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Original Research Article

A Randomized Controlled Trial on Effect of Non-Absorbable Antibiotic, Rifaximin in Patients with Irritable Bowel Syndrome

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Abstract:

Background: The most prevalent functional bowel disorder, irritable bowel syndrome (IBS), has no known cure. Research has shown that bacterial overgrowth plays a role in the pathophysiology of this condition. This study aims to assess the impact of an antibiotic that is not absorbed. The main goal of the trial is to determine whether giving patients with IBS who do not have constipation a 400 mg/d oral rifaximin treatment for 14 days is effective. This study's secondary goal is to determine if a 14-day treatment of 400 mg of rifaximin taken three times a day is as safe for IBS patients without constipation as a placebo.

Methods: We enrolled patients in this two-year, randomized, placebo-controlled study based on Rome III criteria. For two weeks, the treatment group was given 400 mg of rifaximin three times a day. Before being included, at the conclusion of the treatment, and one week after the regimen, each patient had a safety and symptom assessment. The Likert scores of the two groups' symptoms and the primary endpoint the percentage of patients who experienced satisfactory alleviation from IBS symptoms were compared.

Results: The percentage of subjects in the rifaximin arm who had sufficient improvement from their IBS symptoms is higher than that of the placebo (68% vs. 39.1%). Following a two-week course of therapy, there was a sustained significant improvement in both groups' bloating score ($P < 0.002$), pain score ($P < 0.001$), and overall score ($P < 0.002$) after one additional week. There were no noteworthy side effects noted.

Conclusion: Taking 400 mg of rifaximin three times a day for two weeks significantly reduced overall IBS symptoms.

Keywords: Irritable Bowel Syndrome, Rifaximin, Non-absorbable Antibiotic.

Introduction

One of the most prevalent functional gastrointestinal (GI) illnesses is irritable bowel syndrome, or IBS. In the absence of anatomical, inflammatory, or biochemical abnormalities, IBS is typified by recurrent episodes of stomach pain, bloating, and impaired stool function. Suffering from IBS symptoms can also lead to higher levels of stress, worry, and poorer quality of life. IBS seems to impact up to 20% of the population, despite variations from nation to nation. Owing to its significant morbidity, elevated frequency, and exorbitant expense, it holds significant therapeutic significance. Even though the exact cause of the symptoms is unknown, changes to the normal flora are thought to be one of the causes.[1] There is no definite physical abnormality or biological marker to define IBS. The diagnosis is based on ROME III criteria.[2] Researchers first thought about using antidepressants to treat IBS. Although it has reduced symptoms in IBS individuals, it is not very effective and has been linked to major side effects. Research conducted in the 1980s demonstrated that individuals with IBS frequently have aberrant intestinal motility. In particular, gut motility is too fast in IBS that is predominately diarrheal and too sluggish in IBS that is predominately constipated. Researchers therefore concentrated on medications that modulate serotonin levels in the GI tract as a result of the correlation between IBS and peristalsis. At first, these medications were effective in relieving IBS symptoms. Alosetron hydrochloride, however, is the only medication that is both marketed and FDA-approved. Owing to significant side effects such as constipation and ischemic colitis, its use is

limited to female patients with IBS who have severe diarrhea and have not responded to standard treatments. For women with constipation-predominant IBS, tegaserod maleate (5-HT4 agonist) is an additional serotonin medication that has been approved. However, it was taken off the market because of significant detrimental effects on the cardiovascular system.

Researchers therefore concentrated on bacterial involvement in IBS because there were no safe serotonin-based medications or other viable therapies for IBS available[3,4]. Up to 84% of IBS patients get aberrant results on the lactulose hydrogen breath test, according to studies[5,6]. Clinical investigations using antibiotics (ciprofloxacin, doxycycline, metronidazole, and neomycin) suggested that antibiotic therapy might be a useful treatment for IBS symptoms. Neomycin has very mediocre effectiveness in completely eliminating bacterial overgrowth, but it does diminish it.[7] Moreover, neomycin's negative effects restrict its utilization. It was also shown that other antibiotics used to treat SIBO were less effective. These antibiotics are also only meant to treat systemic infections.

An antibiotic with low systemic absorption, few side effects, and strong efficiency in preventing bacterial overgrowth is unquestionably the best option for treating irritable bowel syndrome. High rates of bacterial overgrowth eradication have been observed using RIFAXIMIN, an antibiotic that is poorly absorbed and has excellent tolerability.[8]

A novel non-absorbable oral antibiotic called rifaximin is derived from rifamycin. Its effectiveness against aerobic, anaerobic, and Gram-positive and Gram-negative Enterobacteria is wide-ranging.[9] It can be used to treat GI tract infections because of its limited systemic absorption.

When taken three times a day for three days, adults and children over the age of twelve can take 200 mg of rifaximin for traveler's diarrhea, according to a May 2004 FDA approval. Few studies support the use of rifaximin in the management of irritable bowel syndrome. Nevertheless, there are no reports of analogous investigations from Asian nations. For this reason, the purpose of this study is to evaluate the safety and effectiveness of rifaximin in individuals with IBS.

Materials and Methods

The study was carried out in the pharcology department at Jawaharlal Nehru Medical College and Hospital in Bhagalpur, Bihar, in cooperation with the gastrointestinal outpatient department of Surgery. This was a one and a half year, randomized controlled study that took place between June 2022 and December 2023. Rome III criteria were used to diagnose IBS patients.[2] After providing their consent, patients were questioned in order to gather pertinent information. In a case record form (CRF) created especially for the study, data was collected.

Participants in the study were to be at least 18 years old, female, and have a verified diagnosis of IBS. A symptom score of greater than three was needed during the screening phase in order to be admitted into the research. Throughout the investigation, the subject must adhere to a consistent diet.

The study will not include participants who exhibit symptoms of constipation-predominant IBS, ulcers, diverticulitis, gastroesophageal reflux diseases, inflammatory bowel disease, GI cancer, pancreatitis, mental illnesses, HIV infection, or thyroid disorders. Those who abused drugs or alcohol were also not allowed to participate in 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 study took about four weeks in total, depending on whether a colonoscopy was necessary. Throughout the trial, there was routine safety monitoring, which included laboratory tests, tracking adverse events, symptom-directed physical examinations, and vital sign measurements.

The study's primary effectiveness outcome is the percentage of participants who saw sufficient improvement from their IBS symptoms after two weeks of treatment. When an individual answers "yes" to the following subject global evaluation question, their IBS symptoms are considered adequately relieved.

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 evaluations were conducted one week following the commencement of treatment, throughout treatment, and prior to treatment.

Hemoglobin, total leukocyte count, platelet count, serum creatinine, serum bilirubin, ALT, and AST are among the laboratory markers evaluated in this investigation. These parameters were compared in the pre- and post-treatment periods for both groups.

Only those patients who appeared for routine follow-up visits after completing the two-week course of treatment were included in the final analysis.

The independent sample t-test was used to compute and compare the mean ages of the two groups.There is a binomial data as the main efficacy objective. We used the Chi-square test to determine the significance. Using a 7-point Likert scoring system, the symptoms, including bloating, stomach discomfort, and overall symptoms, were evaluated prior to, during, and after treatment. The significance test that was employed was the Kruskal-Wallis test. In this manner, symptoms including the quantity and consistency of stools were also evaluated.

Prior to and following the treatment, we evaluated the degree of urgency. We computed the response rate among patients who felt a sense of urgency prior to receiving therapy. The Chi-square test was used to determine the significance of any response to therapy in both groups. $P < 0.05$ was regarded as statistically significant in every analysis. The statistical software SPSS version 17 was used for the analyses.

Results

This study had 149 patients in total. Patients were randomized to the placebo and therapy groups. There were 74 participants in the placebo arm and 75 patients in the therapy arm overall. The mean age of the patients in the placebo group was 39.01, while it was 35.15 in the rifaximin group. Basic laboratory markers that are comparable include bilirubin, creatinine, ALT, AST, hemoglobin, total count, ESR, platelet count, and RBS. The study demonstrates that when it comes to the overall symptoms of IBS, people treated with rifaximin respond better than the control group.

68% of patients in the rifaximin group and 39.1% of patients in the control group responded well. With rifaximin medication, IBS-related symptom scores, including bloating, pain, and overall score, improved. When compared to a placebo, there was a statistically significant difference.

This study also showed that, when compared to the control group, the rifaximin group experienced a substantial improvement in additional IBS symptoms such as stool consistency, quantity, and urgency.

There were no significant rifaximin-related adverse effects reported in the current trial. Minor side effects were present, albeit they were similar in the control group and the rifaximin arm.

Discussion

Life quality is greatly impacted by IBS. IBS treatment is crucial since it raises quality of life, which in turn raises health resources and lowers productivity at work. According to this study, IBS patients who do not have constipation can benefit greatly from a brief course of rifaximin. According to the study, rifaximin, a non-absorbable broad-spectrum antibiotic, significantly reduced overall symptoms when compared to a placebo.The topic of antibiotic use in IBS patients has been the subject of numerous studies in the past. There aren't many researches on rifaximin, though. Since no comparable study on this antibiotic was discovered in India during the literature search, this study is regarded as the first of its kind from our nation.

In this trial, response to treatment was shown in 68% of patients in the rifaximin arm and 39% of patients in the placebo arm. The patients in the rifaximin arm benefited from the treatment, and the difference was statistically significant. Patients receiving rifaximin arm showed improved response in terms of overall assessment, bloating score, and

pain score. The quantity and consistency of stools were two other factors this study looked at. When compared to the placebo arm, the rifaximin arm's improvements in these metrics were similarly noticeably greater. 64.1% of participants in the rifaximin arm and 32.4% of patients in the placebo arm of this research reported alleviation from urgency. There was a statistically significant difference.In the current trial, all study parameters showed that the rifaximin arm outperformed the placebo arm. The function of rifaximin in IBS has been the subject of several earlier investigations.

The first research on rifaximin in IBS was released by Sharara et al. in 2006.[10] Every IBS patient, regardless of subgroup, was included in this study. Seventy patients had their global symptom improvement examined. For 10 days, a 400 mg twice-daily dose of rifaximin was administered. Patients who took rifaximin appeared to respond better, as evidenced by the response rate of 27% in the rifaximin group and 9.1% in the placebo group. A 2006 study by Pimental et al. also demonstrated that IBS patients responded better to rifaximin.[7] Here, a 400 mg dose of rifaximin was administered three times a day, along with an antibiotic for ten days. 32.6% of those in the rifaximin group and 9.1% of those in the placebo group responded.

Lembo et al. (2008) found that when rifaximin was given to patients with IBS, the response was superior to a placebo.[11]

Only IBS patients with diarrhea as their primary symptom were included in this study. Patients' reaction rate was 52.3%, whereas the placebo group's response rate was 44.2%.

There was a statistically significant difference. Patients with IBS who did not experience constipation were included in a 2011 study conducted by Pimental et al.[12] For two weeks, patients were divided into two groups and given either 550 mg of rifaximin or a placebo three times a day. Ten more weeks were spent monitoring these patients. The main goal was to sufficiently relieve the symptoms of IBS. Every week, the percentage of patients who experienced sufficient relief from gas and bloating associated with IBS was evaluated.

Individuals who took rifaximin reported an improvement rate of 40.8%, while individuals who took a placebo reported an improvement rate of 31.2%. The percentage of patients who responded to treatment was one of the secondary objectives. During the follow-up period, the response was measured by daily self-rating of overall IBS symptoms as well as specific symptoms like bloating, stomach pain, and consistent stools. According to the study's findings, rifaximin significantly reduced the symptoms of IBS, such as bloating, stomach pain, and loose or watery feces. The lack of a breath test to determine the proportion of patients with small intestinal bacterial overgrowth (SIBO) was one of the study's limitations. Therefore, all IBS patients without constipation were included in the trial, rather than just those with SIBO.

150 individuals participated in a recent trial on rifaximin in IBS with a positive LHBT.[13] 106 (71%) out of 150 IBS patients tested positive for LHBT. Evaluation conducted four weeks after treatment started revealed that rifaximin significantly reduced the symptoms of IBS, including pain, gas, diarrhea, and bloating. The authors came to the conclusion that rifaximin medication improved symptoms in IBS patients who tested positive for LHBT, and that this improvement persisted for three months following a two-week course of treatment.

Menees et al. presented the sole meta-analysis that is currently available in the literature in 2012.[14] The results of this meta-analysis also showed that rifaximin is a more effective medication for IBS patients than a placebo.

The study yielded a high response rate of 68% when compared to earlier research. This high response rate could be explained by two factors: (1) we only considered IBS types other than constipation, for which an infectious etiology may be present; and (2) GI illnesses are more common in tropical countries like India.

We selected a subgroup of diarrhea predominating IBS patients for our investigation on the assumption that this population of patients has a higher likelihood of an infectious etiology. Rifaximin's antibacterial activity is thought to be the mechanism underlying its long-lasting positive effects in IBS patients.

Previous investigations have demonstrated a correlation between the normalization of lactulose hydrogen breath test results and an antibiotic response in IBS patients. The purpose of the lactulose hydrogen breath test is to identify any signs of small bowel bacterial overgrowth in IBS patients.

Our main goal in this particular study was to determine how subjectively the participants felt their symptoms had improved. The secondary objectives that we selected were the patient assessment of the overall score, the pain score, and the bloating score. Patients in the rifaximin group showed symptomatic improvement in both primary and secondary goals, according to the study. This finding is encouraging since it suggests that rifaximin may be helpful in treating IBS.

Given that IBS is a functional bowel condition, evaluating the patient's subjective sense of improvement is crucial for determining how well a treatment is working. Additionally, the trial included certain objective measures, such as the quantity and quality of feces, which also demonstrated im-

proved response in the rifaximin arm. Therefore, in patients with non-constipation predominate IBS, rifaximin has shown promise based on both subjective and objective criteria.In this investigation, the main rifaximin side effects were also observed. Nevertheless, no significant side effects were noted. In both groups, a comparable proportion of patients experienced mild adverse effects. Moreover, no instances of intolerance or allergic reaction to rifaximin medication were found. Prior research conducted by Pimentel et al., Lembo et al., and Sharara et al. demonstrated that rifaximin treatment did not have any significant side effects.In addition, mild adverse effects were similar in the placebo and rifaximin groups. The relative safety of rifaximin in IBS is suggested by the unchanged baseline laboratory parameters in both groups. The earlier research by Pimental et al., Lembo et al., and Sharara et al. likewise demonstrated that rifaximin administration has no effect on the laboratory measurements.

Conclusion

For two weeks, rifaximin 400 mg TID was found to be more beneficial than a placebo in alleviating overall symptoms in patients with IBS who did not have constipation. After two weeks of rifaximin therapy, symptoms of IBS, including bloating, stomach pain, general symptoms, loose stools, frequent stools, and a feeling of urgency, improved. The one-week follow-up phase saw the treatment response remain. Significant adverse effects were not documented in the research. Minor side effects were comparable in the control and rifaximin groups. Rifaximin is a safe and efficient medication for IBS characterized by diarrhea.

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