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RESEARCH ARTICLE

Effect of non-absorbable antibiotic, rifaximin in patients with irritable bowel syndrome: A single-center randomized controlled study

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ABSTRACT

Background: Irritable bowel syndrome (IBS), most common functional bowel disease, does not have a definite treatment. Studies revealed the involvement of bacterial overgrowth for its pathology. The aim of this study is to evaluate the effect of a non-absorbable antibiotic. **Aims and Objectives:** The primary objective of the study is to assess the efficacy of a 14 days course of oral rifaximin at 400 mg thrice daily in patients with IBS without constipation. The secondary objective of this study is to evaluate the safety of a 14 days course of rifaximin at 400 mg thrice daily as compared with placebo in patients with IBS without constipation. **Materials and Methods:** In this single-center, randomized, placebo-controlled study, we recruited patients, using Rome III criteria in 2 years. Treatment group received rifaximin 400 mg thrice daily for 2 weeks. All patients underwent symptom assessment and safety assessment before inclusion, at the end of the treatment and 1 week after the regimen. Primary endpoint (proportion of patients who achieved adequate relief of IBS symptoms) and Likert scales of symptoms of both groups were compared. **Results:** Proportion of subject, who achieved adequate relief of IBS symptoms in the rifaximin arm, is more than placebo (68% vs. 39.1%). At the end of 2 weeks therapy, both groups show significant improvement in bloating score ($P < 0.002$), pain score ($P < 0.001$), and overall score ($P < 0.002$) and it continued for 1 more week. There were no significant adverse effects reported. **Conclusion:** A 2 weeks course of 400 mg rifaximin thrice daily regimen provided a significant improvement in global IBS symptoms**.**

KEY WORDS: Irritable Bowel Syndrome; Rifaximin; Non-absorbable Antibiotic; Randomized Controlled Study

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorders. IBS is characterized by recurring symptoms of abdominal pain, bloating, and altered bowel function in the absence of structural, inflammatory, or biochemical abnormalities. Living with IBS symptoms can also result in increased social anxiety, stress, and a lower quality of life. Even though there is variation from country to country, IBS appears to affect up to 20% of the given population. Due to its high prevalence, substantial morbidity, and enormous cost,[1] it is an important clinical entity. Even though etiology is unknown, alteration in normal flora is considered among the contributors of symptoms associated with IBS.

There is no definite physical abnormality or biological marker to define IBS. The diagnosis is based on ROME III criteria.[2]

Initially, investigators considered antidepressants for treatment of IBS. In IBS patients, it has improved symptoms,

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but it has low efficacy and was associated with serious side effects. In 1980s, studies proved that abnormal gut motility was commonly found in patients with IBS. Especially in diarrhea predominant IBS, gut motility is too fast, and in constipation-predominant IBS, gut motility is too slow.

Due to this association of IBS with peristalsis, researchers then focused on drugs that mediate serotonin levels in the GI tract. Initially, these drugs were successful in improving IBS symptoms. However, the only marketed and approved drug by the Food and Drug Administration (FDA) is alosetron hydrochloride. Due to serious adverse effects like ischemic colitis and constipation, its use is restricted to female patients with severe diarrhea predominant IBS in whom conventional treatments have failed. Tegaserod maleate (5-HT_4 agonist) is another serotonin agent approved for women with constipation-predominant IBS. However, due to serious cardiovascular adverse effects, it was withdrawn from the market.

Due to lack of serotonin-based safe drugs and other effective IBS treatments,[3,4] researchers then focused on bacterial involvement in IBS.[5] Studies revealed that up to 84% of IBS subjects have an abnormal lactulose hydrogen breath test.[6] Clinical trials using antibiotics (metronidazole, neomycin, ciprofloxacin, and doxycycline) indicated that antibiotic therapy may be an effective treatment for symptoms associated with IBS. Neomycin reduces bacterial overgrowth, but it has only suboptimal efficacy in the elimination of bacterial overgrowth.[7] Furthermore, side effects limit the use of neomycin. Other antibiotics used in controlling SIBO were also found to be less efficacious. Moreover, these antibiotics are reserved for systemic infection.

An ideal antibiotic for IBS is definitely one with low systemic absorption, minimal side effects and good efficacy for controlling bacterial overgrowth. RIFAXIMIN, a poorly absorbed antibiotic with excellent tolerability, has shown high eradication rates of bacterial overgrowth.[8]

Rifaximin is a new non-absorbable oral antibiotic derived from rifamycin. It has a broad spectrum of activity against Gram-positive, Gram-negative aerobic and anaerobic enterobacteria.[9] Due to its low systemic bioavailability, it is suitable in the treatment of GI tract infections. In May 2004, the FDA approved rifaximin for travellers' diarrhea at the dose of 200 mg taken 3 times a day for 3 days in adults and children >12 years. There are few studies suggesting the role of rifaximin in the treatment of IBS. However, no such studies are reported from Asian countries. Therefore, we are conducting this study to assess the efficacy and safety of rifaximin in IBS patients.

MATERIALS AND METHODS

The study was conducted in the outpatient department of gastroenterology of a tertiary care hospital in Kerala. This was a randomized controlled study for 1½ year. IBS patients were diagnosed using Rome III criteria.[2] Patients who consented to participate were then interviewed to collect relevant data. Data were collected in a case record form (CRF) specifically designed for study.

The study included subjects more than 18 years of age of both gender**,** with confirmed IBS diagnosis. During the screening phase, symptom score required for entry into the study was scores more than three. Subject must maintain a stable diet during the course of study.

Subjects presenting with symptoms of constipation-predominant IBS, ulcer, diverticulitis, gastroesophageal reflux diseases, inflammatory bowel disease, GI malignancy, pancreatitis, psychiatric disorders, HIV infection, and thyroid disorder are excluded from the study. Persons with drug or alcohol abuse also were excluded from the study.

The Institutional Ethics Committee approval was obtained before commencement of the study. All recruited subjects were randomized in 1:1 ratio in the following two treatment arms by simple systematic randomization.

Treatment A: Rifaximin 400 mg TID for 14 days.

Treatment B: Placebo TID for 14 days.

Subjects were undergone the following phases, and we recorded the relevant details in the CRF.

1. Screening phase: This includes informed consent, screening assessments including colonoscopy. In this phase, the subjects were asked to score the IBS-related symptoms according to their severity in a severity scoring system.
2. Treatment phase: (Day 1–14): Starting on day 1, eligible subjects received the study drug and the placebo according to the randomization for 14 days. Interim clinic visits occurred at day 7 and day 14.
3. Follow-up phase: Subjects were followed up for a minimum of 1 week after completion of treatment. During this phase, subject's response to treatment and severity scores were recorded again.

The total duration of the study was approximately 4 weeks depending on whether a colonoscopy is required. Periodic safety monitoring (symptom-directed physical examination, vital sign measurement, laboratory testing, and recording adverse events) was done during the study.

Primary efficacy endpoint of the study is the proportion of subjects who achieved adequate relief of IBS symptoms at the end of 2 weeks treatment. Adequate relief of IBS symptoms is defined as a response of "yes" to the following subject global assessment question.

Q: In regard to your IBS symptoms, compared to the way you felt before you started study medication, have you had adequate relief of your IBS symptoms? (yes/no)."Secondary efficacy endpoint is the proportion of subjects who achieve adequate relief of IBS-related symptoms such as bloating, abdominal pain, and overall symptoms were scored in a 7-point LIKERT scoring system as 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal 5 = a great deal, and 6 = a very great deal.

Assessment is done by asking the following questions to the patients:

1. In regard to your specific IBS symptom of bloating; on a scale of 0–6, how bothersome was your IBS-related bloating today?
2. In regard to your specific IBS symptom of abdominal pain and discomfort; on a scale of 0–6, how bothersome was your IBS-related abdominal pain and discomfort today?
3. In regard to all your symptoms of IBS; on a scale of 0–6, how bothersome were your symptoms of IBS today?
4. Number of stools
5. Consistency of stool is recorded in a 5-point scoring system (1 = very hard, 2 = hard, 3 = formed, 4 = loose, and 5 = watery)
6. Sense of urgency asked as follows: Have you felt or experienced a sense of urgency today? (yes/no).

These assessments were carried out before starting treatment, during treatment, and 1 week after treatment.

The laboratory parameters assessed in this study include hemoglobin, total leukocyte count, platelet count, serum creatinine, serum bilirubin, ALT, and AST. We compared those parameters in both groups before and after treatment.

Patients who completed the 2 weeks treatment and came for regular follow-up were only included in the final analysis.

Statistical Analysis

Mean age of both groups was calculated and compared using independent sample *t*-test.

The primary efficacy endpoint is a binomial data. We assessed the significance using Chi-square test. The symptoms such as bloating, abdominal pain, and overall symptoms were assessed before treatment, during treatment, and during follow-up using a 7-point Likert scoring scale. Kruskal–Wallis test was used as the test of significance**.** Symptoms such as consistency of stool and number of stools were also assessed this way.

We assessed the presence of urgency before and after the treatment. We calculated the response rate in those who had a feeling of urgency before treatment. Any response to treatment and its significance among both groups was assessed using Chi-square test. In all analysis, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 17.

RESULTS

A total of 149 patients were included in this study. Patients were randomized into treatment and placebo arm. A total of 75 patients were included in the treatment arm, and 74 patients were included in the placebo arm. Mean age of patients in rifaximin group was 35.15 and that of placebo group was 39.01. Baseline laboratory parameters such as hemoglobin, total count, ESR, platelet count, RBS, creatinine, bilirubin, ALT, and AST are comparable. The study shows that patients treated with rifaximin respond better than control group with regard to the global symptoms of IBS.

In rifaximin group, 68% of patients had a good response, and in the control group, 39.1% of patients had response. IBS-related symptom scores such as bloating score, pain score, and overall score improved with rifaximin treatment. The statistical difference was significant when compared to placebo.

This study also revealed that other IBS symptoms such as consistency of stool, number of stool, and urgency to pass stool also improved significantly in rifaximin group compared to control group.

The current study did not report any major side effects related to rifaximin. However, there were minor adverse effects which were comparable in both rifaximin arm and control group.

DISCUSSION

IBS has a great impact on the quality of life. Treating IBS is important because it improves the quality of life and hence improves the health resources and the reduced work productivity. This study has shown that a short course of rifaximin is highly effective in IBS patients without constipation. The study has demonstrated that the non-absorbable broad-spectrum antibiotic, rifaximin had a statistically significant improvement in global symptoms compared to placebo.

Several studies were conducted in the past to address the issue of antibiotics in IBS patients. However, studies pertaining to rifaximin are limited. During literature search, a similar study of this antibiotic in India was not found, thereby considering this study as the first study from our country in this regard.

In this study, 68% of patients in the rifaximin arm and 39% of patients in the placebo arm showed response to treatment. The difference was statistically significant and patients in the rifaximin arm benefited from the treatment. Better response was demonstrated in patients of rifaximin arm in terms of

pain score, bloating score, and overall assessment. Other parameters addressed in this study were a number of stools and consistency of stool. These parameters also improved significantly better in rifaximin arm compared to placebo arm. In this study, 64.1% of patients had relief of urgency in the rifaximin arm compared to 32.4% of patients in the placebo arm. This difference was statistically significant. In current study, the rifaximin arm performed better than placebo arm in all parameters assessed in the study.

There are a number of previous studies which addressed the role of rifaximin in IBS.

An initial study of rifaximin in IBS was published in 2006 by Sharara *et al*.[10] In this study, all IBS patients irrespective of subgroups were included in the study. The global symptom improvement was studied in 70 patients. Rifaximin 400 mg twice daily dose was given for 10 days. The response rate was 27% in rifaximin group and 9.1% in placebo group, suggesting that patients who used rifaximin had a better response. Another study which was published in 2006 by Pimental *et al*. also showed a better response of rifaximin in IBS patients.[7] Here, rifaximin 400 mg thrice a day dose was used and antibiotic was given for 10 days. The response rate was 32.6% in rifaximin group and 9.1% in placebo group.

In 2008, Lembo *et al.* revealed that in patients, IBS rifaximin produced a better response when compared with placebo.[11]

In this study, only patients with diarrhea predominant IBS were included. The response rate of patients was 52.3% and that of placebo was 44.2%.

This difference was statistically significant. Another recent study by Pimental *et al*. in 2011 included patients who had IBS without constipation.[12] Patients were assigned to either rifaximin group at a dose of 550 mg or to placebo group 3 times daily for 2 weeks. These patients were followed for additional 10 weeks. The primary endpoint was adequate relief of IBS symptoms. The proportion of patients who had adequate relief of IBS in terms of bloating and gas was assessed weekly. 40.8% of improvement was reported in patient who had taken rifaximin compared to 31.2% for patients who had taken placebo. Secondary endpoints included the proportion of patients who had a response to treatment. The response was assessed by daily self-rating of global IBS symptoms and individual symptoms of bloating, abdominal pain, and stool consistency during follow-up period. The study concluded that rifaximin was effective in significant relief of IBS symptoms including bloating, abdominal pain, and loose or watery stools. One limitation of the above study was no breath test was performed to define the percentage of patients who had small intestinal bacterial overgrowth (SIBO). Hence, the study did not specifically consider the patients with SIBO but included all patients of IBS without constipation.

Another recent study of rifaximin in IBS with a positive LHBT was conducted in 150 patients.[13] Of 150 IBS patients, 106 were LHBT positive (71%). Assessment at 4th week following commencement of therapy showed that rifaximin provided a significant improvement of IBS-associated symptoms such as bloating, flatulence, diarrhea, and pain. The authors concluded that rifaximin treatment reduced symptoms in patients with IBS who were LHBT positive and this improvement was observed for 3 months after 2 weeks of treatment with rifaximin.

The only meta-analysis available in literature was published by Menees *et al.* in 2012.[14] This meta-analysis also concluded that rifaximin is better than placebo in the treatment of IBS patients.

In our study, the response rate was 68% which is high when compared with previous studies. The reason for this high response rate might be due to (1) we included only non-constipation variety of IBS for which main etiology might be infective and (2) in a tropical country like India, GI infections are more prevalent.

In this study, we chose a subset of IBS patients with diarrhea predominance, assuming that diarrhea predominant IBS has a higher chance for infective etiology. The antibacterial activity of rifaximin is the presumed mechanism for its sustained beneficial effects in patients with IBS.

A response to antibiotics in patients with IBS has been shown to correlate with normalization of the results of lactulose hydrogen breath tests in previous studies. Lactulose hydrogen breath test is a test to document evidence of small bowel bacterial overgrowth in patients with IBS.

In this particular study, our primary endpoint was the patients' subjective assessment of symptomatic improvement. We choose the secondary endpoints of bloating score, pain score, and overall score assessment by patients. The study has revealed that patients in the rifaximin group have symptomatic improvement in both primary and secondary endpoints. This result is encouraging as the role of rifaximin in the treatment of IBS is found beneficial.

Since IBS is a functional bowel disorder, patient's subjective feeling of improvement is very much important in assessing treatment response. Moreover, we used certain objective criteria in the study such as a number of stools and consistency of stool which also showed a better response in the rifaximin arm. Hence, based on subjective and objective criteria, rifaximin has proved useful in patients with non-constipation predominant IBS.

The major side effects of rifaximin were also monitored in this study. However, no major adverse events were reported. Similar percentage of patients reported minor adverse events in both the groups. Furthermore, there were no reports

suggesting intolerance or allergic response to rifaximin therapy. The previous studies by Pimentel *et al*., Lembo *et al*., and Sharara *et al*. all showed that there were no major side effects of rifaximin treatment.

Furthermore, minor side effects were comparable in both rifaximin arm and placebo arm. Unaltered baseline laboratory parameters in both groups suggest the relative safety of rifaximin in IBS. The previous studies by Pimental *et al*., Lembo *et al*., and Sharara *et al*. also showed that the laboratory parameters are not altered by rifaximin treatment.

Limitation of the present study is the short follow-up period. The patients in this study were followed up for only 1 week which was not sufficient to document the persistence of relief attained during the end of treatment. To prove the sustained response, we need longer follow-up. However, based on a current study, it can be assumed that the response attained at the end of the treatment continued for at least 1 week. Another limitation of our study was that it does not have the power to detect the adverse events. To document adverse events probably, we need a more number of patients and we need a longer duration of follow-up. The third limitation of this study was that no breath test was performed at baseline to define the percentage of patients who had SIBO or after the course of rifaximin to assess symptom correlation.

CONCLUSION

Among the patients who had IBS without constipation, rifaximin 400 mg TID for 2 weeks proved more effective than placebo for alleviation of global symptoms. IBS-associated symptoms such as bloating, abdominal pain, overall symptoms, loose stools, frequent stools, and feeling of urgency improved after 2 weeks therapy with rifaximin. Treatment response persisted during 1 week follow-up period. No major adverse events were reported in the study. Minor adverse events were similar in both rifaximin and control group. Rifaximin is a safe and effective treatment for diarrhea predominant IBS.

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