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EFFICACY OF RIFAXIMIN VERSUS PROBIOTICS IN THE PATIENTS OF DIARRHEA PREDOMINANT IRRITABLE BOWEL SYNDROME

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ABSTRACT

Background: IBS-D is chronic functional GI disorder characterized by abdominal pain, diarrhea, bloating and mucus discharge. Along with disturbance in brain gut axis, dysbiosis i.e. imbalance in gut microbiota plays an important role in the development of symptoms. Literature showed that both rifaximin, a non-systemic antibiotic which acts by suppressing bacterial gene expression and probiotics (VSL#3) by modulating the gut microbiota helps in amelioration of disease symptoms. This study was carried out to compare efficacy and safety of rifaximin and probiotics, when given in IBS-D patients. **Methodology:** It was an open-label, parallel group, prospective, randomized and comparative study, in 138 patients diagnosed with IBS-D using ROME IV criteria, who were divided into two groups with either tab rifaximin 550 mg BD or tab VSL#3 BD for 14 days. Assessment was done by using symptom score scale and pre-prepared adverse drug monitoring performa at 2weeks, 4 weeks and 6 weeks after treatment. **Results:** Both rifaximin and VSL#3 were found to be effective in improving total relief after treatment. Improvement in total relief rate from baseline was 69.4% and 75% (p=0.578) of patients at 2 weeks in rifaximin and VSL#3 respectively which increased to 86% with rifaximin whereas decreased to 56.25% (p=0.004) with VSL#3 during follow up period at 6 weeks. During 6 weeks of the study, adverse drug events were found comparable in both the groups i.e. 47% in rifaximin and 28% in VSL#3. **Conclusion:** VSL#3 was found to be non-inferior with rifaximin during treatment period in the patients of IBS-D.

KEYWORDS: IBS-D, Rifaximin, ROME IV, VSL#3.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder that affects 4.2%-7.5% of the population in India, with diarrhea predominant IBS being the commonest of the four subtypes.[1] IBS is more commonly seen in the age group of 50-60 years, with an increasing prevalence seen with advancing age.[2]

The Rome IV Committee has redefined IBS based on abdominal and bowel symptoms that occur with sufficient frequency in affected patients in 2016.[3] According to these criteria, IBS with predominant diarrhea (IBS-D) was classified when there is >25% of bowel movements with bristol stool form scale (BSFS) types 6 or 7 and<25% with BSFS types 1 or 2.[4] So far, IBS has been strictly attributed to dysbiosis i.e alteration in gut microbiota[5] seems to be responsible for visceral hypersensitivity leading to abdominal pain and diarrhea which are the most bothersome features to the patient.[6] In addition to abdominal pain and diarrhea, patients also present with abdominal distension, bloating and mucus discharge in stool which altogether significantly affects the quality of life.[7] If not treated, patients can develop non gastro-intestinal symptoms as well, like headache, myalgias, sleep disorders and depression.[8] No laboratory tests are available for its exact diagnosis, it is mostly based on clinical history and the latest Rome IV criteria.[9] Both non-pharmacological and pharmacological options are available for the treatment. Though non pharmacological treatments are safer but their efficacy is not well defined, and there is less patient compliance with these interventions.[10] Pharmacological treatment is the mainstay and drugs like loperamide,[11] eluxadoline,[12] TCA's (tricyclic antidepressants), SSRIs (selective serotonin reuptake inhibitors) and serotonin antagonists[13] have been tried and found to be effective in improving few symptoms but are associated with several side effects.[14] Since alteration in gut microflora has a significant role in its pathogenesis, so drugs which either kill or modulate the gut bacterias are found to be helpful in reducing help reduce symptoms. Rifaximin, a rifamycin derivative, which acts by bacterial gene

suppression is preferably being used in the patients of IBS-D, since its approval in 2015.[15] Probiotics, which contain live organisms, act by modulating the pathogenic bacterial species in the gut,[16] VSL#3 being a multi-strain probiotic (three strains of Bifidobacterium (B. breve, B. infantis and B. longum); one strain of Streptococcus (S. salivarius subspecies thermophilus) and four strains of Lactobacillus (L. plantarum, L. bulgaricus, L. acidophilus and L. casei) has also been found to improve the overall symptoms of IBS-D patients.[17]

During thorough literature search, no such study has been found worldwide which compares the efficacy of Rifaximin and VSL#3 in the patients of IBS-D. The present study was therefore conducted in Indian population to compare the efficacy of rifaximin and VSL#3 in patients of irritable bowel syndrome with diarrhea using symptom score scale.

MATERIAL AND METHODS

Study design

The present study was as an open labelled, parallel group, prospective, randomized, comparative clinical study conducted by the Department of Pharmacology and Department of Internal Medicine at Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India from February 2019-January 2020. The study was done by the principles of Good Clinical Practice (GCP) and Declaration of Helsinki and was approved by Institutional Ethics Committee (IEC). The study included 138 patients, who were initially screened according to predefined inclusion and exclusion criteria. The eligible patients were randomly assigned to two study groups i.e. Group 1 and Group 2 with the help of randomly generated computer numbers. All patients were followed up for six weeks. During the study, patients were not permitted to take any non-study drugs.

Inclusion criteria- i) Patients aged between 18 years to 60 years of either gender

ii) Patients fulfilling ROME Criteria IV of IBS:
Recurrent abdominal pain, on an average, at least 1 day/week in the last 3 months, accompanied by two or more of the following criteria:

- Related to defecation
- Related to change in frequency of stool
- Related to change in form (appearance) of stool.

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Exclusion criteria i) Severe systemic disease or diabetes or hyperthyroidism ii) Other complications that mimic the symptoms of IBS (lactose and fructose intolerance, celiac disease, ulcerative colitis and crohn's disease) iii) IBS patients undergoing treatment with antimicrobials, probiotics, antidiarrheal agents or spasmolytics in the last two weeks iv) Pregnant and lactating women v) Any previous bowel surgery.

The eligible patients, after screening, were randomly assigned to two treatment groups.

Drug treatment- Each study group received a tablet Rifaximin (550 mg) twice a day or tablet VSL # 3 (112.5 billion bacteria / tablet) twice daily for 2 weeks.

Symptoms were assessed by a range of symptoms at baseline, two weeks, four weeks and six weeks after treatment. Six subscales of pain intensity, frequency of pain, stool character, frequency of stool, mucous discharge in stool and abdominal distension were included in the symptom score scale. Each symptom was scored from 0 to 3 according to intensity and a total symptom score thus obtained from 0 to 18. Relief in single symptom: (1) obvious relief: either the symptom disappeared or the total score reduced> 80%; (2) moderate relief: total score reduced by 50% ~ 80%; (3) no relief: total score reduced <50%. Relief in one symptom: (1) obvious relief: two points reduction in score; (2) moderate relief: one point reduction; (3) no relief: no relief or worse. If the score dropped from 1 to 0, it was considered an obvious relief. Total relief rate was the sum of obvious relief rate and moderate relief rate. Safety assessment was carried out for both the treatment groups at 2^{nd}, 4^{th} and 6^{th} week.[18] Adverse effects of both the treatments were recorded in a pre-prepared adverse drug monitoring performa based upon the known adverse effects of the study medications along with the provision for recording any new adverse effects.

Statistical Analysis

For all descriptive and analytical analysis, Statistical Package for Social Sciences (SPSS) Version 23 was used. Relief rate was counted as percentage; statistical analysis was performed using chi square test. Value of p-value < 0.05 was considered statistically significant. The frequency of ADRs in different drugs groups was expressed as percentage.

RESULTS

Demographic characteristics

A total of 138 patients were screened for the study, 18 patients were excluded for not fulfilling inclusion criteria and 10 patients refused to give informed consent. After exclusion, 110 patients were enrolled in the study and underwent randomization to take at least one dose of the study drug. Fifty four patients were randomly assigned to rifaximin and fifty six patients to VSL#3 **(Figure 1)**. Demographic and baseline characteristics were broadly comparable among the study population (**Table-1**). The mean age of the patients was 35.38 ± 2.54 and 33.29 ± 2.56 years in Group 1 and 2 respectively. The male patients were 59.4% in rifaximin group and 63.8% males in VSL#3 group. The median duration of diarrhea-predominant irritable bowel syndrome was 4.4 years in rifaximin group and 5.2 years in VSL#3 group. At baseline, routine investigations such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), thyroid function tests (TFT), random blood sugar (RBS)

were recorded and the values of all parameters were in normal range in patients of both the treatment groups.

Table 1: Baseline characteristics of study population.

Variables		Group 1 (n=47) Rifaximin	Group2 (n=47) VSL#3	'p' value*
Age (years)		35.38 ± 2.54	33.29 ± 2.56	N.S
Sex	Male	59.4%	63.8%	N.S
	Female	40.6%	36.2%	
Marital Status	Married	59.8%	61.4%	N.S
	Unmarried	40.2%	38.6%	
Education	Illiterate	18.6%	16.9%	N.S
	High school	28.2%	26.6%	
	Graduate	53.2%	56.5%	
History of drug allergy		None	None	-
Duration of IBS		4.4 years	5.2 years	N.S

***N.S–Non significant**

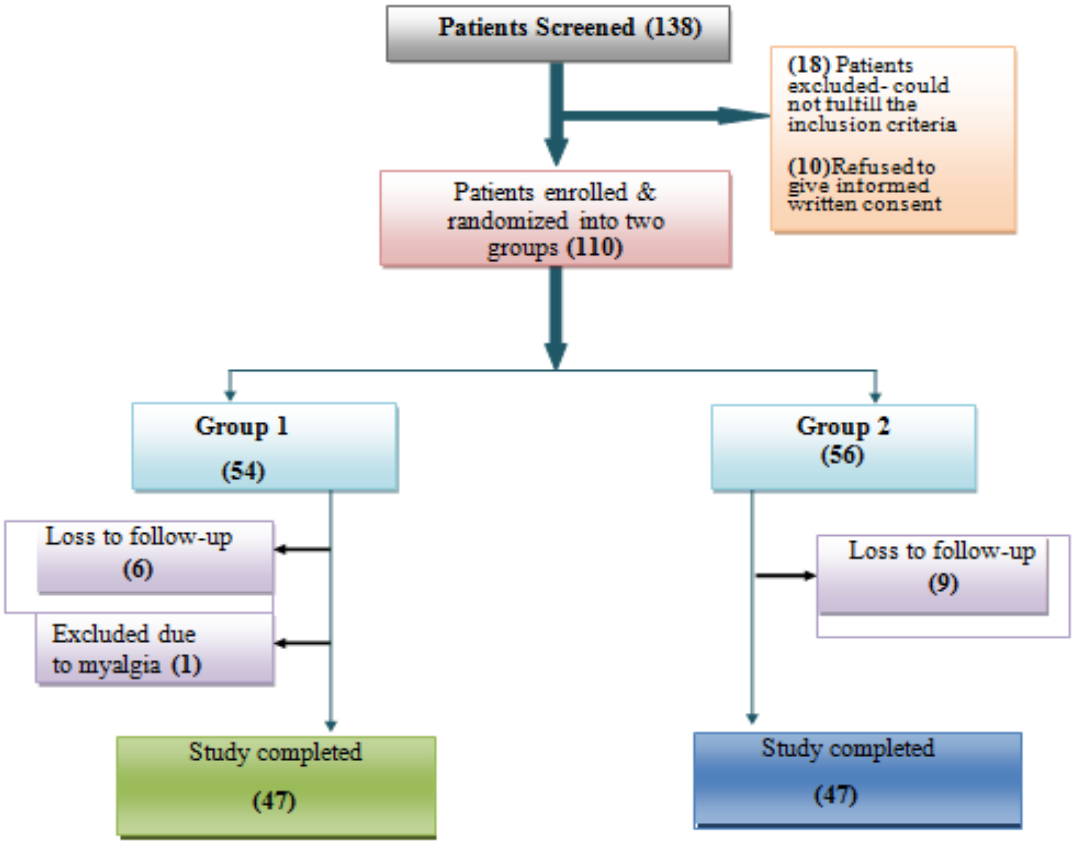

Fig. 1: Consort Chart.

Symptom Score Analysis

In Table 2, total relief was seen in 69.4% of patients in rifaximin group at 2 weeks as compared to baseline which increased to 91% at 4 weeks and 86% at 6 weeks. Similarly, in VSL#3 group, total relief was seen in 75% at 2 weeks, 62.4% at 4 weeks and 56.25% at 6 weeks as compared to baseline (Fig. 2). The maximum total relief rate was seen at 4 weeks in rifaximin group while at 2 weeks in VSL#3 group. The percentage of total relief rate was indicative that, both drugs were effective in improving symptom score scale in patients with irritable bowel syndrome. The improvement was seen during the treatment period in both the groups but during the follow up period rifaximin showed sustainable improvement whereas slight decrease was seen in total relief rate with VSL#3 due to relapse in few subscale parameters in some patients. Fourteen percent of the patients in rifaximin group had relapse in pain and stool symptoms while 19% of patients in VSL#3 group had relapse at the end of 6 weeks. On simultaneous intergroup analysis

both drug treatments were comparable at the beginning of treatment till week 2 as there was no statistical difference in both the groups whereas rifaximin showed statistically significant difference at week 4 (p value= 0.016) and at week 6 (p value= 0.004), in improving the symptom score as compared to VSL#3.

Table 2: Comparison of overall symptom score in both the groups.

Symptom Score	Group 1 (%)(n=47)			Group 2 (%)(n=47)			p value
	Obvious relief	Moderate relief	Total Relief rate	Obvious relief	Moderate relief	Total Relief rate	P – value$^{\beta}$
Week 2	9.4%	60%	69.4%	9.7%	65%	75%	0.578
Week 4	34.4%	56.3%	91%	28%	34.4%	62.4%	0.016
Week 6	40%	46%	86%	25%	31.25%	56.25%	0.004

- $^{\beta}$ **- Inter-group p value**

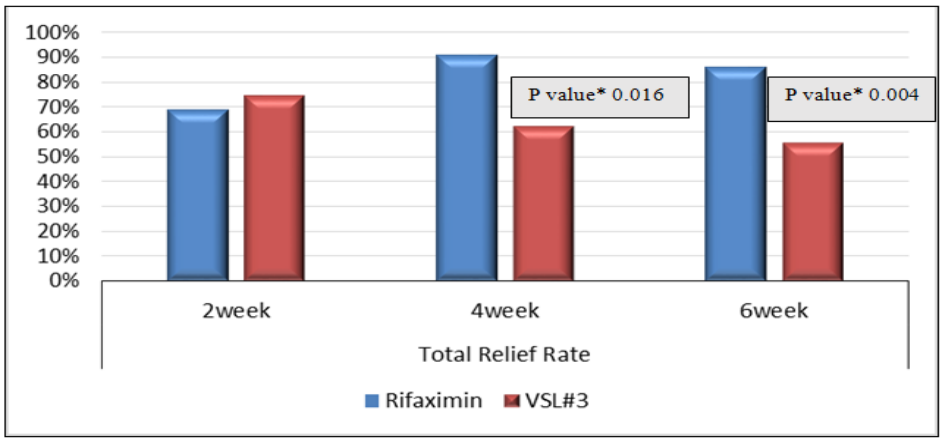

Fig. 2: Comparison of changes in Symptom score after treatment, graph shows significant relief in patients with rifaximin as compared to VSL#3 (p value- <0.05).

On subscale analysis, patients with both rifaximin and vsl#3 showed improving trend from baseline till week 2 and 4, abdominal distension was better treated with VSL#3 as compared to rifaximin at 2 weeks. While at 6 weeks VSL#3 showed more relapse in symptoms as compared to rifaximin so p-value comes out to be significant in pain intensity and stool consistency subscales showing better relief with rifaximin than VSL#3 (Table 3).

Table 3: Comparison of symptom score subscales post treatment.

Weeks	Groups	Subscales					
		Pain Intensity	Pain Frequency	Stool Consistency	Stool Frequency	Mucus Frequency	Abdominal Distension
0 weeks	Rifaximin	2.78 ± 0.42	2.84 ± 0.37	2.75 ± 0.44	2.28 ± 0.46	1.13 ± 0.83	1.66 ± 0.65
	VSL#3	2.88 ± 0.34	2.78 ± 0.42	2.88 ± 0.34	2.44 ± 0.5	1.56 ± 1.05	1.44 ± 0.72
P value (intergroup)		0.328	0.529	0.206	0.199	0.069	0.206
2 weeks	Rifaximin	1.69 ± 0.74	1.50 ± 0.76	1.16 ± 0.68	1 ± 0.62	0.22 ± 0.42	0.94 ± 0.84
	VSL#3	1.41 ± 0.50	1.47 ± 0.57	1.25 ± 0.57	0.84 ± 0.63	0.5 ± 0.51	0.50 ± 0.62
P value (intergroup)		0.079	0.853	0.551	0.321	0.019	0.021
6 weeks	Rifaximin	1.03 ± 0.90	1.09 ± 0.96	0.66 ± 0.94	0.66 ± 0.83	0.09 ± 0.30	0.44 ± 0.72
	VSL#3	1.66 ± 0.90	1.53 ± 0.92	1.25 ± 7.08	1.06 ± 0.98	0.25 ± 0.62	0.47 ± 0.57
P value (intergroup)		0.007	0.067	0.022	0.078	0.206	0.847

Pain intensity was assessed by NRS scale, pain frequency by item derived from IBS-SSS scale, stool character and frequency by BSFS 7-point scale**.** P value* - intra group in both the groups from baseline is found to be significant after treatment < 0.001 with all the subsclaes.

In Group 1, flatulence and constipation were more frequent, whereas bloating, nausea and vomiting were more common adverse events among patients in Group 2 (Fig. 3). Overall, above observations indicate that adverse events were comparable among both the groups (p <0.05). One patient was discontinued from the study, who was on rifaximin as she experienced severe myalgia after 2 doses, conservative treatment was given after, which patient recovered few days later. No other patient discontinued the study medication due to adverse drug events in any of the groups.

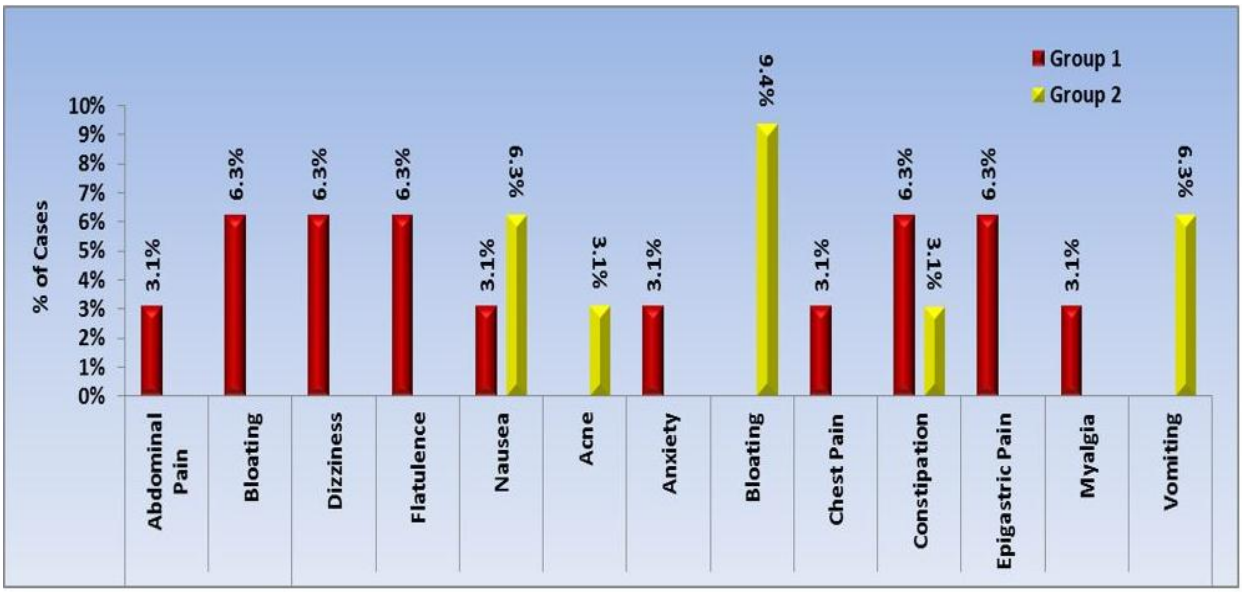

Fig. 3: Comparison of percentage of adverse drug reactions in both the groups during the study period of 6 weeks.

DISCUSSION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder encountered by gastroenterologists in the out day practice.[19] Being a multi-system disorder, IBS presents with various symptoms in number of patients leading to significant impact on the quality of life and healthcare system.[20] Recently, the altered gut microbiota i.e dysbiosis is being considered as important contributor to the development of IBS.[21] Both Rifaximin and VSL#3 have proven to be effective in patients of IBS-D by modulating the altered gut microbiota and abating the bothersome symptoms of the disease. Study results showed that both rifaximin and VSL#3 caused significant relief in symptoms after 2 weeks of treatment. Total relief rate was 69% and 75% at 2 weeks, 91% and 62% in the fourth week and 86% and 56% in the sixth week of study with rifaximin and VSL#3, respectively. The findings of this study match with the pharmacological profile of the therapy as these drugs help in amelioration of the symptoms such as abdominal pain by decreasing inflammation and less release of lymphocytes and mast cells and diarrhea by decreasing the osmotic load of intestines by modulating the dysbiotic microbiota.[22]

VSL#3 was better at 2 weeks i.e during treatment period because of more relief in all the subscale parameters as compared to rifaximin, while during the follow up period relief was more with rifaximin due to its sustained effect and patients with VSL#3 showed relapse in symptoms impeding the relief. This study results were consistent with those of a study in which eighty-five patients were given capsules of Bifidobacterium, Lactobacillus and Enterococcus with a dose of 1260 mg/d t.i.d. for 4 weeks and it was found that total relief rate was 56.8% in the second week, 74.3% in the fourth week and 73.0% in the sixth week.[18]

In the present study, after 2 weeks of treatment period, few patients suffered relapse in their symptoms during the post treatment period in both the groups. Fourteen percent of the patients in rifaximin group had relapse in pain and stool symptoms after 2 weeks of treatment while 19% of patients in VSL#3 group had relapse during follow up period i.e from 4 to 6 weeks. The findings in the present study showed better response than a study in which 1074 patients were analyzed, who responded to open-label rifaximin (550mg tds for 2 weeks), 692 (64.4%) suffered relapse in symptoms while 382 (35.6%) did not relapse and showed improvement in abdominal pain and stool consistency during 4 weeks of post treatment period.[23] This difference can be attributed to the fact that more number of patients were evaluated in the above mentioned study.

In the present study, a total of 47% (22) and 28% (13), patients in Group 1 and Group 2, respectively reported some ADEs, only one patient receiving rifaximin was excluded from study due to severe myalgia. This study results were consistent with those of a study conducted in IBS-D patients, in which rifaximin 550 mg (n=1008) was compared with placebo (n=829) for 10 weeks. In rifaximin group, adverse events reported were 52.5% and drug-related AEs (adverse events) were 12% out of which 0.8% observed severity and resulting in study discontinuation.[24] In another study conducted by Sisson et al, reported that total number of adverse events were 28% in probiotic (multi-strain) vs 30% in placebo group with 12 weeks of study duration. Most common events were nausea (4%), bloating (8.1%) and diarrhea (4.8%). Other less common adverse events included acne (0.8%), flatulence (1.6%), and vomiting (1.6%).[25] The adverse events observed in these studies are mostly similar to those observed in our study.

CONCLUSION

During treatment, both rifaximin and probiotic (VSL#3) have shown their efficacy in improving symptom score in the patients of IBS-D. Both rifaximin and probiotic can be used in patients of diarrhea predominant irritable bowel syndrome as per physician's preference and patient's satisfaction. Though rifaximin was found superior than VSL#3 during the follow up period because of relapse in patent symptoms with these strains of probiotics. Further research is needed, comparing rifaximin with other strains of probiotics to known their efficacy in the patients of IBS-D.

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