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Original Article

Efficacy of Rifaximin Therapy in Patients with Irritable Bowel Syndrome without Constipation- A Tertiary Hospital Based Clinical Trial

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ABSTRACT

Introduction: *Irritable bowel syndrome (IBS) is a common clinical problem encountered by primary care physicians and gastroenterologists. Studies have demonstrated the variable efficacy of Rifaximin in adult with IBS.* ***Objective:*** *To see the efficacy of Rifaximin, the non-absorbed antibioticwith the placebo in reducing symptoms in adults with IBS without constipation and also compare its side effects with placebo.* ***Methods and Materials:*** *A total of 108 patients from 18-60 years of both sexes with the diagnosis of IBS were selected purposively form the Gastroenterology OPD ofBSMMU. Diagnosis of IBS weremade on the basis of Rome III criteria and who did not have red flags sign. Then all patients underwent screening investigations (Hb%, TC, DC, ESR, Stool R/E, Blood glucose, serum TSH, and short colonoscopy) to exclude organic disease. Improvement was assessed by changes of symptoms monitored by 7 point Likert scale for Global IBS Symptom, abdominal bloating, abdominal pain, 5point stool consistency and average daily bowelmovement.* ***Result:*** *At the end of treatment Rifaximin group showed significant improvement of Global IBSsymptom (Rifaximin vs. placebo 50% vs. 14%). The response was persistent up to 10 weeks after treatment. Other symptoms like bloating, abdominal pain, stool consistency and daily bowel movement improved significantly. But this symptom somewhat deteriorated at the end offollow up (At 70 days after treatment).* ***Conclusion:*** *Rifaximin was effective in reducing Global IBS symptom without constipation and the effect waspersistent. However, it is relatively more effective than placebo. Rifaximin also* show significant clinical improvement in bloating, abdominal pain,

Key words: Rifaximin, Irritable bowel syndrome, Efficacy

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INTRODUCTION

The irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurring symptoms of abdominal pain, bloating, and altered bowel function in the absence of structural, inflammatory, or biochemical abnormalities [1]. IBS often does not respond to current treatment options, including dietary and lifestyle modifications, fiber supplementation, psychological therapy, and pharmacotherapy [2, 3]. Because no reliable biologic or structural markers have been identified, the effects of pharmacotherapy are typically assessed by asking patients to report whether they had adequate relief of IBS symptoms (with a binary response of yes or no)[4]. Given the limitations of available therapies, there is an unmet medical need for novel therapeutic approaches.

Alterations in gut flora have been identified as potentially important. Results of recent studies indicate that up to 84% of patients with IBS have an abnormal lactulose breath test result, suggesting small intestinal bacterial overgrowth [5, 6]. On the basis of this concept, the antibiotic neomycin can significantly improve the symptoms of IBS [7, 8]. Although neomycin seems to improve symptoms, it effectively eliminates bacterial overgrowth in only about 25% of patients with IBS [6]. Ciprofloxacin, levofloxacin, neomycin, and metronidazole can all be effective for the treatment of bacterial overgrowth associated with IBS, but they have not tested for IBS. An ideal antibiotic for IBS is, arguably, one with negligible systemic absorption, minimal side effects, and high efficacy for bacterial overgrowth. Rifaximin is a gut-selective antibiotic with negligible systemic absorption (0.4%) and broad-spectrum activity vitro against gram-positive and gram-negative aerobes anaerobes [6]. On the basis of this broad spectrum, eradication rates with rifaximin in bacterial overgrowth are high as 70% [9]. Furthermore, rifaximin has a similar tolerability profile to that of placebo and has known activity against Clostridium difficile [10]. These properties make it a good candidate for treating a condition that is as common as IBS. Moreover, Rifaximin become recently available in our country and there is no previous study of Rifaximin on IBS without constipation in our country, as far as I have searched the literature and web.

Bangladesh is a country where study shown that 24.4 % population are suffering from IBS [11]. It is a foremost responsibility of the clinical researchers to develop an appropriate management for IBS patients. Thus they can live a well-off life reducing the symptoms of IBS. Antibiotic therapy could be a good option for controlling microbial effect of IBS. In that case oral administration of Rifaximin should be used due to its good efficacy against both gram positive and gram negative organism as well as it has reduced chance of systemic absorption.

OBJECTIVE

To see the efficacy of Rifaximin, the non-absorbed antibioticwith the placebo in reducing symptoms in adults with IBS without constipation and also compare its side effects with placebo.

MATERIALS AND METHOD

Thisdouble blinded randomized control trial done from Sept 2012 to May 2013, in the department of Gastroenterology, BSMMU, Dhaka. Patients fulfilling Rome III criteria for IBS without constipation attending Gastroenterology department of BSMMU was selected as the study population. Patient excluded from study were Constipation predominant IBS,

History of Inflammatory Bowel Disease, Diabetes Mellitus, Unstable thyroid disease, previous abdominal surgery (other than cholecystectomy or appendicectomy). Calculated sample size was 284, but for time and resource constrain 108 were enrolled purposively and were randomized by lottery method, 54 in each group. Seven patients in placebo group left the study. So 54 in Rifaximin group and 48 in placebo group completed the study.

All recruited patients were assigned with a unique ID number. The drug Rifaxamin and placebo was confined to the co-investigator only. All patients were assessed using 7 point Likert scale for abdominal pain and bloating and 5-point scale for stool consistency.

Statistical analysis was done using the statistical package for social science (SPSS version 20). Both primary and secondary outcome were assessed. Paired T test was done to compare the symptom before and after treatment for Rifaxamin group and placebo group and Chi square test was applied to compare between Rifaximin group and placebo group. Every ethical issue was discussed with the patients regarding the study and informed written consent was obtained.

RESULTS

In total 101 patients had completed the study. Fifty-four received Rifaximin, 54 patients to received placebo preparation. Seven patientswere dropped out from the study in placebo group. Ultimately 101 patients completed the trial, 54 (33 Males, 21 Female) patients in the Rifaximin and 47 (32 Male, 15 Female) patient in the placebo group.

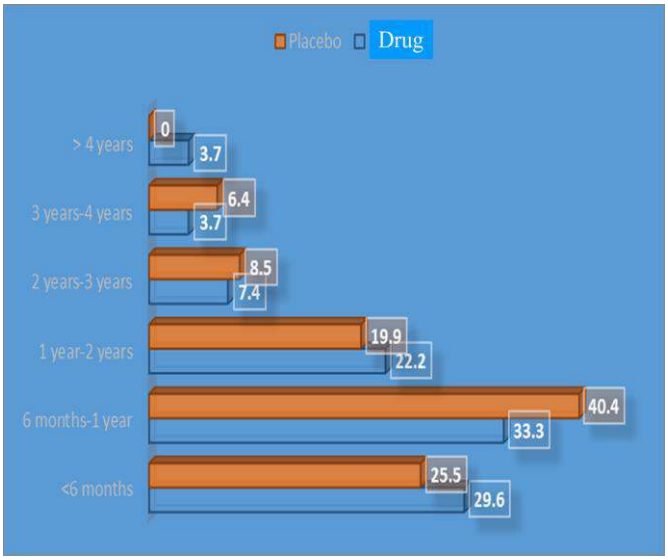

Figure-I: Duration of symptom

Table-I: Global IBS Symptom for the Subject who are at baseline Likert scale 5,6

			Baseline	Day 7	P Value	Day 14	P Value	Day 28	P Value	Day 70	P Value
Global IBS Symptom	Drug	Likert 5,6	32	0	.241	1	.776	1	.658	2	.370
		Likert 3,4	0	8		15		14		14	
		Likert 0,1,2	0	24		16		17		16	
		Total	32	32		32		32		32	
	Placebo	Likert 5,6	35	7	.o89	2	.156	10	.150	13	.621
		Likert 3,4	0	23		28		21		18	
		Likert 0,1,2	0	5		5		4		4	

		Total	35	35		35		35		35

Table-II: Global IBS Symptom for the Subject who are at baseline Likert scale 5,6

			Baseline	Day 7	P Value	Day 14	P Value	Day 28	P Value	Day 70	P Value
Global IBS Symptom	Drug	Likert 5,6	32	0	.241	1	.776	1	.658	2	.370
		Likert 3,4	0	8		15		14		14	
		Likert 0,1,2	0	24		16		17		16	
		Total	32	32		32		32		32	
	Placebo	Likert 5,6	35	7	.089	2	.156	10	.150	13	.621
		Likert 3,4	0	23		28		21		18	
		Likert 0,1,2	0	5		5		4		4	
		Total	35	35		35		35		35	

Table-III: Bloating Symptom for the Subject who are at baseline Likert scale 3,4

			Baseline	Day 7	P value	Day 14	P value	Day 28	P value	Day 70	P value
Bloating	Drug	Likert 5,6			.001		.093		.065		.027
		Likert 3,4	27	9		9		9		12	
		Likert 0,1,2		18		18		18		15	
		Total	27	27		27		27		27	
	Placebo	Likert 5,6									
		Likert 3,4	31	17	.058	17	.015	19	.003	24	.001
		Likert 0,1,2		14		14		12		7	
		Total	31	31		31		31		31	

Table- IV: Abdominal pain Symptom for the Subject who are at baseline Likert scale 5,6

		Baseline	Day 7	P value	Day 14	P value	Day 28	P value	Day 70	P value
Drug	Likert 5,6	20			1		1		1	
	Likert 3,4		18	.040	8	.482	7	.384	13	.447
	Likert 0,1,2		2		11		12		6	
	Total	20	20		20		20		20	
Placebo	Likert 5,6	18	2		2		1		4	
	Likert 3,4		15	.003	15	.006	16	.427	14	.044
	Likert 0,1,2		1		1		1		0	
	Total	18	18		18		18		18	

Table- V: Abdominal pain Symptom for the Subject who are at baseline Likert scale 3,4

			Baseline	Day 7	P value	Day 14	P value	Day 28	P value	Day 70	P value
Abdominal pain	Drug	Likert 5,6									
		Likert 3,4	33	22	.040	18	.428	15	.384	21	.447
		Likert 0,1,2		11		15		18		12	
		Total		33		33		33		33	
	Placebo	Likert 5,6						1		1	

	Likert 3,4	27	23	.003	22	.006	23	.427	23	.044
	Likert 0,1,2		4		5		3		3	
	Total		27		27		27		27	

Table-VI: Average Bowel Movement for the Subject who are at baseline movement scale 5,6

			Baseline	Day 7	P value	Day 14	P value	Day 28	P value	Day 70	P value
Average daily Bowel Movement	Drug	Bowel mov 5,6	3		.160		.459		.090		.198
		Bowel mov 3,4		2		1		2		2	
		Bowel mov 1,2		1		2		1		1	
		Total	3	3		3		3		3	
	Placebo	Bowel mov 5,6	4	1	.007	1		1		2	.00
		Bowel mov 3,4		3		3	.003	3	.132	2	
		Bowel mov 1,2									
		Total	4	4		4		4		4	

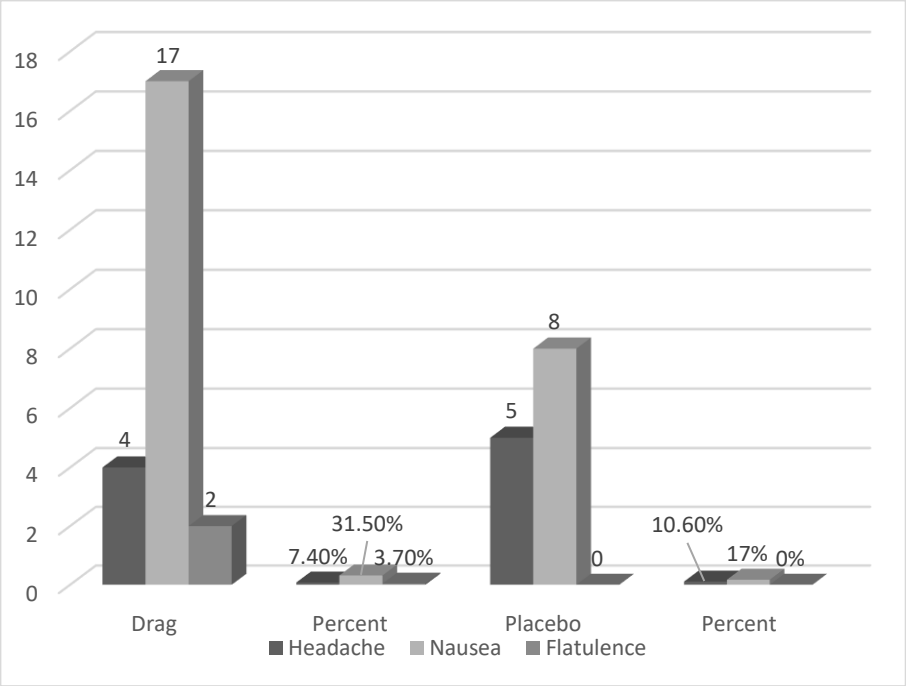

Figure 2: Adverse Effect

DISCUSSION

Irritable bowel syndrome is the most common functional disorder of the alimentary tract which may affect up to 24.4% of adult populationin our country. Several groups of drugs are used in treatment of irritable bowel syndrome such as antispasmotics, anticholenargicsanti depressant. Rifaximin is non-systemic antibiotic which has <0.4% absorption and excellent gastrointestinal bioavailability. It has been shown to affect the alteration of normal gut flora. Several studies showed that Rifaximin could be efficacious for symptoms relief in irritable bowel syndrome. But in view of methodological defects associated with most of the studies no definitive judgment about the efficacy can be given, so a well-designed, carefully executed study is needed, to clear the issue.

Till date no such study has been conducted in Bangladesh. So a prospective double-blind, placebo controlled, randomized trial has been conducted on the Bangladeshi patients with irritable bowel syndrome to see the efficacy of Rifaximin. 101 patients completed the trial. Among them, 65 patients were males and 36 were females. Although the prevalence is more in the female, in this study female patients were less in number because they were reluctant to attend repeatedly for follow-up and they were not interested to perform colonoscopy for social and cultural problem.

In this study it was found that Rifaximin improved the global IBS symptom in 50% patients which was statistically significant. Improvement of other symptom like-bloating, abdominal pain, stool consistency and average daily bowel movement was also noticed and the improvement was relatively better than placebo ($p<0.05$). The study thoroughly investigated the patients to exclude the organic disease. But we did not exclude the coeliac disease and lactose intolerance by appropriate investigation, such as enteroscopy or ileoscopy. We could not exclude the phychiatric association by structured psychiatric evaluation or all study sample.

Mark Pimentel et al performed two identically designed, phase 3, double-blind,placebo-controlled trials (TARGET 1 and TARGET 2), patients who had IBS without constipation were randomly assigned to either Rifaximin at a dose of 550 mg or placebo, three times daily for 2 weeks, and were followed for an additional 10 weeks. The primary endpoint, the proportion of patients who had adequate relief of global IBS symptoms, and the key secondary end point, the proportion of patients who had adequate relief of IBS-related bloating, were assessed weekly. Adequate relief was defined as self-reportedrelief of symptoms for at least 2 of the first 4 weeks after treatment. Other secondary end points included the percentage of patients who had a response to treatment as assessed by daily self-ratings of global IBS symptoms and individual symptoms of bloating, abdominal pain, and stool consistency during the 4 weeks after treatment and during the entire 3 months of the study.
Significantly more patients in the Rifaximin group than in the placebo group hadadequate relief of global IBS symptoms during the first 4 weeks after treatment (40.8% vs. 31.2%, $P = 0.01$, in TARGET 1; 40.6% vs. 32.2%, $P = 0.03$, in TARGET 2; 40.7% vs. 31.7%, $P<0.001$, in the two studies combined). Similarly, more patients in the rifaximin group than in the placebo group had adequate relief of bloating (39.5% vs. 28.7%, $P = 0.005$, in TARGET 1; 41.0% vs. 31.9%, $P = 0.02$, in TARGET 2; 40.2% vs. 30.3%, $P<0.001$, in the two studies combined). In addition, significantly more patients in the rifaximin group had a response to treatment as assessed bydaily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency. The incidence of adverse events was similar in the two groups.In our study, following Rifaximin consumption, Global IBS symptom was improved in 50% patients at 14 days after treatment and the improvement was persistent up to 70 days after treatment. This improvement was a bit more than that of Pimentel et al result. It may be due to variation of body mass index and variation of colonic bacteria of our study populations.

CONCLUSION

From this study it can be concluded that Rifaximin was effective in reducing Global IBS symptom in IBS without constipation and the effect was persistent. However, it is relatively more effective than placebo. Secondly Rifaximin also show significant clinical improvement in bloating, abdominal pain, stool consistency and average daily bowel movement. But the effect was not

persistent. The safety profile of Rifaximin was similar to that of placebo. So a large placebo control trial for longer period are warranted for further evaluation of efficacy of Rifaximin before its recommendation as a therapeutic agent for the treatment of irritable bowel syndrome patients in Bangladesh.

CONFLICT OF INTEREST:
No conflict of interest.

FUNDING:
None

ETHICAL APPROVAL:
Ethical approval was taken from the ethical review board of the hospital.

REFERENCES

1. *Brandt LJ2009;.An evidence-based position statement on the management of irritable bowel syndrome . Am J Gastroenterol. 104:1–35.*
2. *Cash BD, Chey WD 2003. Advances in the management of irritable bowel syndrome. CurrGastroenterol Rep .5:468-75.*
3. *Schoenfeld P 2005. Efficacy of current drug therapies in irritable bowel syndrome: what works and does not work. Gastro-enterolClin North Am:34:319-35.*
4. *Spiegel B, Camilleri M, Bolus R, et al 2009. Psychometric evaluation of patient-report-ed outcomes in irritable bowel syndrome randomized controlled trials: a Rome Foundation report. Gastroenterology. 137:1944-53.*
5. *PimentelM,ChowEJ,LinHC2000.Eradicationo fsmallintestinalbacterialovergrowthreducessy mptomsofirritable bowel syndrome.AMJGastroenterol.95:3503-6.*
6. *PimentelM,ChowEJ,LinHC 2003.Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study.AmJGastroenterol.98:412-9.*
7. *7.AttarA,FlourieB,RambaudJC,Franchisseur C,RuszniewskiP,BouhnikY 1999.Antibioticefficacyinsmallintestinalbacter ialovergrowth-relatedchronicdiarrhea:acrossover,randomize dtrial.Gastroenterology.117:794-7*
8. *JiangZD,DuPontHL 2005.Rifaximin:invitroandinvivoantibacterial activity— areview.Chemotherapy.51Suppl1:67-72.*
9. *Drossman DA, Camilleri M, Mayer EA, Whitehead WE 2002. AGA technical review on irritable bowel syndrome. Gastroenterology.;123:2108-31.*
10. *Masud MA, Hasan M, Khan AK 2001.Irritable bowel syndrome in a rural community inBangladesh: prevalence, symptoms pattern, and health care seeking behavior. Am J Gastroenterol. 96 :1547-52.*
11. *Mayer EA 2008 .Clinical practice. Irritable bowel syndrome. N Eng J Med. 358:1692–9.*