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Original Article

Comparison of Metronidazole and Placebo in Control of Gaseous Symptoms in Patients with Functional Bowel Disorders; A Randomized Double- blind Controlled Study

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ABSTRACT

Background: To compare the efficacy of metronidazole versus placebo in the control of gaseous symptoms in patients with functional bowel disease.

Materials and Methods: In the absence of organic or systemic diseases, all cases with chief complaints of bloating and normal laboratory tests were consecutively enrolled in this double-blind study. Lactase deficiency and bacterial overgrowth were ruled out by the lactose breath test. Patients were randomly assigned to receive either metronidazole or placebo. Demographic characteristics as well as frequency and severity of the patients' scores (mean total symptom score) before and after therapy, their compliance and drug adverse effects were evaluated. A 50% decrease in the total symptom scores was defined as effective treatment.

Results : During one year, 46 patients (17 males, 29 females, mean age: 38.9 ± 9.9 years) were enrolled in the study. A total of 23 patients received metronidazole (cases) and 23 received placebo (controls). Two patients in the metronidazole group did not tolerate the drug and one patient in the placebo group did not continue with follow-up. Patients responded similarly to both regimens: 59% of patients in the placebo group and 52.2% of patients in the metronidazole group had a 50% decrease in their total symptom score ($p = 0.64$). Side effects of metronidazole were frequent, but tolerable. Bad taste in the mouth and anorexia were the most common complaints in the metronidazole group.

Conclusion : This study showed no difference between placebo and metronidazole in relief of bloating and other related complaints in patients with functional bowel disease.

Keywords : Irritable bowel syndrome; Antibacterial agents; Colonic Diseases; Functional

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INTRODUCTION

Functional abdominal bloating comprises a group of functional abdominal disorders dominated by a feeling of abdominal fullness or bloating that lack sufficient criteria to be defined as another functional gastrointestinal disorder. There is no proven effective therapy for functional bloating and its cause is unknown(1).

Drugs such as simethicone and activated charcoal have been used to treat gaseous symptoms, but the few studies attempting to demonstrate their efficacy have reported contrasting results(2-3). Antimicrobials have also been tested for reducing colonic H_2 production, although with conflicting results(4-7). Personally, we have seen that antibiotics may be effective in the control of gaseous symptoms in patients with functional bowel disease. We selected metronidazole which has been shown to be highly effective against

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anaerobic bacteria. Our aim was to compare the effect of metronidazole and placebo on the gas-related symptoms of functional abdominal bloating patients.

MATERIALS AND METHODS

The study was approved by the institutional review board of the Digestive Diseases Research Center of Tehran University of Medical Sciences, according to the declaration of Helsinki. Informed consent was obtained according to the guidelines of the institute.

Subjects

Patients seen consecutively in private clinics or the GI clinic of Shariati hospital who suffered from functional abdominal bloating, fulfilled the functional abdominal bloating criteria1(1) and presented with chief complaint of bloating were enrolled in the study. The absence of any organic disorder was confirmed by physical examination and patients underwent the following laboratory tests: complete blood count, erythrocyte sedimentation rate, serum calcium level, fasting blood sugar, T4, TSH, AST, ALT, alkaline phosphatase, creatinine, and stool culture (for occult blood, leukocytes, ova and parasites), and lactose hydrogen breath test (H_2BT)(8). Patients with an early rise in breath hydrogen were considered to be probably affected by bacterial overgrowth; those with a late rise with lactose deficiency(9).

Exclusion criteria were: any underlying condition diagnosed by abnormal findings in the above-mentioned evaluation (including but not limited to malabsorption and diarrhea), pregnancy, breast feeding, history of sensitivity to metronidazole, age less than 12 years, history of liver diseases, history of organic diseases (including diabetes mellitus, hypothyroidism, and scleroderma), the use of antibiotics within one month prior to entering the study, previous abdominal surgery, and refusal to give informed written consent.

Study design

This study was a randomized, controlled double-blind trial to compare the effect of metronidazole with that of placebo upon frequency and severity of abdominal gaseous symptoms. Both placebo and metronidazole (250 mg) in the same shape were used orally three times daily for ten days.

Patients were instructed to maintain their usual diet throughout the entire study period and not to take any drugs with gastrointestinal effects during the study period.

Symptom score

Before and three weeks after receiving the drugs, symptoms were evaluated in all patients by means of the severity and frequency of bloating, abdominal pain, borborygmi, gas incontinence, eructation and flatulence. Each of these symptoms was given a score depending on its severity and frequency as presented in Table 1. The symptom score, assessed by personal interview, was used as a global index for the assessment of each gaseous symptom. The sum of the scores attributed to the individual symptoms (total symptom score, TSS) was then calculated to obtain the final score for the above-mentioned symptoms. A 50% decrease in the total symptom scores was defined as treatment success.

Data analysis

Quantitative data were presented as mean±standard deviation. Paired samples t-test was used to compare the change of TSS and the McNemar test was used to compare treatment success, in each group. The chi-square test (and Fischer's exact test where appropri-

Table 1: Scores for gaseous symptoms.

	Description	Score
Severity	No complaint	0
	Mild: tolerable	1
	Moderate: intervention required (diet change or drugs)	2
	Severe: interrupting daily activity	3
Frequency	No complaint	0
	Less than once a week	1
	1-2 days per week	2
	More than 2 days per week	3
Symptom score	Severity score × frequency score	0 - 9

Table 2: The frequency of associated gaseous symptoms.

Symptom	Frequency (%)
Flatulence	95.6
Borborygmi	68.9
Abdominal pain	55.6
Eructation	57.8
Gas incontinence	33.3

Table 3: Symptom scores before and after treatment in each group.

Symptom		Score before therapy	Score after therapy	*p*-value
Bloating	Placebo	7.09±2.11	3.22±3.2	<0.001
	Metronidazole	6.5±2.3	3.65±2.9	0.001
Abdominal pain	Placebo	1.90±2.07	0.85±1.1	0.014
	Metronidazole	1.27±2.02	0.50±0.50	0.06
Flatulence	Placebo	3.7±2.8	2.1±2.2	0.009
	Metronidazole	4.8±3.3	2.6±3.3	0.001
Eructation	Placebo	2.4±3.06	1.2±2.2	0.024
	Metronidazole	2.2±3.1	1.5±2.6	0.162
Borborygmi	Placebo	2.5±2.4	1.4±1.9	0.032
	Metronidazole	2.13±2.4	1.5±2.4	0.019
Gas incontinence	Placebo	0.95±2.2	0.35±0.9	0.186
	Metronidazole	2.31±3.5	1.7±3.2	0.142

Table 4: Side effects of metronidazole and placebo in the control of gaseous symptoms of patients with bloating.

Side effect	Metronidazole, n (%)	Placebo, n (%)	*p*-value
Bad taste	11 (47.8)	3 (13)	0.01
Nausea	7 (30.4)	4 (17.4)	0.49
Vomiting	4 (17.4)	2 (8.7)	0.67
Headache	7 (30.4)	4 (17.4)	0.49
Diarrhea	5 (21.7)	3 (13)	0.70
Skin rash	4 (17.4)	2 (8.7)	0.67
Anorexia	8 (34.8)	4 (17.4)	0.18

ate) was used to compare success and side-effects of the regimens. $P < 0.05$ was considered significant for all tests.

RESULTS

During one year, 78 patients with gaseous symptoms and normal laboratory findings underwent lactose H_2BT. There were 21 patients with bacterial overgrowth (BOG) and 11 with lactase deficiency who were excluded. A total of 46 cases (17 male and 29 female) with a mean age of 38.9 ± 9.9 years were enrolled in the study. A total of 23 patients received metronidazole (cases) and 23 placebo (controls). The frequency of associated gaseous symptoms is shown in Table 2.

Two patients in the metronidazole group did not tolerate the drug and one patient in the placebo group did not continue the follow-up. Patients responded similarly to both regimens: 13 (59.1%) patients in the placebo group and 12 (52.2%) patients in the metronidazole group had a 50% decrease in their TSS ($p = 0.64$). The mean TSS in the placebo group was 17.8 ±5.7 before and 9.1±7.1 after treatment ($p < 0.001$). The mean TSS in the metronidazole group was 19.7±8.9 before and 11.2±11.4 after the treatment ($p < 0.001$). Symptom scores before and after treatment are presented in Table 3.

Side-effects were seen more frequently in the metro-

nidazole group (Table 4), but the difference was not statistically significant for most variables.

DISCUSSION

This study showed that the effect of metronidazole in the treatment of patients with gaseous symptoms may be due to a "placebo effect" rather than the antimicrobial activity of the drug.

We used the lactose H_2BT for our patients because the use of two separate breath tests for BOG (lactulose or glucose) and lactase deficiency (lactose) in patients with IBS is time consuming and unfeasible. This test may not accurately distinguish between BOG and lactase deficiency(9), however this limitation will not affect our results, because we excluded both groups from the study.

Another issue for our diagnostic approach is the sensitivity of the lactose H_2BT for the detection of BOG. Pimentel et al. have reported that on comparing the maximum hydrogen production between the lactose and lactulose breath tests, there was a significant correlation between these two tests, which suggested that the abnormality seen on the lactose breath test could represent bacterial overgrowth rather than lactose intolerance(10). However, breath tests have a moderate sensitivity (16.7%-78%) for the detection of BOG(11-15) and we believe that in using this approach, some cases with BOG might not have been excluded from our study. However, a similar response of our patients in both groups may support the concept that the majority of our patients were not affected by BOG.

Pimentel et al. have reported that the lactulose H_2BT was abnormal in up to 84% of IBS subjects and that neomycin resulted in a 35.0±5.0% reduction in composite score, when compared with a 11.4 ± 9.3% reduction in the placebo group ($p < 0.05$)(11). Their primary outcome measure was based on a composite score calculated from the three main IBS symptoms (abdominal pain, diarrhea, and constipation). The scoring system used in our study comprised of only gaseous symptoms and not symptoms of other types of functional abdominal disorders. We found higher response rates in our study. The inclusion of symptoms such as constipation might result in a misclassification bias leading to lower response rates, as seen in Pimentel's study.

DiStefano et al.(12) compared rifaximin and activated charcoal for patients with gas-related functional bowel disorders, including BOG. They showed that in patients with gas-related symptoms, the colonic production of H_2 increased and rifaximin significantly reduced the overall severity of symptoms in contrast to charcoal. Some studies(13-16) have also found better symptom relief in IBS subjects treated with antibiotics than placebo-treated patients, which suggested that bacteria may play a role in IBS symptoms. These studies have recruited IBS patients and antibiotics were effective (in contrast to placebo) in the presence of BOG or excessive H_2 production. There are two major differences to be considered; first, we included patients with functional abdominal bloating who were unlikely to have BOG and second we found a considerable efficacy for placebo in these patients. An explanation for this finding is that the response of our patients might be due to a "placebo effect" in patients with a probable underlying psychological condition. In a recent study, Pimentel et al.(7) found a significant effect of rifaximin for relief of IBS symptoms that included bloating. In this study, the patient who might have BOG or lactase deficiency was not excluded, which may have been a major limitation. Another limitation was the small number of patients enrolled in the study.

Our study is in agreement with the fact that, as with other manifestations of functional abdominal disorders, psychological factors, a low threshold for distention of the colonic lumen, an exaggerated motor response to normal amounts of gas and gut hyperalgesia are the pathophysiologic basis of gaseous symptoms(14-15). This variety of gastrointestinal complaints is commonly attributed by the patient to "excess gas" even though this perception is usually incorrect. In one study, the average volume of intestinal gas in patients with complaints of chronic gaseousness and controls was similar(16). We did not assess any psychological factor in our patients and a final judgment on the matter requires further investigation.

Because of recurrent symptoms, some patients with proven BOG require repeated courses of therapy and others need treatment on a regular basis (e.g. the first 5 to 10 days out of every month)(17). However, treatment for IBS is likely to be long-term and the use of antibiotics might be detrimental for intestinal bacteria or might also influence the development of functional bowel syndromes(18).This approach could also produce side-effects and is not cost effective. Therefore unless it is proven that the patient has bacterial over-

growth, it is not recommended to use antibiotics in cases with gaseous symptoms. If these cases are unresponsive to other modalities such as the avoidance of foods that may contribute to the problem as an obvious initial step, additional tests, such as testing for bacterial over growth, are recommended.

In conclusion, we suggest that patients with functional abdominal bloating should be treated with other modalities used to reduce the threshold of pain sensation. Antibacterial agents should be kept for unresponsive cases with proven BOG. Current treatment recommendations for functional abdominal bloating include "reassurance and education" and "restriction of gas forming foods"1, but addition of an inert drug might be considered, if our findings are approved by other studies. Until now, probiotics seem to be safe and well tolerated in patients who suffer from frequent bloating and flatulence(19).

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