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ORIGINAL ARTICLE

Comparison of Rifaximin and Trimebutin Maleate Treatment for Irritable Bowel Syndrome with Constipation and Diarrhea

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Abstract

Introduction: Irritable bowel syndrome (IBS) is a functional gastrointestinal disease with changes in bowel habits, abdominal pain, and gas without any organic pathology. IBS is divided into three types as constipation – IBS (IBS-C), diarrhea – IBS (IBS-D), and mixed. Rifaximin is an antibiotic that improves IBS symptoms by improving the flora in the intestine. The aim of the study was to determine whether the treatment of rifaximin is superior to treatment.

Methods: This study performed retrospectively and patients were divided into two groups as IBS-C and IBS-D. Each group was divided into two groups as rifaximin and Trimebutin Maleate treatment. Rifaximin at a dose of 200 mg, 3×2 daily for 15 days. Trimebutin Maleate group includes lifestyle modification and Trimebutin Maleate 200 mg 3×1. At the end of the treatment and after 20 days, the patients were re-evaluated.

Results: A total of 179 subjects had examined. In terms of IBS symptoms; bloating, abdominal pain, and stool consistency, both treatments are effective as long as patients continue treatment; however, 20 days after the end of the treatment, rifaximin treatment was found to be more effective than trimebutin maleate treatment.

Discussion and Conclusion: The use of rifaximin provides significant long-term improvement in both diarrhea and constipation IBS patients compared to Trimebutin Maleate treatment.

Keywords: Constipation; diarrhea, irritable bowel syndrome; rifaximin; trimebutine maleate.

Irritable bowel syndrome (IBS) is a chronic, recurrent disease characterized by abdominal pain, bloating, discomfort, constipation, and diarrhea attacks without detectable organic problems. The prevalence of the disease ranges from 1% to 20% and is the most common gastrointestinal functional disorder, mostly seen in the 20–50 years age group. Although seen in both genders, it mainly affects females, with approximately 75% of patients reported to be female[1]. The pathophysiology is not fully known, but genetic predisposition, intestinal permeability, and intestinal-brain interaction are defined as the underlying mechanisms. It is also thought that intestinal microbiology may be a major cause[2]. Since there is no clear diagnostic marker to confirm the diagnosis of IBS, the diagnosis can be made by exclusion of other possible diseases and is based on the ROME IV criteria. In these criteria, diarrhea is classified as diarrhea dominant (IBS-D), constipation dominant (IBS-C), and mixed type (IBS-M) (Table 1). In addition, IBS subtypes are determined according to stool consistency using the Bristol stool form scale (Fig. 1). Constipation is a very common clinical entity and is thought to be caused by extension

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Table 1. Rome IV ırritable bowel syndrome-subtypes criteria

IBS-C: More than one-fourth (25%) of bowel movements with Bristol stool scale types 1–2 and less than one-fourth (25%) with Types 6–7.

IBS-D: More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 6–7 and less than one-fourth (25%) with Types 1–2.

Figure 1. Bristol stool scale.

of colon transit time. IBS-C is at least as common as IBS-D. In both of these forms, diarrhea and constipation treatment, nutritional and lifestyle changes, and symptomatic treatment are used. However, patients often benefit from these treatment methods only for as long as they use the drugs or they do not benefit at all. This situation requires new treatment approaches. It has been suggested that intestinal mycobacteria in IBS patients may be different from those of healthy individuals. According to this, an effective treatment method on the microbiota is expected to improve the symptoms of the disease[3]. Rifaximin is an effective antibiotic produced from rifampin active ingredient and is reliable because of its low systemic absorption[4]. It is also effective on gram negative, gram positive, aerobes, and anaerobes. This wide spectrum of effects is thought to have a healing effect on the intestinal flora.

Materials and Methods

This retrospective study was performed between 2016 and 2017. Cases with abdominal pain, bloating, mild-to-moderate diarrhea, and constipation were included in the study. The patients included were those with no pathology found in laboratory tests for the past 3 years. Patients with inflammatory bowel disease, thyroid hormone disorder, cancer history, electrolyte disorder, drug use, chronic disease, or antibiotic use in the past 3 months were excluded from the study, and those with a history of intra-abdominal surgery, including cholecystectomy and except appendectomy, were also excluded from the study. The patients were separated into two groups as IBS-C and IBS-D. Each group was sub-divided into two groups as the rifaximin and Trimebutine Maleate group. 200 mg rifaximin, 3×2 per day for 15 days and Trimebutine Maleate 200 mg 3×1 per day for 15 days. All the patients were evaluated for IBS symptoms before and 20 days after treatment. The number of stools was counted per week in the IBS-C patients and per day in the IBS-D patients. The Bristol stool form scale was used for the fecal form (Fig. 1). Statistical analyses were performed using the Statistical Package for the Social Sciences Program (SPSS) 13.0 software. Chi-square and Student's t-tests were applied in the comparisons of data. $p<0.05$ was accepted as statistically significant.

Statistical Analysis

We estimated the sample size for trimebutin maleate group and rifaximin group would meet the criteria for the primary end point (i.e., would have adequate relief of global IBS symptoms, as assessed weekly) for at least 2 of the first 3 weeks after treatment. With these assumptions, a sample of 179 patients would be needed in each group for the studies to have 95% power to show the 15-percentage-point difference between the groups, at a significance level of 0.05.

All efficacy and safety analyses were performed on a modified intention-to-treat population, which included all patients who received at least one dose of the study drug. Missing data were imputed with the use of the last-observation-carried-forward method, whereby missing values were replaced with the last nonmissing value; baseline values were not carried forward. Two sensitivity analyses were conducted, one in which missing data were regarded as indicating that the patients who terminated the study prematurely had had no relief of symptoms, and the other in which missing data were imputed with the use of the multiple-imputation method.

Binary data (i.e., data on the proportion of patients who had or did not have adequate relief of symptoms) were analyzed with the use of logistic regression; fixed-effect terms included the study group and the analysis center. There were five analysis centers, which we formed prospectively by group-

ing the study centers according to geographic region to assess the effects of geographic location on the end points. For the analysis of ordinal data (i.e., data on the number of months in which patients had relief for at least 2 weeks), we used the proportional-odds model for the ordinal outcome. The number of consecutive months with relief during the first 3 weeks after treatment. We analyzed the changes from baseline in continuous outcomes (i.e., symptom scores) by fitting fixed-effects linear models to the data. An initial model with terms for treatment, analysis center, baseline ratings of the response variable, and interaction of baseline ratings with treatment was fitted. The interaction term was tested at the 0.05 level. A non-significant interaction was dropped from the model in subsequent analyses.

Spearman correlation analyses were applied to the mean change from baseline in daily assessments of adequate relief of IBS symptoms (yes or no) to determine whether the weekly assessments of adequate relief paralleled the pattern seen with the daily assessments. Safety data were summarized with the use of descriptive statistics.

The study was approved by our local ethical committee (Antalya Training and Research Hospital Ethical Committee).

Results

Evaluation was made of 64 IBS-D and 33 IBS-C patients in the rifaximin group (Tables 2, 3). The mean age was 38 years (range, 22–54 years) and 43 years (range, 24–52 years), respectively, with no statistically significant difference determined (p>0.05). The ratio of females was 52.4% in the IBS-D group and 51.7% in the IBS-C group compatible with literature. In the rifaximin IBS-D group, abdominal pain and abdominal discomfort were reported in 58 (90.6%) patients before treatment, 24 (37.5%) patients after the treatment, 25 (39%) patients 20 days after treatment, and a significant difference was determined (p=0.001). Defecation with mucus was observed in 21 (32.8%) patients in the rifaximin IBS-D group before treatment, in 4 (6.2%) patients after treatment, in 4 (6.2%) patients 20 days after treatment, and a significant difference was determined (p=0.001). The mean number of daily defecations in the rifaximin IBS-D group was 3.8 (2–9) before treatment and this decreased significantly to 2.1 (2–5) after treatment and 2.3 (2–5) at 20 days after treatment (p<0.05). In the rifaximin IBS-D group fecal form according to the Bristol scale was type 5–6 in 47 (73.3%) patients and type 7 in 17 (26.7%), type 5–6 in 24 (37.4%), type 7 in 5 (8%), and type 3–4 in 35 (54.6%) after treatment. At 20 days after treatment, the rates were almost the same.

Before treatment, the duration of defecation (stay time in the toilet) in the IBS-D group was 10 min at a time and 60 min per day. After treatment, the stay time in the toilet was 5 min at a time, 45 min per day.

As can be seen from all these results, the clinical improve-

Table 2. Clinical features of rifaximin IBS-D group before and after treatment

	Irritable bowel syndrome - diarhea (n/%) 64 (100%)			p	
	Before treatment, n (%)	After treatment, n (%)	20 days after treatment, n (%)	p1	p2
Bloating	52 (81.25)	38 (59.3)	34 (53.1)	<0.001	<0.0.1
Abdominal pain, discomfort	58 (90.6)	24 (37.5)	25 (39)	0.001	<0.00.1
Mucus defecation	21 (32.8)	4 (6.2)	4 (6.2)	0.001	0.001
tenesmus	22 (30.2)	12 (18.7)	13 (19.2)	<0.05	<0.00.1
Number of defecation, day	3.8 (2–7)	2.1 (2-5)	2.3 (2–5)	<0.05	<0.05
Stool form (Bristol)					
Type 3–4		35 (54.6)	34 (53.1)	<0.001	<0.01
Type 5–6	47 (73.3)	24 (37.4)	26 (38.9)	<0.001	<0.01
Type 7	17 (26.7)	5 (8)	5 (8)	<0.05	<0.05
Defecation time (min)					
At once	10	5	5	<0.05	<0.05
Day	60	15	15	<0.05	
Anal disease (hemorrhoids, fissure)	33 (51.5)	25 (39)	25 (39)	<0.05	<0.05

IBS-D: Irritable bowel syndrome – diarrhea; min: Minute; p1: Ratio between pretreatment and post-treatment; p2: Ratio between pretreatment and 20 days after treatment.

Table 3. Clinical features of rifaximin IBS-C group before and after treatment

	Irritable bowel syndrome - constipation (n/%) 33 (%100)			p	
	Before treatment, n (%)	After treatment, n (%)	20 days after treatment, n (%)	p1	p2
Bloating	30 (90.9)	16 (48.4)	15 (47)	<0.00.1	<0.00.1
Abdominal pain, discomfort	29 (87.8)	14 (42.4)	13 (39.3)	<0.00.1	<0.00.1
tenesmus	19 (57.5)	9 (27.2)	8 (24.2)	<0.00.1	<0.00.1
Number of defecation, week	1	3	3	<0.05	<0.05
Stool form (Bristol)					
Type 3–4	24 (72.7)	13 (39.3)	12 (36.4)	<0.05	<0.05
Type 5–6	9 (27.2)	12 (36.3)	13 (39.4)	<0.05	<0.05
Type 7		8 (24.2)	8 (24.2)	<0.01	<0.01
Feeling of anal blockage	16 (48.4)	8 (24.2)	9 (27.2)	<0.05	<0.05
Manual evacuation	8 (24.2)	2 (6.06)	2 (6.06)	<0.05	<0.05
Defecation time (min)	20	10	10	<0.05	<0.05
Laxative use	23 (69.6)	8 (24.2)	9 (27.2)	<0.01	<0.01
Anal disease (hemorrhoids, fissure)	28 (84.8)	22 (66.6)	19(57.5)	>0.05	>0.05

IBS-C: Irritable bowel syndrome – constipation; min: minute; p1: Ratio between pretreatment and post-treatment; p2: Ratio between pretreatment and 20 days after treatment.

ment continued even 20 days after the end of treatment.

Evaluation was made of 44 IBS-D and 38 IBS-C patients in the Trimebutine Maleate treatment group (Tables 4, 5); The mean age was 37 years (range, 21–48 years) and 40 years (range, 27–51 years), respectively, with no statistically significant difference determined (p>0.05). The ratio of females was 54% in the IBS-D group and 52.6% in the IBS-C group compatible with literature. In the trimebutine maleate treatment IBS-D group, abdominal pain and abdominal discomfort were reported in 36 (81.8%) patients before treatment and in 28 (63.6%) patients after the treatment and a significant difference was determined (p<0.05). At 20 days after the end of the treatment, abdominal pain and discomfort were reported in 32 (72.7%) patients, with no significant difference determined (p>0.05).

Defecation with mucus was observed in 16 (36.3%) patients in the Trimebutine Maleate therapy IBS-D group before treatment, in 12 (27.2%) patients after treatment, and in 13 (29.5%) at 20 days after treatment, and a significant difference was determined (p>0.05). The mean number of daily defecations in the Trimebutine Maleate therapy IBS-D group was 4 (2–8) before treatment and this decreased significantly to 2.9 (2–7) after treatment (p<0.05). At 20 days after treatment, the number was 3.5 (2–8) (p>0.05). Fecal form, according to the Bristol scale was type 5–6: 32 (72.7%) and type 7: 12 (27.2%) before treatment and type 5–6: 23 (52.2%), type 7: 8 (18.1%), and type 3–4: 13 (29.5%) after treatment. At 20 days after treatment, these rates were type 5–6: 28 (53.6%), type 7: 10 (22.7%), and type 3–4: 8 (18.1%). Before treatment, the duration of defecation (stay time in the toilet) in the Trimebutine Maleate IBS-D group was 10 min at a time and 60 min per day, and after treatment, 5–10 min at a time, 45 min per day. At 20 days after treatment, the stay time in the toilet was the same as before treatment. When the rifaximin IBS-D and trimebutine maleate therapy IBS-D groups were compared, the rifaximin group was significantly different in terms of abdominal pain, discomfort in the abdomen, mucus stools, number of daily stools, normalization in the form of stools, and the duration of defecation at the end of treatment and 20 days after treatment.

33 patients were evaluated in the rifaximin IBS-C group (Table 3). Abdominal pain and abdominal discomfort were seen in 30 (90.9%) patients before treatment, in 16 (48.4%) patients after treatment, and in 15 (47%) 20 days after treatment and a significant difference was observed (p<0.001).

The mean number of defecations per week was 1 (1–4) before treatment, 3 (2–7) after treatment, and at 20 days after treatment was the same as after treatment (p<0.05).

The defecation time (duration of toilet stay) in the rifaximin IBS-C group was 20 min at 1 time before treatment and 10 min after treatment and at 20 days after treatment (p<0.05).

Thirty-eight patients were evaluated in the trimebutine maleate treatment IBS-C group (Table 5). Abdominal pain and abdominal discomfort were seen in 33 (86.8%) patients

Table 4. Clinical features of Trimebutin Maleate therapy IBS-D group before and after treatment

	Irritable bowel syndrome – diarrhea (n/%) 44 (100%)			p	
	Before treatment, n (%)	After treatment, n (%)	20 days after treatment, n (%)	p1	p2
Bloating	38 (86.3)	28 (63.6)	33 (75)	<0.05	>0.05
Abdominal pain, discomfort	36 (81.8)	28 (63.6)	32 (72.7)	<0.05	>0.05
Mucus defecation	16 (36.3)	12 (27.2)	13 (29.5)	>0.05	>0.05
tenesmus	14 (31.8)	10 (22.7)	12 (27.2)	>0.05	>0.05
Number of defecation, day	4 (2–8)	2.9 (2–7)	3.5 (2–8)	<0.05	>0.05
Stool form (Bristol)					
Type 3–4		13 (29.5)	8 (18.1)	<0.05	>0.05
Type 5–6	32 (72.7)	23 (52.2)	28 (63.6)	<0.05	>0.05
Type 7	12 (27.2)	8 (18.1)	10 (22.7)	<0.05	>0.05
Defecation time (min)					
At once	10	5–10	10	<0.05	>0.05
Day	60	45	60	<0.05	>0.05
Anal disease (Hemorrhoids, fissure)	23 (52.2)	14 (31.8)	20 (35.4)	<0.05	>0.05

IBS-D: Irritable bowel syndrome – diarrhea; min: Minute; p1: Ratio between pretreatment and post-treatment; p2: Ratio between pretreatment and 20 days after treatment.

before treatment and in 24 (63.1%) patients after treatment and there was a significant difference (p<0.05). This finding in 28 (73.7%) patients 20 days after treatment showed no significant difference (p>0.05).

In the trimebutine maleate treatment IBS-C group, the mean number of weekly defecations was 1.1 before treatment and 3.1 after treatment (p<0.05). At 20 days after treatment, the mean number of weekly defecations was 1.3 and there was no significant difference (p>0.05).

The defecation time (stay time in toilet) in the trimebutine maleate IBS-C group was 20 min at 1 time before treatment and 15 min after treatment and 20 days after treatment and there was no significant difference (p>0.05).

Table 5. Clinical features of trimebutin maleate therapy IBS-C group before and after treatment

	Irritable bowel syndrome – constipation (n/%) 38 (%100)			p	
	Before treatment, n (%)	After treatment, n (%)	20 days after treatment, n (%)	p1	p2
Bloating	33 (86.9)	24 (72.7)	28 (84.8)	p<0.05	p>0.05
Abdominal pain, discomfort	32 (96.8)	26 (78.7)	28 (84.8)	p<0.05	p>0.05
tenesmus	18 (54.5)	10 (30.3)	14 (42.4)	p<0.05	p>0.05
Number of defecation, week	1.1	3.1	1.3	p<0.05	p>0.05
Stool form (Bristol)					
Type 3–4	28 (84.8)	19 (57.5)	24 (63.1)	p<0.05	p>0.05
Type 5–6	10 (30.3)	11 (33.3)	10 (26.4)	p<0.05	p<0.05
Type 7		8 (24.2)	4(10.5)	p<0.05	p<0.05
Feeling of anal blockage	14 (42.4)	8 (24.2)	10 (30.3)	p<0.05	p<0.05
Manual evacuation	7 (21.2)	2 (6.06)	5 (13)	p<0.05	p>0.05
Defecation time (min)	20	15	20	p>0.05	p>0.05
Laxative use	28 (84.8)	18 (54.5)	24 (72.7)	p<0.05	p>0.05
Anal disease (hemorrhoids, fissure)	30 (90.9)	24 (72.7)	22 (66.6)	p>0.05	p>0.05

IBS-C: Irritable bowel syndrome – constipation; min: Minute; p1: Ratio between pre-treatment and post-treatment; p2: Ratio between pre-treatment and 20 days after treatment.

When the rifaximin and trimebutine maleate treatment groups were compared, the rifaximin group was significantly different in terms of abdominal pain and abdominal discomfort, weekly number of stools and defecation time especially in respect of the findings at 20 days after treatment. Stool form was significantly improved in both groups at the end of treatment and no difference was observed between the groups. At 20 days after treatment, the stool forms of the Trimebutine Maleate treatment group were similar to before the treatment.

Discussion

IBS is the most common digestive system disease in adults. However, almost half of patients have complaints that start in childhood, occur from time to time and progress until adulthood. Although it is not an organic problem, IBS disrupts quality of life, and the treatment cost is a serious economic burden. Current therapies are generally only symptomatic and are only useful for as long as they are used. Despite lifestyle changes and fiber supplementation, patient recovery does not reach desired levels. Therefore, research is ongoing into both the cause and new treatment methods. Although it is controversial whether bacteria play a role in IBS, 165 intestinal floras have been shown to trigger symptoms. It has been shown that effective and long-term symptomatic relief can be achieved in IBS patients with appropriate antibacterial treatment[5]. Recently, rifaximin has been used in IBS patients because of the lack of systemic absorption, wide spectrum of effects and changes in intestinal flora. Nearly 97% of rifaximin is excreted in the feces without being absorbed, so systemic side effects will be negligible[6]. Rifaximin was first approved in 2004 by the FDA for tourist diarrhea induced by Escherichia Coli. Since 2010, it has been used in hepatic encephalopathy patients as it decreases the ammoniac level by decreasing the number of bacteria in the small intestine. It is also used to treat bacterial overgrowth in the small intestine through the same mechanism[5], then it also started to be used in IBS-D[6]. However, recent studies have been conducted on the use of rifaximin in IBS-C patients[7]. Numerous studies have been conducted on patients with IBS-D. In the randomized, double-blind, placebo-controlled phase 3 TARGET 1 and TARGET 2 trials, 1260 patients were given 550 mg rifaximin 3 times a day for 15 days. After treatment, the patients were followed up for 10 weeks and significant improvements were reported. In comparison with the placebo group ($p<0.001$). Other studies have shown that recurrent rifaximin treatment was beneficial at the rate of almost 75%, and even with repeated treatment, there was no drug resistance and the efficacy increased significantly[8,9]. The randomized, double-blind, and placebo-controlled TARGET 3 trial was performed in 270 centers in 2014. Rifaximin was given 550 mg 3 times a day for 2 weeks and after 4 weeks, a significant improvement was observed in abdominal pain and stool consistency[10]. In the current study, IBS-D symptoms were significantly improved with rifaximin treatment and this improvement was maintained at 20 days after the end of the treatment. However, the continuity of improvement in the trimebutine maleate treatment group was low as the improvement in complaints was only observed for as long as the treatment was taken, and the disease symptoms were observed again at 20 days after the cessation of treatment.

Recently, there have been promising results of the effectiveness of rifaximin on IBS-D. As constipation is known to develop with an increase in colon transit time a study published in 2018 examined the effect of rifaximin on colon transit time. In that study, 23 patients with constipation and 68 patients without constipation were evaluated in respect of stool shape, colon transit time, and frequency of defecation. Patients who received rifaximin and placebo were compared, and the results showed that colon transit time improved by 66.7% in the rifaximin group and there was no improvement in the placebo group. Similarly, the frequency of defecation and stool form was significantly improved in the rifaximin group ($p=0.05$)[11]. In another study, 33 patients with IBS-C used rifaximin for 14 days and it was seen to be highly effective[13]. In the current study, a significant improvement was determined in the frequency of defecation with rifaximin treatment in the IBS-C group ($p<0.05$). In general, both the IBS-D and IBS-C groups benefitted significantly from rifaximin treatment. However, in the trimebutine maleate group, despite the significant improvement in the complaints and findings of the patients during the treatment period the improvements were not maintained.

The small groups of the study sample and the retrospective nature of the study can be viewed as limitations of this study. Another limitation was that the findings were subjective rather than objective measurements. For example, a study by Ghoshal et al.[8] was based on the more objective finding of evaluation of the improvement in constipation with rifaximin by the reduction of methane production.

Conclusion

İn this study, rifaximin improved the constipation in IBS-C patients by decreasing the colon transit time, decreasing

the number of daily stools and improving the fecal form in IBS-D patients compared to the Trimebutine Maleate treatment group. To support the outcome of this study, there is a need for further, more extensive, and prospective studies.

Ethics Committee Approval: Antalya Training and Research Hospital, 2019-189.

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