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Rifaximin Therapy in Patients of Irritable Bowel Syndrome Without Constipation Randomized Controlled Trial

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ABSTRACT

Irritable Bowel Syndrome (IBS) is a common condition affecting lives of patients across the globe. The statistics are much worse than previously thought. Studies showed that 9 - 23% of the world population is suffering from IBS. Very few options are available with inadequate efficacy and a dire need for newer options. Rifaximin is one such promising drug. This study has been conducted to determine the efficacy of rifaximin therapy in IBS patients. **Objective:** The efficacy of rifaximin was compared with a placebo in controlling the symptoms of irritable bowel syndrome. **Study design:** Randomized Controlled Trial. **Setting:** Medicine Outpatient Clinical Department, Allied Hospital, Faisalabad. **Duration of study:** 27-05-2015 to 26-11-2015. **Sample size:** 620 (310 in each group) were enrolled in the study after fulfilling inclusion criteria. **Sampling technique:** Non-Probability Consecutive Sampling. **Results:** 620 patients were enrolled in this study. Mean age of study population was 28.31 ± 6.45 (Table I). 298 (48.1%) were male and 322 (51.9%) were female. Patients were divided into group A and Group B. Group A received rifaximin and group B received placebo. In group A, improvement in IBS symptoms with Rifaximin was noted in 171 (55.1%) as compared to 90 (29.03%) in group B (p-value <0.0001). **Conclusion:** Rifaximin is effective in treatment of IBS without constipation. Prescribing rifaximin should be considered in treatment of IBS patients as it provides a promising treatment option which is cost effective and has fewer side effects.

Keywords: Irritable Bowel Syndrome, Rifaximin, Placebo

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INTRODUCTION

Irritable bowel syndrome (IBS) is a clinical condition of unknown etiology characterized by abdominal pain or discomfort for more than 3 months duration associated with altered bowel habits.[1] IBS is a widespread condition with a huge health related costs marked by impaired health-related quality of life (HRQOL), loss of working productivity and huge expenditures.[2] It has been estimated that, more than 10% of population is suffering from IBS resulting in considerable healthcare costs.[3] unfortunately, treatment options are scarce and not well established.[4] Efficacy of pharmacotherapy is typically assessed by patients subjective reporting of symptoms relief because of absence of any biological or structural markers of IBS.[5] it is of utmost importance for the physician to realize the role of a strong physician patient relationship for building up realistic expectations and treatment options efficacy[6]. IBS is a chronic condition in which patient faces difficulties because of bouncing around to different specialties over many years with different diagnosis and battery of investigation mainly because of lack of interest and frustration of physician in treatment of IBS, stigma of condition being a psychiatric disorder or lack of clinical, physical, or laboratory diagnostic criteria.[7] Given the limitations of available therapies, there is an unmet medical need for novel therapeutic approaches.[8]

There is alteration of intestinal flora in patients of IBS.[9] This intestinal microbiota is necessary for maintaining normal GI function.[10] Its important functions are trophic, metabolic and protective. It helps in digestion and absorption of nutrients and produces beneficial substances such as short-chain fatty acids (SCFA)[11]. It is a barrier against bacteria by preventing adherence to intestinal mucosa and interaction with epithelial cells, influencing proliferation and differentiation of epithelial cell layer and the development of the enteric immune system. This lead investigator to use new antimicrobial drugs for treatment of irritable bowel syndrome. The use of systemic antibiotics has been reported with mixed results.[12]

Rifaximin is a semisynthetic derivative of rifamycin, which contains an additional benzimidazole ring that prevents rifaximin from being absorbed systemically (absorption 0.4% after oral administration).

Rifaximin targets the gut flora and has shown efficacy in small-scale studies of IBS.[13] Recently a study, has showed that rifaximin was effective in adequate relief of symptoms of Irritable bowel syndrome in 40.8% of patients as compared to 31.2% taking placebo.[14]

Current therapeutic options available are not effective in controlling symptoms of Irritable bowel syndrome. New therapeutic strategies like rifaximin are required to solve this problem. We studied the role of rifaximin in irritable bowel syndrome to formulate new recommendations for irritable bowel syndrome treatment.

METHODOLOGY

Study Design: Randomized Controlled Trial.

Place of Study: Medicine Outpatient Clinical Department, Allied Hospital, Faisalabad.

Duration of Study: 27-05-2015 to 26-11-2015.

Sample Technique: Non-Probability Consecutive.

Sample Size: 620 (310 in each group) were enrolled in the study after fulfilling inclusion criteria.

Methods: Approval of ethical review committee was obtained. It was a randomized Controlled Trial done at Department of Medicine, Allied Hospital, Faisalabad for duration of 6 Months from 27-05-2015 to 26-11-2015. 620 (310 in each group) were enrolled in study after fulfilling inclusion criteria. Sample size was calculated by using WHO sample size calculator for two proportions (2-sided) taking P1=40.8%, P2=31.2%, power of study=80% and level of significance = 5%. Efficacy of rifaximin was compared with placebo in controlling the symptoms of irritable bowel syndrome. Irritable bowel syndrome was defined by Rome III criteria i.e., Symptoms of recurrent abdominal pain or discomfort at least three days per month in the last three months, associated with two or more of the following symptoms: a) pain is relieved by a bowel movement, b) onset of pain is related to a change in frequency of stool, c) Onset of pain is related to a change in the appearance of stool. Efficacy was measured in terms of relief of IBS symptoms (bloating, abdominal pain, diarrhea) as assessed by Likert scoring system. An average improvement of $\geq$3 score on Likert scoring system from baseline score of $\geq$7 at 10 weeks of follow up was taken as significant. Patients of both genders with ages between 18 to 70 years patients of irritable bowel syndrome (as assessed by Rome III criteria) without constipation with a mean Likert Score of $\geq$7 at baseline were be included. Patients who have taken antibiotics during last two weeks or rifaximin within 60 days of randomization of participant, patients who were pregnant, lactating, diabetes mellitus (Fasting Blood Sugar >126mg/dl and random blood sugar >200mg/dl), diagnosed case of thyroid disease, history of previous abdominal surgery, renal (creatinine >3.0mg/dl) were excluded from study. Informed consent was taken from each participant of the study. Patients were randomly divided into two group (A & B) using computer generated random number table. Group A was given Rifaximin (550mg) twice daily for 2 weeks. Group B was given placebo (multivitamin) for 2 weeks.

Patients were followed for adequate relief of symptoms of irritable bowel syndrome for 10 weeks. Adequate relief was defined as self-reported relief of symptoms assessed by a standardized questionnaire filled by principal investigator at end of treatment and 10 weeks after treatment.

All the collected information transferred to SPSS version 20 and analyzed accordingly. Mean and standard deviation were calculated for all quantitative variables like age. Frequency and percentage were calculated for all qualitative variables like gender and efficacy of drug. Chi square test was applied to compare efficacy for both groups. P value of <0.05 was considered as significant. Effect modifiers like age and gender were controlled by stratification. Post-stratification chi-square test was applied.

RESULTS

Total 620 patients were enrolled in this study. Mean age of study population was 28.31$\pm$6.45 (Table 1). 298 (48.1%) were male and 322 (51.9%) were female (Figure 1). Patients were divided into group A and Group B. Group A received rifaximin and group B received placebo. In group A, improvement in IBS symptoms with rifaximin was noted in 171 (55.1%) as compared to 90 (29.03%) in group B (p-value <0.0001) (Table 2).

Effect modifiers were calculated for age, gender and duration of symptoms which were statistically insignificant. (Table 3, 4, 5)

Table 1: Demographics of Study Population

	Age
Mean	27.31
Std. Deviation	6.452
Minimum	18
Maximum	50

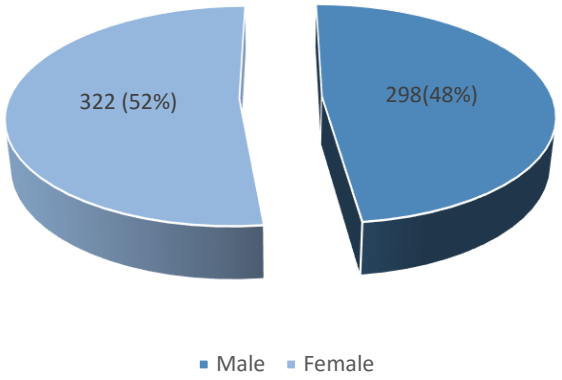

Figure 1: Gender Distribution

Table 2: Efficacy in group A and group B

		Efficacy		Total
		Yes	No	
Groups	A	171	139	310
	B	90	220	310
Total		261	359	620
Pearson Chi-Square		43.414		
P-value		0.0001		

Table 3: Effect modifier for age stratification

		Groups		Total
		A	B	
Age Stratification	18-30	202	205	407
	31-45	108	103	211
	>45	0	2	2
Total		310	310	620
Pearson Chi-Square		2.141		
P-value		0.343		

Table 4: Effect modifier for gender

		Groups		Total
		A	B	
Gender	Male	151	147	298
	Female	159	163	322
Total		310	310	620
Pearson Chi-Square		0.103		
P-value		0.748		

Table 5: Effect modifier for duration of symptom

		Duration of Symptoms			Total
		<1 years	1-3 years	>3 years	
Groups	A	99	95	116	310
	B	117	83	110	310
Total		216	178	226	620
Pearson Chi-Square		2.468			
P-value		0.291			

DISCUSSION

IBS is a very common gastrointestinal disease which is affecting the quality of life of affected population. Its incidence and prevalence is far more than what was expected before. It has been reported to be from 10% in some populations to 23% in more severely affected populations. The pathophysiology of this disease though extensively studied still remains elusive.[15] There are multiple theories regarding the pathogenesis of this disease one more complex than other. There is no cure available for the treatment of this disease and physicians solely rely on symptomatic treatment.[16] These symptomatic treatments are not satisfactory and there is a continued unmet need for new treatment options. Many new treatment options are emerging on the horizon and one of these treatment options is rifaximin therapy which has shown promising results in initial trials though more trials are needed on a larger scale and randomization of study population to document the efficacy of this novel option in IBS.

This study was conducted to establish the efficacy of rifaximin in patients of IBS without constipation. Efficacy of rifaximin was compared with placebo in this study. It was a small study with 620 patients enrolled and 310 patients were assigned to each group, Group A received Rifaximin and Group B received placebo.

It was found that rifaxmin is more efficacious in IBS patients as compared to placebo drug. These results are supported by many other clinical trials which show that rifaxmin is effective in IBS patients.

In a study by Pimentel M, it was found that 2-week rifaximin treatment achieved symptom improvement that persisted ≥12 weeks post-treatment.[17] It supports the results of this study which also shows the efficacy of rifaximin treatment after 10 weeks follow up. This persistent effect of rifaximin makes it a desirable drug in IBS patient as compared to other treatment options in which long term daily administration of medication is needed to achieve

desired results. This effect also makes it cheaper as compared to other medication.

In 2016, DuPont HL shed light on the understanding mechanisms of the actions of rifaximin in selected gastrointestinal diseases.[18] Gut microbiota dysbiosis and proinflammatory activities are thought to significantly contribute to disease pathophysiology of these conditions. Rifaximin may resolve gut microbiota dysbiosis by promoting GI colonization of beneficial bacterial species without drastic alterations in overall diversity. Rifaximin-induced changes in the production and metabolism of bacteria-produced agents (e.g. deoxycholic acid, lipopolysaccharides) also may help to preserve normal gut microbiota. Rifaximin may suppress local and systemic inflammatory processes by preserving epithelial function (e.g. limiting bacterial translocation), modulating bacterial virulence and reducing proinflammatory cytokine production. It explains the efficacy of rifaximin in IBS.

Laterza L et al conducted a study in 2015 on Rifaximin for the treatment of diarrhoea-predominant irritable bowel syndrome. Rifaximin, with its low systemic absorption and no clinically significant interactions with other drugs, may represent a treatment of choice for IBS, mainly due to its ability to act on IBS pathogenesis, through the modulation of gut microbiota. It is in accordance with my study which concluded the superior role of rifaximin in IBS.[19] It was a small study with no double blinding and larger studies are required to draw further conclusions.

CONCLUSION

Rifaximin is effective in treatment of IBS without constipation. Prescribing rifaximin should be considered in treatment of IBS patients as it provides a promising treatment option which is cost effective and has fewer side effect.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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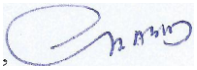
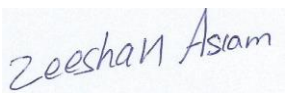
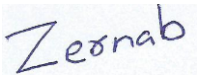
Dr. Ghulam Abbas Tahir Assistant Professor of Medicine, FMU/Allied Hospital, Faisalabad	Data collector & Manuscript writing	
Dr. Muhammad Zeeshan Aslam Assistant Professor, Independent Medical College, Faisalabad	Results, Discussion & References	
Dr. Zernab Postgraduate Trainee, Madina Teaching Hospital, Faisalabad	Co-Author	
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