International Journal of Research in Medical Sciences
Podder S et al. Int J Res Med Sci. 2024 Apr;12(4):1056-1064
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20240825

Original Research Article

Efficacy of rifaximin among non-constipated irritable bowel syndrome patients with or without small intestinal bacterial overgrowth: a randomized, double-blind, placebo-controlled trial

Subrata Podder*, M. Masudur Rahman, Mohammad Iqbal Hossain, Raj Datta, Jane Alam, M. Golam Kibria

Department of Medical Gastroenterology, Sheikh Russel National Gastroliver Institute and Hospital, Bangladesh

Received: 17 January 2024
Revised: 14 February 2024
Accepted: 13 March 2024

***Correspondence:**
Dr. Subrata Podder,
E-mail: spchayank56dmc@gmail.com

ABSTRACT

Background: IBS is a functional gastrointestinal disorder marked by abdominal pain and changes in stool frequency or form. Recent studies indicate a link between IBS, especially the diarrhea-predominant subtype, and small intestinal bacterial overgrowth. This study aimed to evaluate symptom resolution among IBS patients with or without SIBO on rifaximin treatment as compared with placebo.

Methods: A double-blind, placebo-controlled, randomized clinical trial took place at the Department of Gastroenterology, Dhaka Medical College and Hospital, from January to December 2019. In the study 104 non-constipated IBS patients were assessed for SIBO using gut aspirate culture. Those with SIBO (≥105 CFU/ml) and those without were randomly assigned (computer-generated) to receive either 1500 mg/day of rifaximin for 14 days or a placebo.

Results: Among 104 non-constipated IBS patients, 39% had SIBO, with IBS-D patients more associated (83% vs. 60%). Rifaximin significantly improved symptoms in the SIBO group at 4 and 16 weeks (90% vs. 20%, p<0.001; 66% vs. 15%, p<0.001). In the non-SIBO group, significant improvement was observed at 4 weeks (38.7% vs. 18.8%, p<0.001) but not at 16 weeks (25.8% vs. 18.8%, p=0.501). Rifaximin significantly improved abdominal pain, stool form, and frequency in the SIBO group compared to placebo. However, there was no significant improvement in the non-SIBO group.

Conclusions: Rifaximin is superior to placebo in relieving symptoms of non-constipated IBS patients with SIBO.

Keywords: Irritable bowel syndrome, Rifaximin, Gastrointestinal disorder, Dysbiosis, Antibiotic therapy

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (FGID) disorder, characterized by abdominal pain in association with altered stool form or stool frequency.[1] IBS is commonly sub classified based on the predominant bowel habit i.e., constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D) or mixed IBS (occurrence of both constipation and diarrhea). It is an important disease entity because of its high prevalence, morbidity, negative impact on quality of life, social impact and enormous cost.[2] Data suggest that patients with IBS-D experience significantly greater degrees in health-related quality of life and increased impairment of daily activities compared with healthy individuals.[3] IBS vary globally related to differences in study populations, diagnostic criteria and study

methodology.[4] It is most prevalent in South America (21%) and least in Southeast Asia (7%).[5] Two different studies in Bangladesh on healthy volunteers found that prevalence of IBS was 7.7% in urban population and 8.5% in rural population.[6,7] The etiology and pathogenesis of IBS is not still understood and possibly multidimensional. Several hypotheses have been suggested that altered gut motility, abnormal brain-gut interaction (i.e., interactions between the gut microbiota and central nervous system), visceral hypersensitivity, autonomic dysfunction, and immune activation are responsible for IBS. Recently, small intestinal bacterial overgrowth (SIBO) has drawn attention as a potential treatable factor in patients with irritable bowel syndrome.[8] Several recent studies have suggested that patients with IBS, particularly those with a diarrhoea-predominant subtype, have SIBO more often than controls using an upper gut aspirate culture.[9-11] Moreover, qualitative alteration of the gut microbiota, also known as dysbiosis, is being reported increasingly among patients with IBS.[12,13]

Recently, evidence from several studies reporting the efficacy of antibiotics in resolution of symptoms of IBS has been viewed.[14] Two double blind randomized controlled trials (target I and target II) on rifaximin therapy in 1260 non-constipating IBS patients showed that rifaximin therapy had 10% therapeutic benefit over placebo (40.7% vs 31.7%, p<0.001) in adequate relief of global IBS symptoms. These studies showed that rifaximin therapy in non-constipating IBS has only small therapeutic benefit over placebo.[15] Such a low frequency of response in that study might be related to the fact that all the patients with IBS do not have dysbiosis or SIBO. In a randomized, double bind, placebo controlled trial, the efficacy of norfloxacin on symptom resolution in relation to its effect on SIBO patient with IBS was seen on 2016 in India.[16] In that study, at one month follow up, 87.5% patients of IBS with SIBO turned Room III negative, 25% of non SIBO turned Room III negative treated with norfloxacin.[16] On the other hand, no patient turned Room III negative treated with placebo.[16] Importantly, to date there is little published data on the efficacy of rifaximin on symptom resolution in relation to its effect on SIBO among patients with IBS. So, the probability of response to treatment could be higher if we use rifaximin in selected patient of IBS with SIBO. So, the study was done to see the efficacy of rifaximin among non-constipated irritable bowel syndrome patients with or without small intestinal bacterial overgrowth.

Objectives

The general objective of this study is to assess the efficacy of rifaximin in providing satisfactory relief of global IBS symptoms among both SIBO-positive and SIBO-negative IBS patients. Specific objectives include evaluating the relief of abdominal pain, improvement in stool consistency, and changes in stool frequency.

METHODS

Study design, location, duration and population

A prospective, double-blind, placebo-controlled, randomized, single center trial was conducted at gastroenterology department of Dhaka Medical College and Hospital. This study was conducted from January 2019 to December 2019. Consecutive patients of 18 years or above with non-constipated IBS fulfilling Rome IV criteria.

Sampling technique and sample size

Non probability purposive sampling technique was used. Sample size was determined using the formula mentioned below:

$$n = \frac{P_1(1-P_1)+P_2(1-P_2)}{(P_1-P_2)^2} x\left(Z_\alpha + Z_\beta\right)^2$$

Where, Z_α=Z value at a definite level of significance e.g. 2.81 at 0.5% level of significance, Z_β=Z value at a definite power 1.64 at 95% power when ß=0.05, P1=Rifaximin response from previous study, P2=Placebo response from previous study. Thus, sample size was calculated to be 28 (estimated sample size in IBS with SIBO group). The sample size of the IBS patients with SIBO was 28. Considering the frequency of SIBO is 30% in IBS patients, a total number of non-constipated IBS patients in this study was 93. After the addition of 10% loss to follow-up, a total sample of non-constipated IBS patients was 102.

Inclusion and exclusion criteria

Consecutive patients of 18 years or above with non-constipated IBS fulfilling Rome IV criteria. Respondents who had given consent and were willing to comply with the study procedure were included. IBS-C or pregnancy, unstable medical or gastrointestinal disorders, major psychiatric history or substance abuse within the past 2 years, presence of hyperthyroidism or hypothyroidism, and current use of specific medications in the last 4 weeks; anti-diarrheal, anti-spasmodic, probiotics, narcotics, anti-psychotics, or antibiotics were excluded.

Study procedure

Formal ethical clearance was taken from the Ethical Review Committee of Dhaka Medical College before starting the data collection. This prospective, double-blind, randomized, placebo-controlled clinical trial was conducted at the Department of Gastroenterology of Dhaka Medical College Hospital (DMCH) from January 2019 to December 2019. Patients and key relatives were comprehensively informed about the study's scope and limitations. Written consent was diligently obtained from the patients, ensuring strict confidentiality of their

personal information. Participants retained the right to withdraw from the study at any point for any reason. The study prioritized the avoidance of physical, mental, or social harm, and measures were implemented to minimize procedural risks.

Patient selection

Consecutive 230 non-constipated IBS patients by applying Rome IV criteria were screened from the Gastroenterology department of Dhaka Medical College Hospital. 40 patients were excluded due to a history of recent intake of antibiotics and PPI, and 28 patients didn't give consent. 162 patients gave consent and were advised to do some routine investigations.

Routine investigations were stool microscopy, complete blood count, random blood sugar, thyroid function test (if indicated), faecal calprotectin (if indicated) and colonoscopy. 38 patients didn't complete their investigations. 124 patients completed their investigations. Among them, 20 had organic disease. Finally, 104 patients were enrolled into the study and a data collection sheet was filled up by them; which included the demographic profile of the patients and symptom-based criteria. The demographic profile included name, age, sex, religion, marital status, education, family income. The Rome IV questionnaire for diagnosis of IBS was included in this study.

Evaluation for small intestinal bacterial overgrowth

With all aseptic precaution after introducing upper GI endoscope (Olympus cv, 170, Europe) 1ml of undiluted aspirate was collected in a 20 ml sterile syringe by ERCP (Boston Scientific corp, Marlborough, USA) catheter from distal duodenum of all enrolled non-constipated IBS patients.

Aspirate was sent to department of Microbiology, Dhaka medical college. In case of bacterial overgrowth, counting of the colonies were performed using a serial dilution technique. After each use ERCP catheter was autoclaved and reused for 4 times. SIBO was defined as overgrowth of $\geq 10^5$ colony forming unit (CFU) per ml of bacteria in the proximal small bowel.

Randomization procedure

Patients were randomized using a computer-generated stratified randomization table according to the result of quantitative culture of the upper gut aspirate separately. No constipated IBS with SIBO patients were randomized to 550 mg rifaximin thrice daily or identical placebo for 14 days. Non-SIBO patients were similarly randomized to rifaximin or placebo. After treatment period of 14 days, both group of patients were followed up for next 16 weeks on the basis of global satisfactory relief and individual IBS symptoms.

Outcome assessment

Outcome was evaluated on the basis of global satisfactory relief of IBS symptoms, individual IBS symptoms and Bristol stool form scale.

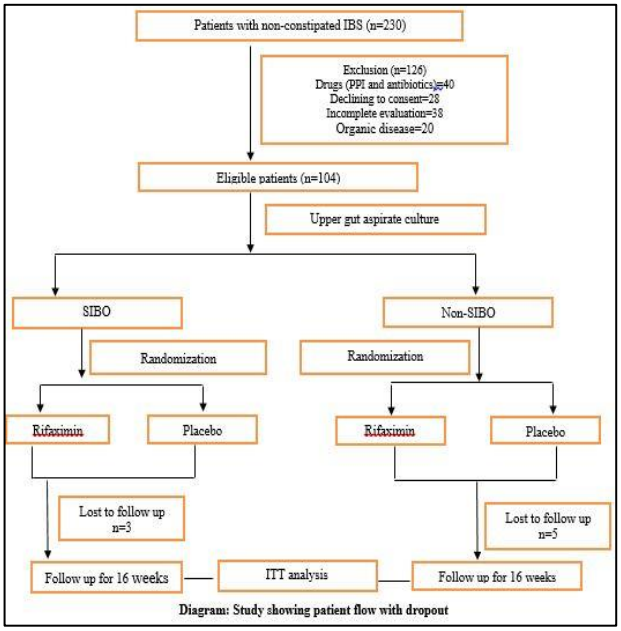

Figure 1: Study procedure with patient flow and dropout.

The primary endpoint

The primary endpoint was patient's reported satisfactory relief of global IBS symptoms. The patient's response to the following question: "Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS compared to the state when you started taking the medications?" (Yes/No) was recorded during the entire study period. Patients were instructed that "satisfactory" in this context mean that in comparison with their typical experience of the disease in the past, the patient felt that the symptoms of IBS had been alleviated during that week to the extent that they would take a medication to maintain that state, even if no medication was actually being taken at that time.

The secondary endpoint

The secondary endpoints were satisfactory relief of abdominal pain and improvement in stool consistency and stool frequency.

Efficacy measures

Symptoms score was applied for 1 week before starting the treatment as baseline and weekly for 16 weeks after completion of 14 days treatment. Patients were maintained a paper diary and records his symptoms at every night at bedtime. Global symptoms of IBS were

recorded at the end of every week on the paper diary. The number of patients who reported satisfactory relief of Global IBS symptoms at least 2 of the 4 weeks during were considered as adequate relief in evaluation as primary end point (global IBS symptoms). Abdominal pain was recorded in a 11-point Likert scale in a paper diary. A colored laminated Bristol stool chart was provided to every patient and he recorded his stool type on the diary at every night. Type III-V, type I-II, type VI-VII Bristol stool forms were considered normal, constipation and diarrhoea respectively. Stool frequency was recorded daily. All side effects were recorded in each follow-up. Study visit was scheduled at week 4, 8, 12 and 16.

Table 1: Comparison of Socio-demographic profile of patients of IBS with SIBO and non-SIBO group.

Socio demographic variable	SIBO (n=41)		Non-SIBO (n=63)		P value
	N	%	N	%	
Age (years)					
18-30	23	56.1	34	54	0.857
31-40	12	29.3	17	27	
40-50	4	9.8	6	9.5	
>50	2	4.9	6	9.5	
Sex					
Male	32	78.0	47	74.6	
Female	9	22.0	16	25.4	
Marital status					
Married	24	58.5	36	57.1	0.881
Unmarried	17	41.5	27	42.9	
Profession					
Service holder	21	51.2	20	31.7	0.306
Business	2	4.9	7	11.1	
Housewife	6	14.6	12	19	
Student	4	9.8	11	17.5	
Labour	8	19.5	13	20.6	
Education					
Illiterate	4	9.8	11	17.5	0.133
Class I-X	21	51.2	18	28.6	
SSC	4	9.8	8	12.7	
HSC and above	12	29.3	26	41.3	
Place of living					
Urban	23	56.1	38	60.3	0.669
Rural	18	43.9	25	39.7	
Religion					
Islam	37	90.2	51	81	-
Hindu	4	9.8	12	19	
Smoking status					
Smoker	9	22	14	22.2	0.974
Non smoker	32	78	49	77.8	

No statistical difference was found between two groups.

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 22.0 (SPSS Inc.; Chicago, IL, United States). IBS patients with SIBO or without SIBO were analysed between rifaximin and placebo by intention to treat analysis. Quantitative or continuous data was presented with mean and standard deviation and qualitative data or categorical data was presented with as proportions or frequency. Categorical variables were analysed using the $\chi 2$ and Fisher's exact tests, as applicable. Parametric paired and unpaired continuous data was analysed using paired and unpaired t-tests, respectively, p values lower than 0.05 was considered significant.

RESULTS

In this study about one third of the patient was SIBO. In this study it was found that IBS-D were more associated with SIBO. The (Table 3) shows that Rifaximin caused significant global satisfactory relief of symptoms compared to placebo after 4 weeks and 16 weeks in SIBO patients. In non-SIBO patients, rifaximin caused significant global satisfactory relief of symptoms

compared to placebo after 4 weeks but improvement was not significant after 16 weeks.

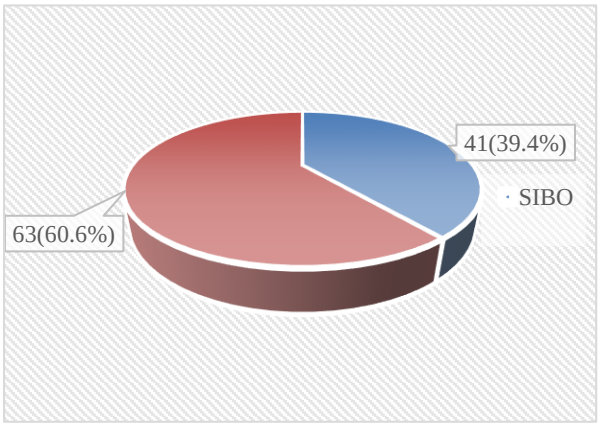

Figure 2: Distribution of the study population by SIBO and Non-SIBO.

It was observed that in SIBO group, Rifaximin caused significant improvement of abdominal pain, bristol stool form and frequency of defecation after 4 weeks and 16 weeks of treatment. But placebo did not show any improvement of abdominal pain, Bristol stool form or frequency of defecation.

Table 2: Distribution of the study patients by IBS subtypes (n=104).

IBS subtypes	SIBO (n=41)		Non-SIBO (n=63)		P value
	N	%	N	%	
IBS-D	34	82.9	38	60.3	0.014
IBS-M	7	17.1	25	39.7	

Table 3: Global satisfactory relief of symptoms in SIBO and non-SIBO group.

Parameters	Rifaximin	Placebo	P value
	N (%)	N (%)	
Global satisfactory relief of symptoms (SIBO group)	(N=21)	(N=20)	
After 4 weeks	19 (90.5)	4 (20)	0.001
After 16 weeks	14 (66.7)	3 (15)	0.001
Global satisfactory relief of symptoms (Non-SIBO group)	**(n=31)**	**(n=32)**	
After 4 weeks	12 (38.7)	6 (18.8)	0.001
After 16 weeks	8 (25.8)	6 (18.8)	0.501

The (Table 5) shows Rifaximin was more effective than placebo in improving abdominal pain, Bristol stool form and frequency of defecation after 4 weeks and 16 weeks of treatment.

It was observed that in non-SIBO patients 4 weeks after Rifaximin treatment, there was significant improvement of abdominal pain, Bristol stool form scale and frequency of defecation but improvement was not observed in placebo group. After 16 weeks of treatment both rifaximin and placebo group showed no improvement of abdominal pain, Bristol stool form and frequency of defecation. It was observed that there was no significant difference in terms of side effect between Rifaximin and placebo.

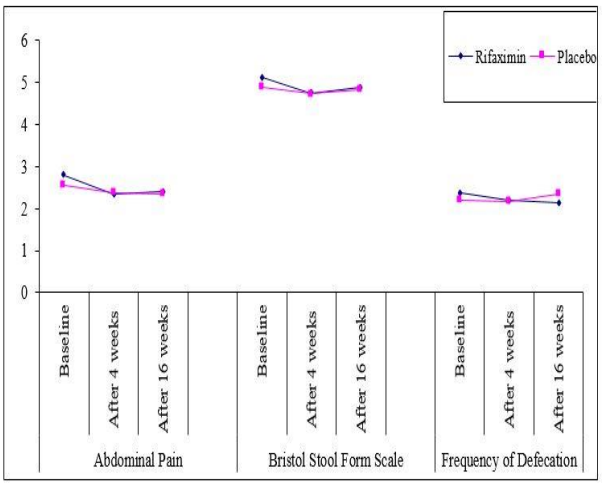

Figure 3: Line graph showing time course of changing abdominal pain, stool form and frequency with rifaximin and placebo in non-SIBO group. Rifaximin and placebo did not show any significant difference in relieving individual IBS symptoms in non-SIBO group.

DISCUSSION

This was a randomized, double blind, placebo-controlled trial conducted in the Gastroenterology department of Dhaka medical college hospital, Dhaka with an objective to find out the efficacy of rifaximin over placebo in non-constipated irritable bowel syndrome with or without SIBO. One hundred four (104) patients were enrolled in this study who were presented with the symptoms of IBS-D and IBS-M. Majority patients were in age 18-30 years in both groups (56.1% in SIBO group and 54% in non-SIBO group). No statistically significant difference had been found in age between two groups. Another study also showed that the prevalence of IBS was highest in 15-24 years of age group. In this study male predominance was seen in both SIBO and non-SIBO group (78% vs. 74.6%).[6] In a study also found male predominance in both SIBO and Non-SIBO group (55.1% vs. 76.0%).[9] Our study was compatible with their findings. The study showed that among 104 non-constipated IBS patients 41 (39%) had SIBO according to culture of proximal small bowel aspirate (distal duodenal), IBS-D patients were more associated with SIBO (83% vs. 60%), Pseudomonas was the most prevalent organism found in culture. In a study in India found 18% SIBO among 80 IBS patients.[9]

Table 4: Comparison between baseline with 4 weeks and 16 weeks diary of the patients in SIBO group.

Symptoms diary	Baseline (n=41) Mean±SD Range (min-max)	After 4 weeks (n=41) Mean±SD Range (min-max)	P value baseline vs. 4 weeks	After 16 weeks (n=41) Mean±SD Range (min-max)	P value baseline vs. 16 weeks
Rifaximin					
Abdominal pain	2.74±1.67 (0.42-7.57)	1.78±1.15 (0.28-6.12)	0.007	2.15±1.66 (0.3-8)	0.033
Bristol stool form scale	5.27±0.57 (4.28-6.42)	4.45±0.69 (3.25-6.5)	0.001	4.57±0.64 (3.3-6.12)	0.001
Frequency of defecation	2.6±0.92 (1.42-5.28)	1.61±0.65 (0.01-3.1)	0.001	1.99±0.88 (1-4.8)	0.001
Placebo					
Abdominal pain	3.05±2.08 (0.37-8.2)	2.75±1.88 (0.62-7.28)	0.719	2.89±1.85 (0.45-7.5)	0.109
Bristol stool form scale	5.25±0.64 (3.71-6.14)	5.15±0.63 (3.91-6)	0.505	5.47±0.46 (4.5-6.12)	0.097
Frequency of defecation	2.73±0.92 (1.42-4.57)	2.52±0.96 (1.45-4.72)	0.119	2.74±0.91 (1.8-5.1)	0.913

Table 5: Comparison of response between Rifaximin and Placebo after 4 and 16 weeks in SIBO group.

Parameters	Rifaximin (n=21) Mean±SD Range (min-max)	Placebo (n=20) Mean±SD Range (min-max)	P value
Symptoms diary 4 weeks after treatment			
Abdominal pain	1.01±0.99 (-1.00-3.01)	0.3±0.46 (-0.63-1.01)	0.006
Bristol stool form scale	0.72±0.61 (-0.65-2.45)	0.10±0.66 (-1.89-1.14)	0.003
Frequency of defecation	0.99±0.76 (-0.1-2.98)	0.21±0.57 (-0.16-1.71)	0.001
Symptoms diary 16 weeks after treatment			
Abdominal pain	0.74±0.95 (-0.89-3.69)	0.16±0.42 (-0.48-0.96)	0.016
Bristol stool form scale	0.70±0.94 (0.81-2.93)	-0.22±0.56 (-1.82-1.13)	0.001
Frequency of defecation	0.61±0.17 (-0.88-1.86)	-0.02±0.16 (-1.29-1.82)	0.013

Whereas in this study we found that frequency of SIBO was 39%. This higher frequency was possibly due to inclusion of IBS patients who had predominance of diarrhea, bloating and flatulence. In a study found that Pseudomonas was the predominant organism in SIBO patients which was compatible with our study.[9]

In this study rifaximin showed statistically significant global satisfactory relief of symptoms over placebo after 4 weeks (90% vs. 20%, p<0.001) and after 16 weeks (66% vs. 15%, p<0.001) in SIBO group. In non-SIBO group, rifaximin showed statistically significant global satisfactory relief of symptoms over placebo after 4 weeks (38.7% vs. 18.8%, p<0.001) but showed no significant response after 16 weeks (25.8% vs. 18.8%, p=0.501). In a study also found that rifaximin had adequate relief in global IBS symptoms during a 4-week follow-up compared with placebo (40% vs. 31%). Their response rate with rifaximin is lower than response rate of this study in SIBO group (90% vs. 40%).[16] Such a low frequency of response in that study might be related to the fact that all the patients with IBS do not have dysbiosis or SIBO. As the patients in that study were not selected for antibiotic treatment by any test for SIBO. In screening phase among SIBO patients mean abdominal pain was 2.74±1.67 in rifaximin group and 3.05±2.08 in Placebo group. Mean Bristol Stool Form scale was 5.27±0.57 and 5.25±0.64 respectively among both groups and mean frequency of defecation per day was 2.6±0.92 and 2.73±0.92 episodes per day. In SIBO group after treatment with rifaximin there was statistically significant improvement of abdominal pain after 4 weeks (2.74±1.67 vs. 1.78±1.15, p=0.007) and the improvement persisted even after 16 weeks (2.74±1.67 vs. 2.15±1.66, p=0.033).

There was also statistically significant improvement in bristol stool form after 4 weeks (5.27±0.57 vs. 4.45±0.69, p =0.001), after 16 weeks (5.27±0.57 vs. 4.57±0.64, p=0.001) and improved frequency of defecation after 4 weeks (2.6±0.92 vs. 1.61±0.65, p=0.001), after 16 weeks (2.6±0.92 vs. 1.99±0.88, p=0.001). But placebo group did not show any statistically significant improvement of abdominal pain, bristol stool form and frequency of defecation after 4 and 16 weeks. When rifaximin was compared with placebo among SIBO group it was found that rifaximin was more effective than placebo in improving abdominal pain after 4 weeks (1.01±0.99 vs. 0.3±0.46, p=0.006), after 16 weeks (0.74±0.95 vs. 0.16±0.42, p=0.016); Bristol stool form after 4 weeks (0.72±0.61 vs. 0.10±0.66, p=0.003), after 16 weeks (0.70±0.94 vs. 0.22±0.56, p=0.001) and frequency of defecation after 4 weeks (0.99±0.76 vs. 0.21±0.57, p=0.001), after 16 weeks (0.61±0.17 vs. -0.02±0.16, p=0.013).

Table 6: Comparison between baseline with 4 weeks and 16 weeks diary of the patients in non-SIBO group.

Symptoms diary	Baseline (n=63) Mean±SD Range (min-max)	After 4 weeks (n=63) Mean±SD Range (min-max)	P value baseline vs. 4 weeks	After 16 weeks (n=41) Mean±SD Range (min-max)	P value baseline vs. 16 weeks
Rifaximin					
Abdominal pain	2.8±1.99 (0.00-7.42)	2.36±1.74 (0.00-7)	0.001	2.41±1.63 (0-6.2)	0.063
Bristol stool form scale	5.12±0.67 (3.42-6.28)	4.74±0.68 (3.89-6.1)	0.001	4.9±0.7 (3.6-6.12)	0.069
Frequency of defecation	2.39±0.82 (1.14-4.14)	2.2±0.78 (1.12-4)	0.001	2.13±0.73 (1.1-4.2)	0.047
Placebo					
Abdominal pain	2.55±1.46 (0.00-5.57)	2.39±1.38 (0.0-6.17)	0.092	2.35±1.35 (0-5.8)	0.106
Bristol stool form scale	4.89±0.88 (3.42-6.98)	4.73±0.85 (3.0-6.21)	0.479	4.84±0.84 3.2-6.34)	0.466
Frequency of defecation	2.21±0.93 (1.14-5)	2.16±0.87 (1.15-4.39)	0.503	2.36±1.05 (1.3-5.4)	0.307

In screening phase among non-SIBO patients, mean abdominal pain was 2.8±1.99 in rifaximin group and 2.55±1.46 in Placebo group. Mean Bristol Stool Form scale was 5.12±0.67 and 4.89±0.88 respectively among both groups and mean frequency of defecation per day was 2.39±0.82 and 2.21±0.93 episodes per day.

Table 7: Distribution of the study patients by side effects (n=104).

Side effects	Rifaximin (n=52)		Placebo (n=52)		P value
	N	%	N	%	
Yes	5	9.61	1	1.92	0.102
No	47	90.39	51	98.08	

In non-SIBO group after treatment with rifaximin, there was statistically significant improvement of abdominal pain, (2.8±1.99 vs. 2.36±1.74, p=0.001), bristol stool form (5.12±0.67 vs. 4.47±0.68, p=0.001), and frequency of defecation (2.39±0.82 vs. 2.2±0.78, p=0.001), after 4 weeks but the improvement did not persist after 16 weeks. But placebo group did not show any statistically significant improvement of abdominal pain, bristol stool form and frequency of defecation after 4 and 16 weeks. When rifaximin was compared with placebo among non-SIBO group, it was found that rifaximin was not more effective than placebo in improving abdominal pain after 4 weeks (0.44±0.98 vs. 0.23±0.65, p=0.318), after 16 weeks 0.39±1.11 vs. 0.27±0.61, p=0.595); Bristol stool form after 4 weeks (0.38±0.54 vs. 0.3±0.84, p=0.655), after 16 weeks (0.22±0.64 vs. 0.19±0.88, p=0.877) and frequency of defecation after 4 weeks (0.19±0.64 vs. 0.1±0.49, p=0.099), after 16 weeks 0.26±0.71 vs. 0.09±0.84, p=0.389). There are several studies showing different antibiotics e.g. metronidazole, norfloxacin, rifaximin which can improve the symptoms of IBS. In a study found that a significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of IBS related abdominal pain (44.3% vs. 36.3%, p=0.03), and Stool form (46.6% vs. 38.5%, p=0.04).[17]

In another study also found that metronidazole improved IBS symptoms significantly compared to placebo.[18] Amoxicillin clavulanic acid and norfloxacin have been shown to reduce stool frequency compared with placebo in a crossover trial in patients with SIBO related diarrhea.[19] Metronidazole and ciprofloxacin have been found to be effective for SIBO associated with Crohn's disease.[20] Similar to their studies our study also showed rifaximin was more effective than placebo in relieving IBS symptoms. In a study also found that antibiotic norfloxacin was more effective than placebo in

improving abdominal pain, Bristol stool form, and stool frequency in patient with SIBO than non-SIBO.[15] In this study we also found rifaximin to be more effective than placebo in improving IBS symptoms in SIBO group than non-SIBO group. In this study 9% patients developed adverse effect predominantly constipation, but it was not statistically significant compared to placebo (9% vs. 2%, p=0.102). In another study also found that the safety profile of rifaximin was similar to that of placebo.[17,21]

Limitations

The study conducted at a single center raises concerns about its generalizability to the broader population within the country, as regional variations could affect outcomes. Additionally, the absence of rifaximin resistance assessment prior to treatment limits the comprehensiveness of the findings. Furthermore, the evaluation solely focused on symptomatic response, neglecting the crucial aspect of bacteriological response through repeat cultures for initially culture-positive patients. These limitations underscore the need for cautious interpretation of the study's results and call for broader, multicenter investigations to obtain a more representative understanding of the population's response to rifaximin treatment.

CONCLUSION

In this study, it was observed that non-constipated IBS patients who had SIBO improved significantly following rifaximin therapy than placebo. Rifaximin reduced abdominal pain, improved stool consistency and reduced stool frequency significantly than placebo in SIBO group and overall improvement of global symptoms. Although improvement also occurred in non-SIBO group but it was not significant compared to placebo. So, it could be a beneficial drug for symptomatic relief of non-constipated IBS patients with SIBO.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130(5):1480-91.
2. Andrews EB, Eaton SC, Hollis KA, Hopkins JS, Ameen V, Hamm LR, Cook SF, Tennis P, Mangel AW. Prevalence and demographics of irritable bowel syndrome: results from a large web-based survey. Aliment Pharmacol Ther. 2005;22(10):935-42.
3. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes. 2017;15(1):35.
4. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA. 2015;313(9): 949-58.
5. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10(7):712-21.
6. Perveen I, Hasan M, Masud MA, Bhuiyan MM, Rahman MM. Irritable bowel syndrome in a Bangladeshi urban community: prevalence and health care seeking pattern. Saudi J Gastroenterol. 2009; 15(4):239-43.
7. Masud MA, Perveen I, Hasan M, Masud MA, Bhuiyan MM, Rahman MM. Irritable bowel syndrome in a Bangladeshi urban community: prevalence and health care seeking pattern. Saudi J Gastroenterol. 2009;15(4):239-43.
8. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol. 2000; 95(12):3503-6.
9. Ghoshal UC, Srivastava D, Ghoshal U, Misra A. Breath tests in the diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome in comparison with quantitative upper gut aspirate culture. Eur J Gastroenterol Hepatol. 2014; 26(7):753-60.
10. Erdogan A, Rao SS, Gulley D, Jacobs C, Lee YY, Badger C. Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. Neurogastroenterol Motil. 2015;27(4):481-9.
11. Ghoshal UC, Kumar S, Mehrotra M, Lakshmi C, Misra A. Frequency of small intestinal bacterial overgrowth in patients with irritable bowel syndrome and chronic non-specific diarrhea. J Neurogastroenterol Motil. 2010;16(1):40-6.
12. Dupont HL. Review article: evidence for the role of gut microbiota in irritable bowel syndrome and its potential influence on therapeutic targets. Aliment Pharmacol Ther. 2014;39(10):1033-42.
13. Shukla R, Ghoshal U, Dhole TN, Ghoshal UC. Fecal Microbiota in Patients with Irritable Bowel Syndrome Compared with Healthy Controls Using Real-Time Polymerase Chain Reaction: An Evidence of Dysbiosis. Dig Dis Sci. 2015;60(10):2953-62.
14. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology. 2016;16:5085.
15. Ghoshal UC, Abraham P, Bhatt C, Choudhuri G, Bhatia SJ, Shenoy KT, et al. Epidemiological and clinical profile of irritable bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. Indian J Gastroenterol. 2008;27(1):22-8.
16. Ghoshal UC, Srivastava D, Misra A, Ghoshal U. A proof-of-concept study showing antibiotics to be more effective in irritable bowel syndrome with than without small-intestinal bacterial overgrowth: a randomized, double-blind, placebo-controlled trial. Eur J Gastroenterol Hepatol. 2016;28(3):281-9.
17. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with

irritable bowel syndrome without constipation. N Engl J Med. 2011;364(1):22-32.
18. Nayak AK, Karnad DR, Abraham P, Mistry FP. Metronidazole relieves symptoms in irritable bowel syndrome: the confusion with so-called 'chronic amebiasis'. Indian J Gastroenterol. 1997;16(4):137-9.
19. Attar A, Flourié B, Rambaud JC, Franchisseur C, Ruszniewski P, Bouhnik Y. Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhea: a crossover, randomized trial. Gastroenterology. 1999;117(4):794-7.
20. Castiglione F, Rispo A, Di Girolamo E, Cozzolino A, Manguso F, Grassia R, Mazzacca G. Antibiotic treatment of small bowel bacterial overgrowth in patients with Crohn's disease. Aliment Pharmacol Ther. 2003;18(12):1107-12.
21. Lauritano EC, Gabrielli M, Scarpellini E, Lupascu A, Novi M, Sottili S, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol. 2008;103(8):2031.

Cite this article as: Podder S, Rahman MM, Hossain MI, Datta R, Alam J, Kibria MG. Efficacy of rifaximin among non-constipated irritable bowel syndrome patients with or without small intestinal bacterial overgrowth: a randomised, double-blind, placebo-controlled trial. Int J Res Med Sci 2024;12:1056-64.