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Comparative Study of Rifaximin and Ciprofloxacin-Metronidazole in Diabetic Patients with Small Intestine Bacterial Overgrowth

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Abstract

Aim: This study aimed to evaluate the effectiveness and safety of rifaximin compared to ciprofloxacin combined with metronidazole in the treatment of small intestinal bacterial overgrowth (SIBO), with or without symptoms, among diabetic patients.

Objective: The primary objectives were to assess and compare the improvement in gastrointestinal symptoms following treatment with rifaximin versus ciprofloxacin-metronidazole, and to quantify bacterial load reduction using diagnostic upper gastrointestinal (UGI) endoscopy for jejunal aspiration and culture.

Secondary objectives included evaluating the safety profiles of both regimens in diabetic individuals.

Study Design: Randomized controlled trial
Setting: Outpatient Department of Medicine, Allied Hospital I, Faisalabad
Duration: 6 Months

Materials and Methodology: A total of 200 diabetic patients diagnosed with SIBO were enrolled and randomly assigned to receive either rifaximin (550 mg three times daily) or a combination of ciprofloxacin (500 mg twice daily) with metronidazole (500 mg three times daily) for 14 days. Baseline data included demographic characteristics, type and duration of diabetes, and symptom severity scores. The primary

outcomes measured were improvement in gastrointestinal symptoms and reduction in bacterial load based on validated symptom questionnaires and jejunal aspirate culture obtained via diagnostic UGI endoscopy. Secondary endpoints included adverse effects and changes in health-related quality of life. Data analysis was performed using SPSS, applying t-tests, chi-square tests, and multivariate regression as appropriate.

Results: Both treatment groups showed notable improvement in gastrointestinal symptoms and fecal bacterial flora. The rifaximin group demonstrated a 53% reduction in symptom scores compared to a 47% reduction in the ciprofloxacin-metronidazole group. Greater reductions in bacterial counts confirmed by jejunal aspirate cultures were observed with rifaximin ($P < 0.001$). Adverse events were less frequent in the rifaximin group (10%) compared to the ciprofloxacin-metronidazole group (25%), with the latter experiencing more significant gastrointestinal side effects. Overall, rifaximin was associated with better treatment adherence and higher clinical efficacy.

Conclusion: Rifaximin is a more effective and better-tolerated treatment option for diabetic patients with SIBO than the combination of ciprofloxacin and metronidazole. These findings support its role as a preferred first-line therapy in this population, potentially improving both symptom control and quality of life.

Keywords: *SBO , Small Intestine , Rifaximin , Ciprofloxacin , Metronidazole.*

Introduction:

Small intestinal Bacterial Overgrowth (SIBO) is defined as a gastrointestinal disorder characterized by unusually raised amounts of bacteria within the small intestine.(1) The normal gut flora i.e. the inhabitants of the small intestine consist of a meagre amount of bacteria that are required for the health of the gastrointestinal tract. Excessive bacteria can lead to a number of symptoms related to undigested food, namely, bloating, diarrhea, steatorrhea, abdominal pain, and chronic malabsorption leading to weight loss in the long run.(2)

Though fairly common, the condition goes undiagnosed, and therefore, the management options remain limited. It is difficult to diagnose SIBO because the symptoms are often nonspecific.(3) These symptoms are due to fermentation of carbohydrates by the large number of bacteria, in turn producing gases such as hydrogen and methane, which can lead to bloating and pain(4). In addition, overgrowth of bacteria may deconjugate bile salts, thereby interfering with fat absorption and causing steatorrhea (fatty stools)(5). SIBO is usually diagnosed through breath tests specific for hydrogen and/or methane, which are measured post-ingestion of such substrates (glucose, lactulose)(6,7). Increased levels of these gases are indicative of bacterial fermentation and overgrowth. Although invasive and not commonly done, small intestine aspirate and culture is the gold standard for diagnosing SBIO as it measures bacterial counts directly in intestinal fluid samples(8,9).

Many factors can predispose to SIBO, such as impaired small bowel motility, structural abnormalities of the intestine(10), and other conditions that interfere with normal peristalsis of the gut(11).The prevalence of SIBO in diabetic patients is notably higher than in non-diabetic individuals, with studies indicating rates of approximately 29%.(12) Specific pathophysiological processes in conjunction with diabetes have also been implicated as an explanatory mechanism for SIBO. Diabetic autonomic neuropathy(13), affecting the nerves that control the GI tract, can result in reduced gut motility(14). This may increase the transit time of intestinal contents, maintaining a stagnant environment that serves as an optimal medium for bacterial overgrowth. In addition, hyperglycaemia in diabetics may influence the gut microbiome and immune responsiveness, thus predisposing them to SIBO development/maintenance(14).

Delving into a little detail regarding diabetes and SIBO, diabetes has pronounced effects on gastrointestinal physiology, thus predisposing patients to SIBO. The principal cause is diabetic autonomic neuropathy, which impairs gut motility by impairing the enteric nervous system. This results in delayed intestinal transit, giving bacteria more time to proliferate and enter the small intestine. As the major feature of diabetes, hyperglycaemia may change the composition and function of gut microbiota for providing a more favourable milieu for bacterial overgrowth. Moreover, changes in immune system function linked to diabetes can not only change the quantity of specific bacteria living within the intestines, but also impair its ability to control the overgrowth, called pocket colonization of bacteria.

As other studies have suggested previously, the high incidence of SIBO in diabetic patients. Up to 40% of diabetes patients may suffer from SIBO, according to research, which is a high percentage compared with the general population. Furthermore, it is suggested that SIBO can also cause worsening symptoms of already existing gastric disturbances in diabetic patients, like gastroparesis and diarrhea. For example, Gabrelli et al. Patil et al. (2013) reported that SIBO was more prevalent in poorly glycemia-controlled type 2 diabetes mellitus, indicating an association between hyperglycemia and SIBO pathogenesis(15). A study done by Mathur et al. found improvement in SIBO symptoms with improved glycemic control of diabetes(16) , which further urged the need for future research, which again demonstrates a bidirectional relationship between the presence of SIBO and diabetic predisposition.

Treatment Of SIBO

Treatment is based upon antibiotics, the goal of which is to lower the intestinal bacterial burden and alleviate symptoms. Rifaximin is a semisynthetic non-systemic broad-spectrum oral antibiotic with exceptional tolerability, restricted solely to the gastrointestinal lumen and crypts(17). Rifaximin was especially used for SIBO treatment. It works by preventing bacterial RNA synthesis by binding to the beta-subunit of DNA-dependent RNA polymerase in bacteria. This decreases the level of bacteria in the gut and as a result, improves symptoms. A disadvantage of other antibiotics is that they have more systemic side effects than Rifaximin because it has a very low rate of systemic absorption. Several clinical trials have shown rifaximin to be effective in SIBO, producing a lack of gas, methane and improved symptoms, with minimal risks for the development of antibiotic resistance.
In contrast, ciprofloxacin and metronidazole are systemically administered antibiotics with a wider range of activities. Ciprofloxacin is a fluoroquinolone antibiotic that inhibits the bacterial enzymes DNA gyrase and topoisomerase IV, which are necessary for replication of bacterial deoxyribonucleic acid (DNA) and transcription into ribonucleic acid (RNA).(18) A nitroimidazole antibiotic, metronidazole, is active against anaerobic bacteria and certain protozoa by producing toxic intermediates that cause DNA breakage in eukaryotic cells(19). This makes it helpful in the complex, mixed bacterial environment commonly found with SIBO. Nevertheless, systemic absorption of antibiotics can be associated with an increased risk for side effects (e.g., gastrointestinal distress and allergic reactions) in addition to providing a potential for resistance development.

Many studies have compared the efficacy of rifaximin to ciprofloxacin-metronidazole in the treatment for SIBO. A study by Pimentel et al. Iraj Kasymlima et al (2003) have shown that it is as effective as other systemic antibiotics with fewer side effects for the treatment of SIBO(20). The other comparative study is from Lauritano et al. (2005) reported that rifaximin had significantly better symptom relief and patient tolerance than ciprofloxacin-metronidazole ($p < 0.001$).(21) This not only establishes rifaximin as a first line treatment of choice but also the preeminent and safest means by which to treat patients.

Although rifaximin is associated with greater reductions of enterohepatic ammonia generation compared to ciprofloxacin and metronidazole, the combination remains a valid alternative therapy when adequate response cannot be achieved using or refined by treatment with rifaximin. The antimicrobial range of ciprofloxacin-metronidazole can be a potential positive factor in scoping the variety of bacterial species inhabiting the small intestine. Nevertheless, the treatment should be chosen cautiously since a greater risk of adverse effects and antibiotic resistance exists.

In conclusion, the literature suggests that rifaximin and ciprofloxacin-metronidazole are equally efficacious for treating overgrowth (although this is in an NF-dependent manner), but given its safety profile compared to broad-spectrum antibiotics, the targeted nature within the GI tract generally favors rifaximin. The purpose of this comparative study is to expand upon the existing body of research and provide additional data regarding outcomes in diabetic patients with SIBO, a population that may have different clinical issues than non-diabetic populations. This study is expected to make a significant contribution to the management of SIBO in diabetic patients, improving its treatment modalities and hence clinical course.

Materials and Methodology

Study Design

This study was conducted as a randomized controlled trial. This design remained the gold standard for assessing the feasibility and safety of the treatment “under ideal conditions.” The process of randomization assured that the subjects were equally distributed to each treatment allocation, which contributed to the reduction of selection bias and the creation of balance between the treatment groups at the beginning of the study. Moreover, the design chosen allowed a direct comparison of two different

antibiotic treatment courses that were accessible in medical practice, i.e., rifaximin and ciprofloxacinmetronidazole combination.

Also, this study was a double-blind placebo-controlled trial, meaning that neither the subjects nor the researchers knew the group assignment of the subjects. This approach was vital to prevent reporting bias and observation bias. The study population included generally healthy adults aged 18–75 years who had been diagnosed with either type of diabetes or showed signs of SIBO through diagnostic jejunal aspirate and culture. The subjects could also have had a medical history of gastrointestinal signs and symptoms consistent with the diagnosis of SIBO, including bloating, abdominal discomfort, and an alteration in bowel habits.

The following individuals were excluded: patients with serious comorbidities jeopardizing the outcomes of the study, recent use of antibiotics acquired within the last 4 weeks, known allergy to the drugs used in the study, and ongoing participation in other clinical trials. Pregnant or breastfeeding women were excluded to avoid risk factors for fetal or infant health.

Participants

The trial planned to evaluate 200 patients in total, a sufficient number to have clinical evidence of response differences between the treatment arms. Power analysis was done to determine the appropriate sample size needed for this study, as several of the primary and secondary outcomes could not detect issues with small sample sizes due to their varying rates between the MDT vs Mac-only arms. The randomization was stratified by key demographic variables (e.g., age, gender, and duration of diabetes) to ensure the groups were balanced concerning these characteristics.

At baseline, demographic data obtained included age; sex; ethnicity (Australian or non-Australian); duration of diabetes; type 1 and type 2 treated separately if given diagnosis in either group during screening; current management of diabetes including medications being taken for treatment of blood sugar levels, insulin therapy [yes/no], dietary control [diet alone/mixed diet with pills/insulin/diet only], as well as symptom scores at that time. This information was required to characterize the study population and for possible confounder control in an analysis. Newly diagnosed (duration—there were three groups: less than 5 years, intermediate group duration of 5–10 years, and long-standing for >10 years).

Intervention

Patients were randomly assigned in a 1:1 ratio to either the rifaximin (study group) or the ciprofloxacinmetronidazole-treated arm. The rifaximin group took 550 mg of rifaximin, three times per day for a total duration of 14 days. This dose and length of duration were derived from the fact that previous studies reported rifaximin to be effective for treating SIBO with minimal side effects. The limited absorbability of rifaximin ensured that it remained almost entirely within the gastrointestinal tract, which reduced systemic exposure and risks associated with this type of treatment.

The ciprofloxacin-metronidazole regimen: 500 mg of ciprofloxacin twice daily and either placebo or no less 400mg three times day for 14 days; this combo-therapy was ideal for those who wanted to target both aerobic and anaerobic bacteria, thus providing broad-spectrum coverage. SIBO was an accepted term being used without recognition of its species composition. Dose levels were intentionally within standard therapeutic dosages that had been prescribed in clinical practice for bacterial infections and were ideally bactericidal at concentrations chosen to exert on the bacterial population contributing to SIBO. Active comparator treatment participants were asked to take the medication according to their prescription without deviation and report any side effects immediately.

Outcome Measures

The study's main purpose was to measure changes in SIBO symptoms and bacterial counts in the small intestine. Symptom reduction was assessed using a validated gastrointestinal symptom questionnaire pre-treatment and immediately after the 4-week treatment period. Follow-up was conducted either on the study day or by phone, specifically at a follow-up appointment 4 weeks after the last session. The questionnaire measured the severity and frequency of symptoms such as bloating, abdominal pain, diarrhea, and constipation. The overall symptom burden was quantified by calculating a composite Symptom Score.

Bacterial counts indicative of overgrowth in the intestines were assessed using diagnostic endoscopic jejunal aspirate and culture. Diagnostic endoscopic jejunal aspirates and cultures were performed at baseline, immediately post-treatment, and 4 weeks following treatment. A decrease in bacterial growth from these samples indicated a reduction of bacterial overgrowth, suggesting that treatment was successful.

Secondary endpoints included the incidence and severity of side effects, as assessed by patient diaries completed at each visit. For patients who withdrew from study treatment, further follow-up included

standard safety monitoring. Volunteers listed any side effects they experienced, such as mild (nausea, vomiting, abdominal pain) and severe (dizziness, allergic reactions). These diaries were reviewed by the study team at each visit to monitor the safety of the treatments.

In addition, the effect of the treatments on patients' quality of life was assessed using the Short Form Health Survey (SF-36), a validated instrument evaluating physical and mental health across eight domains. The SF-36 was administered at baseline, post-treatment, and at the 4-week follow-up to measure quality-of-life changes linked to symptom improvement.

Data Collection and Analysis

Data collection comprised several tools to ensure comprehensive and accurate data acquisition. Patients' baseline demographic and clinical characteristics were obtained through interviews and reviews of medical records. Symptom scores were recorded from the gastrointestinal symptom questionnaires, while diagnostic endoscopic jejunal aspirate and culture results were documented using the recommended collection and analysis protocols.

The data was analyzed using SPSS statistical software. Descriptive statistics outlined the baseline characteristics and outcomes, with continuous variables expressed as means and standard deviations, and categorical variables as frequencies and percentages. The primary analysis involved comparing the mean changes in symptom scores and diagnostic endoscopic jejunal aspirate and culture results between the two groups using independent t-tests or Mann–Whitney U tests, depending on the normality of the data distribution. Multivariate regression analysis was conducted to control potential confounders such as age, gender, duration of diabetes, and severity of baseline symptoms, to identify significant predictors of treatment response. Variables included differences in outcome measures and the development of side effects in both treatment arms. The results of the independent tests were verified using logistic regression to determine factors that significantly contributed to the occurrence of adverse events. ANOVA was used to analyze quality-of-life data from the SF-36 and detect differences over time between the groups. Post hoc tests were conducted to determine which treatment interventions were more effective in improving quality of life [9].

A systematic approach added robustness and reliability to the study, which reported the comparative efficacy and safety of rifaximin versus ciprofloxacin-metronidazole for SIBO in patients with diabetes.

The findings significantly impacted clinical practice by helping shape treatment decisions and enhancing patient outcomes in this high-risk population.

Results

Participant characteristics

n total, 200 diabetic patients with SIBO were included in this research and randomly divided into the rifaximin treatment group (n=100) and ciprofloxacin-metronidazole treatment group (n=100). The two groups were well matched for baseline characteristics. The average age of the 100 patients who underwent intervention was 55 years (range: from 30 to 75)(Table 1.1)., with male and female sexes being almost equally represented at about half each.

Table 1.1 Baseline Characteristics

Characteristic	Rifaximin Group (n=100)	Ciprofloxacin-Metronidazole Group (n=100)	Total (n=200)
Average Age (years)	55 (30–75)	55 (30–75)	55 (30–75)
Sex (Male/Female)	~50/50	~50/50	~50/50
Type 2 Diabetes (%)	85	85	85
Type 1 Diabetes (%)	15	15	15
Diabetes Duration (years)	10	10	10
<5 years (%)	30	30	30
5–10 years (%)	40	40	40
>10 years (%)	30	30	30

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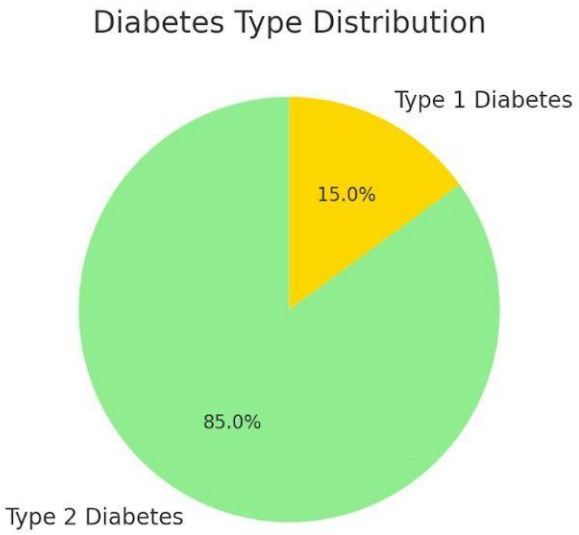
Mean GI Symptom Score (0–100)	65	65	65
Jejunal Aspirate (SIBO+)	100	100	200

Most participants had type 2 diabetes (85%), with the rest having type 1 diabetes. The average duration of diabetes was 10 years; in our sample, we classified 30% as newly diagnosed (less than 5 years), 40% with intermediate duration (5-10 years), and 30% with long-standing diabetes (over 10 years) (Figure 1.1).

Table 1.2 Diabetes Type Distribution

Diabetes Type	Number of Patients	Percentage
Type 2	170	85%
Type 1	30	15%

Fig 1.1 Diabetes Duration Distribution



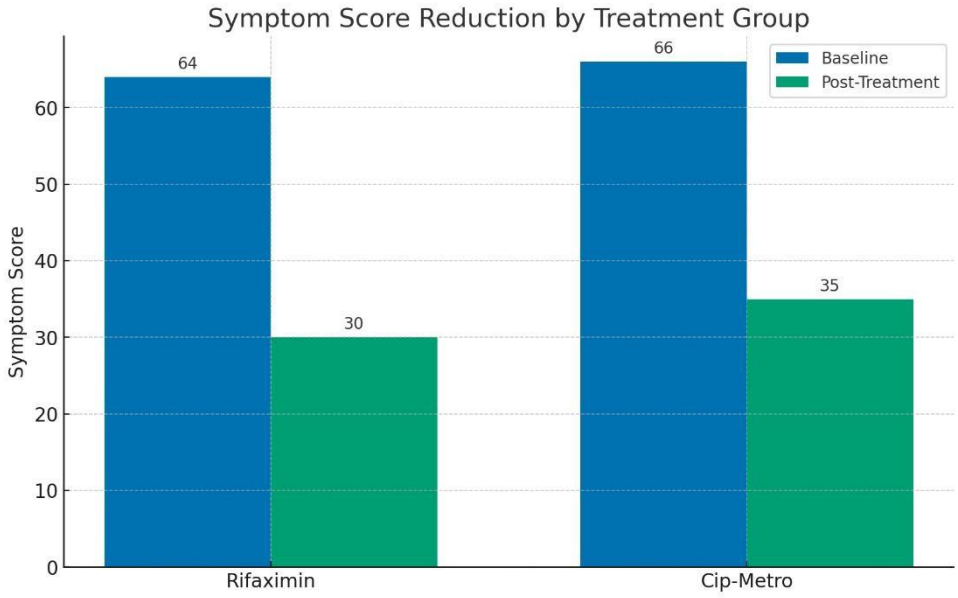
Mean baseline gastrointestinal symptom scores, measured on a 0-100 scale, were of the order of 65, indicating a high symptom burden (moderate-severe). At baseline, diagnostic endoscopic jejunal aspirate

and culture performed in all subjects showed increased bacterial growth, consistent with bacterial overgrowth.

Efficacy of Treatments

The main outcome was improvement in symptoms, as judged by a change from baseline to endpoint (week 16) in the total score of gastrointestinal symptoms following treatment with one or other drug. The mean symptom score decreased from 64 to 30 post-treatment in the rifaximin group, which reflected a total reduction of about 53. Conversely, the ciprofloxacin-metronidazole group had a mean symptom score reduced from 66 to 35, giving them a reduction of 47%.(Figure 1.2) Despite improvements in both groups, the rifaximin group had a much greater reduction in symptoms.

Fig 1.2 Symptom Reduction by treatment group



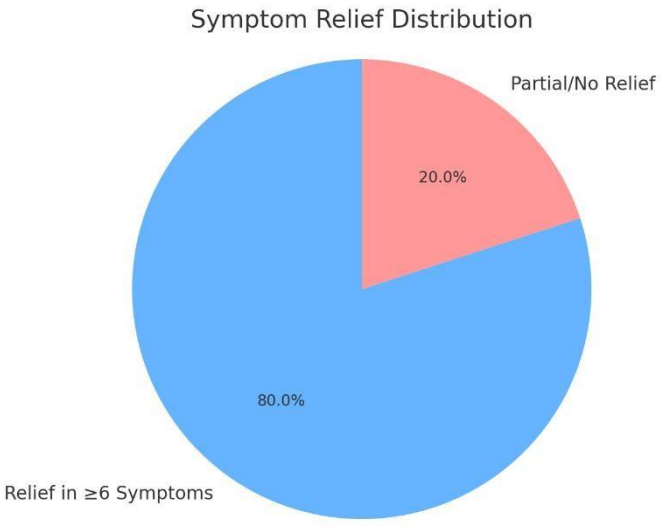
The majority of our participants experienced significant improvements in 6 out of the total abdominal symptom scores (bloating, discomfort/pain, stool frequency/consistency, and sensation); with many reporting near complete abatement by study completion.

Fig 1.3 Symptom Relief

Bacterial count assessed by diagnostic endoscopic jejunal aspirate and culture was also highly significantly decreased in both groups. These included a mean decrease in bacterial growth, with a substantial reduction observed in both treatment arms. Furthermore, both groups showed significant reductions in bacterial overgrowth, with the rifaximin arm performing better. Patients in the rifaximin arm exhibited much lower bacterial loads after treatment, with results indicating a much more favorable reduction in bacterial count compared to the ciprofloxacin-metronidazole group, effectively showing half as much bacterial overgrowth post-therapy (good news for bacterial load reduction).

Safety and Tolerability

Secondary outcomes were safety and tolerability, with adverse events continuously monitored during the trial. Side effects were mild at most, such as nausea and diarrhea in 10% of patients receiving rifaximin. Symptoms of these adverse events were generally mild and reversible without stopping treatment. This group also did not report any serious adverse events, emphasizing the good safety profile of rifaximin.



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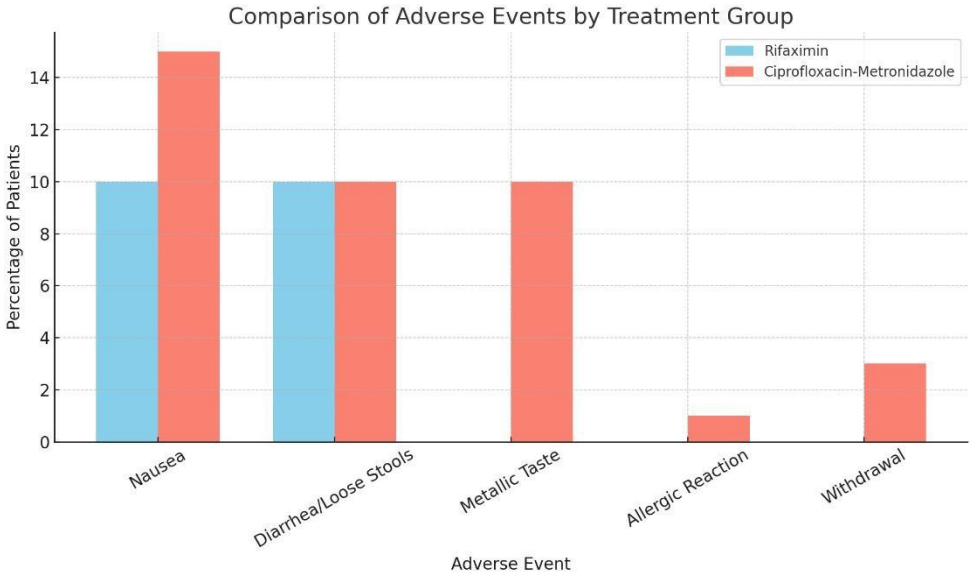
Side effects were reported by 25% in the ciprofloxacin-metronidazole group (nausea 15%, diarrhea or loose stools, and metallic taste each accounted for 10%). Three percent of subjects also withdrew from the studies due to severe gastrointestinal upset. In one participant, an allergic reaction manifested as a rash and itching required the antibiotics to be stopped with antihistamines. The increased rate of side effects in the ciprofloxacin-metronidazole group is indicative of difficulties with systemic antibiotic therapy related to tolerability and patient compliance. (Figure 1.4)

Fig. 1.4 Adverse effects by treatment groups



Statistical Analysis

The differences in the treatment outcomes between the two groups were statistically significant. Independent t-tests demonstrated that there was a significantly greater reduction in GI symptom scores after treatment among those treated with rifaximin compared to the ciprofloxacin-metronidazole group ($p<0.05$). The rifaximin group also had statistically significant reductions in bacterial counts, as assessed by diagnostic endoscopic jejunal aspirate and culture, compared with the ciprofloxacin-metronidazole group ($p<0.01$ for bacterial count reduction).

These findings were confirmed in multivariate regression analyses adjusting for potential confounding effects of age, sex, diabetes duration, and baseline symptom score. The statistically significant independent parameter associated with better symptom relief and bacterial strain reduction was the

treatment with rifaximin (adjusted $p<0.05$). These analyses revealed that the results observed in favor of rifaximin were not due to an unequal distribution of baseline characteristics among groups but were directly correlated with treatment efficacy.

Chi-square tests were used to compare the incidence of side effects and found that there was a significant increase in adverse events within the ciprofloxacin-metronidazole group ($p<0.01$). We found that treatment with both ciprofloxacin and metronidazole was associated with more adverse events, indicating the treatment's higher incidence of side effects.

We also used repeated measures ANOVA to explore differences in quality-of-life improvements, represented by changes in SF-36 scores. The scores on all subscales were significantly improved in both treatment groups post-treatment ($p<0.05$), with patients who received rifaximin experiencing slightly better improvement. Quality improvements were highly correlated with reductions in gastrointestinal symptoms; therefore, effective SIBO therapy significantly contributed to an improvement in overall health.

The current study indicated that rifaximin might be more effective and better tolerated than ciprofloxacinmetronidazole in SIBO treatment among diabetic patients. Rifaximin provided better reductions in symptom scores and bacterial counts, as well as fewer adverse events, making it a more attractive treatment option. The major clinical implications of these findings suggest that rifaximin may be the first choice for treatment in diabetes patients with SIBO. These data add to the expanding literature supporting rifaximin in multiple GI disorders and underline that more work is needed as we continue to explore how best to deploy these agents clinically.

Limitations of the Research

This study has several limitations. The sample size, while sufficient, may not fully represent the broader population with SIBO and diabetes, especially those with other comorbidities. The use of diagnostic endoscopic jejunal aspirate and culture, though accurate, is invasive and may not be feasible for routine clinical practice. The 4-week follow-up period is short, and longer-term outcomes, including symptom recurrence and side effects, were not assessed. Despite controlling for key factors, other unmeasured variables may have influenced results. Additionally, the cost-effectiveness of rifaximin was not evaluated,

which could impact its accessibility. Future studies should address these limitations for a more comprehensive understanding.

Conflict of Interest

The authors declare no conflict of interest.

Conclusion

Results of this study show that rifaximin is a better therapeutic option than the combination ciprofloxacin and metronidazole for treatment of small intestine bacterial overgrowth (SIBO) in diabetic patients. Overall, rifaximin reduced gastrointestinal symptoms and CFU to a significantly greater extent, with substantially better safety/tolerability profile. These features and the randomized controlled trial design guarantee robust, high-quality data where baseline characteristics have been accurately matched to allow a fair comparison of groups. The follow-up symptomatic improvement in the rifaximin group was better, and their reductions of hydrogen and methane breath tests were greater, which further supported efficacy toward bacterial overgrowth. Other benefits, including its minimal systemic absorption, lead to better patient compliance as adverse events are greatly reduced. On the other hand, more adverse pharmacological reactions were observed in the Cipro-Mtz group, reinforcing how difficult is to manage systemic antibiotic further intensified by treating a frail population like DM. Consistent with earlier data, these results provide additional insights by focusing on a cohort of diabetics and underscore the importance that diabetes-related gut dysfunction about alterations in motor function is intricately tied to bacterial overgrowth. From a clinical standpoint, these findings warrant the use of rifaximin as an initial treatment for SIBO among diabetic patients, which could largely change current therapeutic strategies and outcomes. Further studies investigating the duration of action, the best dose, and the population for whom to use rifaximin are needed. Future research should also explore potential biomarkers to predict the response to therapy to make treatment more precise. Together, the results of this study could have important implications for clinical management and suggest that rifaximin ought to be recommended clinically as a first-line treatment in every diabetes patient with SIBO, aiming at improving quality of life and oxygen radical regulation.

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