	19	82.60	
Bowel movements per/week					
≥ 1 /day	10	47.60	14	60.90	0.236 N.S

2-3/wk	1	4.80	3	13.00	
3-4/wk	5	23.80	1	4.30	
4-5/wk	5	23.80	5	21.70	

© independent t-test was used to test between groups, ® chi square test of association was use, N.S: non-significant

According to the findings, after 2 weeks of treatment, group 2 patients who received Fluoxetine with Mebeverine showed a highly significant drop in the proportion of patients reporting substantial abdominal pain and significant urgency compared to baseline ($P < 0.01$), which was not observed in group 1 receiving Mebeverine alone ($P > 0.05$). Compared to baseline, the results showed a high significant decrease in the proportion of patients who demonstrated substantial bloating and flatulence after two weeks of treatment for both study groups ($P < 0.01$). The study showed a highly significant drop in the proportion of patients with severe urgency after two weeks of treatment in group 2 patients ($P < 0.01$), which was not observed in group1 patients ($P >0.05$). The percentage of patients who were reported to have a feeling of incomplete evacuation was significantly decreased ($P <0.05$) after two weeks of group 2 patients, a difference that was not observed in group1 patients ($P > 0.05$).

However, this study did not find a significant difference in gastrointestinal symptoms or abdominal pain between the two study groups before and after treatment ($P > 0.05$).

Table 2 Assessment the effect of fluoxetine adjuvant therapy on IBS symptoms

Gastrointestinal symptoms	**Mebeverine group**		**Fluoxetine +Mebeverine group**		**P value**
	No	**%**	**No**	**%**	
Significant Abdominal pain					
Before	7	33.30	14	60.90	0.591 N.S
After	3	14.30	3	13.00	
P value	0.137 N.S		0.001**		
Significant abdominal bloating					
Before	12	57.10	19	82.60	0.998 N.S
After	2	9.50	3	13.00	
P value	0.001**		0.001**		
Significant urgency					
Before	2	9.50	7	30.40	0.140 N.S
After	1	4.80	0	0.00	
P value	0.547 N.S		0.002**		
Significant flatulence					
Before	16	76.20	18	78.30	0.992 N.S
After	2	9.50	2	8.70	
P value	0.001**		0.001**		
Significant feeling of incomplete evacuation					
Before	1	4.80	5	21.70	0.050 N.S
After	1	4.80	0	0.00	
P value	1.00 N.S		0.011*		

N.S: non-significant, *: significant, **: highly significant

Table 3 revealed no adverse effects in (68.2%) fluoxetine- treated IBS patients. Only 11.1% and 9.1% of IBS patients receiving fluoxetine reported experiencing nausea and headaches, respectively. Only 2.3% of fluoxetine-treated IBS patients reported other adverse effects, such as anorexia, decreased libido, rash, esophagitis, anxiety, and sleeplessness.

Table 3 Adverse effect observed by IBS patients treated with fluoxetine

Adverse effects observed by IBS patients treated with fluoxetine	No	%
No adverse effect	30	68.20
Headache	4	9.10
Nausea	5	11.10
Anorexia	1	2.30
decrease libido	1	2.30
Rash	1	2.30
Esophagitis	1	2.30
Anxiety	1	2.30
Insomnia	1	2.30

4. Discussion

Typically, treating IBS patients presents a challenge (8). Numerous studies demonstrated the effectiveness of antidepressants in treating IBS patients (9-13).

In humans, serotonin (5-HT) demonstrated a critical role in controlling intestinal motility. It is not entirely clear, yet, whether changes to the colonic 5-HT system have a role in the pathogenesis of IBS. One study found that IBS patients with constipation as their primary symptom had considerably higher levels of 5-HT in their mucosal specimens than did IBS patients with diarrhea as their primary symptom and control subjects (14). Additionally, there is mounting evidence that SSRIs can shorten oroceacal transit time (15). Thus, using SSRIs in IBS patients who experience constipation seems hopeful.

According to a previous recommendation, in addition to prescribing lifestyle and nutritional recommendations, it was suggested to take antispasmodics for IBS (16). It is feasible that a successful treatment for gut issues may require a combination or mixed medications due to the process's redundancy in numerous gut functions control, including the neuromuscular, neuro-immune, and neurosensory (17).

In the present study, fluoxetine, an SSRI was used in addition to Mebeverine to determine how well these medications worked to treat gastrointestinal symptoms. The findings revealed a highly significant decline in IBS symptoms like abdominal pain, bloating, urgency and flatulence.

The efficacy of fluoxetine, have been conflicting, but generally favorable. According to one study, a daily dose of 20 mg of Fluoxetine helps reduce the symptoms of IBS without the need for titration (8). If an SSRI is chosen to treat IBS, medication shouldn't be discontinued for lack of effectiveness. Another study by Kuiken et al. indicated that fluoxetine had no effect on IBS patients' rectal sensitivity, but that it did considerably reduce stomach pain in a subgroup of IBS patients known as "hypersensitive individuals exclusively" (18).

The half-life of fluoxetine is 4-6 days, but its activity lasts for a long period since Nor-fluoxetine, its active metabolite, has a half-life of up to 15 days (19). Another possible explanation is that the recurrence threshold is raised once symptoms have normalized. It can be said that taking fluoxetine at a modest dose may help IBS sufferers manage their symptoms. Both of these theories need to be supported by several, carefully constructed investigations (8). It's possible that persons with IBS who are constipation-predominant may benefit from intermittent fluoxetine medication.

SSRI medication may be especially beneficial for IBS patients who also suffer from concomitant anxiety or depression (20). The present study revealed no adverse effects in (68.2%) fluoxetine- treated IBS patients. Only 11.1% and 9.1%, respectively, of patients in the same group of patients reported experiencing nausea and headaches.

Although there was no significant difference between the side effects of any of the SSRIs used to treat IBS patients and placebo in clinical trials, each medication carries the risk of sleep disturbance, sexual dysfunction, weight gain, and serotonin syndrome, which are all conditions that are common in the general population. Given the evidence to support using SSRIs for IBS treatment after trying other options without success (20).

Conclusion: The current study concluded that there is a highly significant and substantial decline in the abdominal pain, abdominal bloating, flatulence and substantial urgency in the group receiving both drugs (Mebeverine and fluoxetine) which result in more relief of irritable bowel symptoms in those patients. However, this study did not find a significant difference in gastrointestinal symptoms or abdominal pain between the two study groups before and after treatment ($P > 0.05$).

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

The samples were collected from the donors with informed verbal consent.

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