ISSN: 2091-2749 (Print)
2091-2757 (Online)

Submitted on: 28 Mar 2024
Accepted on: 30 Apr 2024

https://doi.org/10.3126/jpahs.v11i1.65652

Clinical response to Rifaximin amongst irritable bowel syndrome (IBS) patients at tertiary level hospital in Nepal

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Abstract

Introduction: Irritable Bowel Syndrome (IBS) is common in patients with abdominal symptoms resulting in significant healthcare expenses. The diagnosis relies on ROME criteria, emphasizing recurrent abdominal pain over three months with changes in defecation patterns and stool appearance. Various treatment options are available for IBS including the role of antibiotics such as Rifaximin. The study aimed to assess the efficacy of rifaximin in Nepalese IBS patients.

Method: This was a prospective observational study done in a Nepalese tertiary referral hospital for a period of one year after obtaining the ethical approval. All diagnosed IBS patients fulfilling the eligibility criteria were treated with Rifaximin for two weeks and the improvement in their symptoms was recorded. The data were analyzed using SPSS software.

Result: A total of 33 participants were included, with a majority being female 22(66.70%). The mean age was 36.58±7.19 years, and the majority 31(93.90%) were nonvegetarian. Abdominal pain was the most common symptom 28(84.80%), followed by diarrhea and bloating. IBS-D was the most predominant diagnosis 25(75.8%). After treatment initiation, 26(78.80%) reported symptom improvement. Among those with improvement, 11(36.40%) reported a nearly 50% reduction in symptoms and 6(18.2%) experienced complete relief.

Conclusion: Treatment with Rifaximin resulted in a notable decrease in irritable bowel syndrome symptoms across various subclasses among Nepalese patients.

Keywrods: Developing Country; Irritable Bowel Syndrome; Rifaximin

How to Cite:
Karki B, Sherpa TW, Deo RK, Thapa P. Clinical response to rifaximin amongst irritable bowel syndrome (IBS) patients at a tertiary level hospital in Nepal. Journal of Patan Academy of Health Sciences. 2024 Apr;11(1):21-26.

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Introduction

Irritable Bowel Syndrome (IBS), a prevalent diagnosis in patients with abdominal pain and luminal symptoms like diarrhea or constipation, incurs substantial healthcare costs.[1] IBS is defined as a functional bowel disorder characterized by recurrent symptoms persisting for over six months, without evident anatomical or physiological abnormalities detected by routine diagnostic assessments deemed clinically relevant.[2] Diagnosis relies mainly on clinical assessment using ROME criteria, the latest being ROME IV, necessitating recurrent abdominal pain for at least one day per week over the previous three months, associated with changes in defecation patterns and stool appearance.[3]

Various theories, including abnormal gastrointestinal motility and visceral hypersensitivity, contribute to IBS pathophysiology. Visceral hypersensitivity encompasses the intricate involvement of both the peripheral and central nervous systems, which play a crucial role in the manifestation of symptoms in IBS. Pharmacological research targeting specific ligands offers potential therapies for persistent hyperalgesia.[4] Emerging evidence suggests alterations in gastrointestinal flora, particularly Small Intestinal Bacterial Overgrowth (SIBO), may be implicated.[5] However, data on the IBS-SIBO association are conflicting, with reported SIBO prevalence in IBS patients reaching 80%. SIBO is explored not only in diarrhea but also as a mechanism in constipation, notably methane-producing flora.[6]

Multiple treatment options exist for IBS, including various gut antibiotics. Numerous studies have proposed the effectiveness of rifaximin as a therapy to reduce the bacterial load and alleviate symptoms.[7,8] Yet, research on treatment response among Nepalese IBS patients is scant. Given Rifaximin's accessibility at reduced costs in Nepal, this study aims to evaluate its clinical efficacy in this population.

Method

This was a descriptive cross sectional single center prospective study aimed to evaluate the clinical response to Rifaximin among patients diagnosed with IBS at tertiary-level hospital in Nepal. The study was conducted at Shree Birendra Hospital, a tertiary-level teaching hospital of the Nepalese Army Institute of Health Sciences in Nepal. Patients aged 18 years and above, diagnosed with IBS according to the Rome IV criteria, were included in the study. Patients with a history of inflammatory bowel disease, gastrointestinal malignancy, significant gastrointestinal surgery, or prior history of use of rifaximin were excluded from the study. A non-probability convenience sampling method was used. The study was conducted over one year after ethical approval, from February 2021 to January 2022.

The patients presenting with pain abdomen, diarrhea, and constipation were evaluated using the ROME IV criteria for the diagnosis of IBS.[3] The patients were further subclassified into IBS-D for diarrhea-predominant symptoms, IBS-C for constipation-predominant symptoms, IBS-mixed for both diarrhea and constipation symptoms, and IBS-U for symptoms not meeting any of the criteria for the above subclasses. The patients diagnosed with IBS were approached for participation in the study. After obtaining informed consent, demographic data including age, gender, and clinical history were recorded. Symptoms of the patients were evaluated using the Likert scale as 0=No improvement, 1=slight improvement, 2=50% improvement, 3=significant improvement, and 4=complete improvement. All included patients were treated with rifaximin tablet 550 mg twice daily for 15 days. All patients were informed to communicate either directly or via telephone if they developed any other new symptoms for the assessment of the adverse effects of the medicine. The data were collected at the end of four weeks for the symptom improvement.

Data analysis was performed using appropriate statistical methods. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were presented as mean ± standard deviation or median (interquartile range), while categorical variables were presented as frequencies and percentages. Statistical analysis was done using Statistical Package for Social Sciences (SPSS).

The study protocol was approved by the Institutional Review Board/Ethical Review Committee of Nepalese Army Institute of Health Sciences vide letter no 400 dated January 2021. Informed consent was obtained from all participants before enrollment in the study, and patient confidentiality was maintained throughout the study period.

Result

A total of 33 patients were included in the study, with a majority being female, accounting for 22(66.70%) patients. The average age of the patients was 36.58±7.19 years. Nearly all participants (93.90%) were nonvegetarian. The study participants were queried about their symptoms related to IBS, focusing mainly on four domains: abdominal pain,

diarrhea, constipation, and bloating. Abdominal pain was the most prevalent symptom, reported by 24(84.80%) of the participants, followed by diarrhea and bloating, Table 1.

Table 1. Baseline clinical symptoms of the participants (N=33)

Symptoms	N(%)
Abdominal Pain	28(84.80%)
Diarrhea	26(78.80%)
Constipation	8(34.20%)
Bloating	22(66.67%)

The majority of patients experienced symptoms that could be managed in outpatient settings, with only one patient seeking emergency room care for abdominal pain. This individual was treated symptomatically and discharged home.

Of the participants, 19(57.60%) experienced mild pain, while 11(33.33%) reported moderate intensity pain based on the visual analog score, with 5(15.20%) requiring painkiller medication for symptom relief.

Table 2. Classification of Irritable Bowel Syndrome Subtypes According to ROME IV Criteria Among Study Participants (N=33)

IBS Subtype	Number(%)
D-Diarrhea predominant	25(75.76%)
C- Constipation predominant	6(18.18%)
Mixed	2(6.06%)

According to the ROME IV criteria, most commonly used criteria to diagnose and classify the IBS, the most prevalent diagnosis was Irritable Bowel Syndrome – Diarrhea predominant (IBS-D), accounting for 25(75.8%) followed by IBS-D and others, Table 2.

Table 3. Improvement of overall symptoms among different subgroups of IBS (N=33)

IBS Symptoms	Overall symptoms improved at 4 weeks		p-value
	No	Yes	
IBS-D	4(16.00)	21(84.00)	0.38
IBS-C	2(33.33)	4(66.67)	
Mixed	1(50.00)	1(50.00)	
Total	7(21.21)	26(78.79)	

Following the commencement of treatment, 26(78.80%) patients reported experiencing symptom improvement. The improvement of the symptoms was either in terms of pain abdomen, bloating, diarrhea, or constipation. Analysis of treatment response across different subtypes of IBS revealed a greater number of patients with IBS-D demonstrating overall symptom improvement, although this observation did not achieve statistical significance, Table 3.

Table 4. Frequency of the improvement at week-4 after treatment initiation (N=33)

Symptom improvement	N(%)
No improvement	3(9.1%)
Slight improvement	4(12.1%)
50% improvement	11(33.3%)
Significant improvement	9(27.3%)
Complete improvement	6(18.2%)

Among those who experienced improvement, 11(33.33%) of the total reported a reduction of almost half in their previous symptoms, while 6(18.2%) achieved complete relief of their symptoms at the end of four weeks of treatment initiation, Table 4.

No patients complained of any new symptoms as the adverse effects of the medicine during the study period.

Discussion

There was a notable reaction to rifaximin regarding the improvement of symptoms among Nepalese individuals with diarrhea-predominant IBS. The pathophysiology of IBS is still not fully understood. Various potential mechanisms have been suggested, including genetic and environmental factors, changes in motility, increased sensitivity in the gut, altered communication between the brain and gut, dysfunction of the autonomic nervous system, immune system activation, changes in mucosal permeability, and psychological distress.[9–11] Managing IBS poses a challenge due to its multifaceted origins. It is hypothesized that rifaximin's antibiotic properties contribute to its positive impact on IBS patients by modulating intestinal microbiota which includes both diarrhea as well as constipation-predominant patients.[5] Due to its minimal absorption, this substance exhibits high bioavailability within the gastrointestinal tract, resulting in intraluminal and fecal concentrations of the drug that far surpass the minimal inhibitory concentration values observed in vitro against a broad spectrum of pathogenic organisms.[12]

Patients are diagnosed with IBS and its subtypes based on the ROME IV criteria.[13] In our study, the majority of patients were classified as IBS-D, followed by IBS-C. While there is no prior study on the epidemiology of IBS from Nepal, research

from India revealed that a significant proportion of Indian individuals (57%) exhibited mixed IBS (IBS-M) symptoms, followed by IBS-C (39%).[14] A recent study conducted in Bangladesh revealed an overall prevalence of IBS at 39.3%, with the majority falling under the IBS-C subclassification (54.2%).[14] This variance could stem from subjective interpretations of symptoms among participants in distinct geographical regions as well as the dietary pattern prevalent in our country which includes more fiber.

The majority of participants in our research were primarily young and female. These findings were consistent with other studies from Nepal. A study conducted in Nepal, where the role of vitamin D was assessed for the management of symptoms of IBS, indicated a female predominance of 66.66%, with the average age of the participants being 36.4 years.[15] Likewise, another study carried out regarding the colonoscopy findings of IBS patients in a government-level tertiary hospital found that the average age of their participants was 37.5 years. However, their study revealed a higher proportion of males (52.8%).[16] An epidemiological investigation from India suggested that the majority of patients in the country are middle-aged men, with an average age of 39.2 years.[17] Among the studies conducted in China, it was observed that females aged between 39 and 50 years were more prone to experiencing symptoms of IBS.[18]

Among the total number of IBS patients, nearly 90% reported experiencing improvement, with one-third experiencing more than a 50% alleviation of symptoms and another third achieving significant improvement. Comparing IBS subtypes, those with diarrhea-predominant IBS showed overall symptom improvement compared to constipation and mixed types, although this difference did not reach statistical significance. These findings align with a recent study in China, where following rifaximin treatment, significant improvements were observed in all participants' gastrointestinal symptoms and quality of life scores, sustained for at least 10 weeks.[19] Notably, 57.7% of patients responded positively to rifaximin, experiencing greater symptom relief than non-responders ($p<0.05$). Similarly, a study among Lebanese patients revealed a significant difference in global symptom relief with rifaximin compared to the placebo group (41.3% vs. 22.9%,p-value= 0.03).[20] The efficacy of rifaximin in the diarrhea-predominant group was initially demonstrated in the well-known TARGET1 and TARGET2 trials.[7] In these trials, more patients on rifaximin than placebo experienced relief from IBS symptoms and bloating within the first four weeks of treatment (40.7% vs. 31.7% combined for IBS symptoms, 40.2% vs. 30.3% combined for bloating). The Rifaximin group also showed better response in daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency. Adverse events were similar between groups. Later, rifaximin was also shown to be effective as a repeat treatment in diarrhea-predominant IBS in the TARGET 3 trial[8] where, 636 patients with relapse symptoms received repeat treatment (rifaximin: 328, placebo: 308). Rifaximin showed significantly higher response rates compared to placebo (38.1% vs. 31.5%;p-value=0.03) and in relieving abdominal pain (50.6% vs. 42.2%; p-value= 0.018), but not stool consistency (51.8% vs. 50.0%;p-value=0.42). There were significant improvements in recurrence prevention, durable response, and bowel movement urgency.

Treatment of IBS with antibiotics is based upon the understanding that gut dysbiosis, including small intestinal bacterial overgrowth (SIBO), causes IBS symptoms.[21] This has led to the role of antibiotics as one of the targets of treatment for IBS. Although, association with SIBO explains the role of antibiotics in diarrhea-predominant IBS, the role of antibiotics in constipation-predominant IBS lies in the fact that the microbiotas generate methane gas from the fermentation of endogenous and exogenous carbohydrates. Methane, which was long considered to be an inert gas, is now known to behave as a neurotransmitter that has paved the path for pharmacologic therapy to create novel drugs targeting methanogenesis, in particular, to control IBS-C.[22] In a study on constipation predominant IBS patients, those receiving antibiotics viz neomycin and rifaximin had significant improvement in constipation ($p=0.007$) and bloating ($p=0.002$).[23] In our study, although the constipation-predominant IBS was less in number, almost two-thirds of them had symptom relief with two weeks of rifaximin therapy. The latest Indian consensus guidelines have already incorporated the utilization of Rifaximin across all forms of IBS treatment algorithms.[24]

Limitations include potential bias due to convenient sampling and lack of a control group. The follow-up period was short hence the long-term outcome and the number of relapse cases could not be ascertained in our study. The design of the study was open-label which may affect interpretation. The study conducted in a single center limits generalizability. Utilizing convenience sampling methods may introduce biases and errors when calculating p-values. Unmeasured confounders, self-reported outcomes, and cultural factors could impact the validity and reliability of findings. A long-term prospective study with large sample size and in multiple centers will give more insight into the current research problem in our setting.

Conclusion

In a Nepalese tertiary hospital study on Rifaximin's effectiveness for IBS, predominantly female and young patients were noted. Abdominal pain, mostly mild to moderate, was prevalent, with the majority diagnosed with IBS-D. The treatment resulted in over 50% symptom relief for more than half of the patients, particularly those with the IBS-D subtype.

Funding

The study had obtained research grant from the Nepalese Army Institute of Health Sciences

Acknowledgment

None

Conflict of Interest

None

Authors' Contribution

Concept, Design, Planning: BK, TWS, RKD, PT; Literature review: BK, TWS; Data collection: BK, TWS, RKD, PT; Data Analysis: BK, RKD, PT; Draft manuscript: BK, TWS, PT; Revision of Draft:RKD, TWS, PT; Final Manuscript: BK, TWS, RKD, PT; Accountability of the work: BK, TWS, RKD, PT

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