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COMPARATIVE EVALUATION OF RIFAXIMIN AND VSL#3 IN THE PATIENTS OF IRRITABLE BOWEL SYNDROME WITH DIARRHEA

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ABSTRACT

Introduction: Abdominal pain and frequent loose stools are the most characteristic features of IBS-D which relates to disturbance in gut microbiota. Both rifaximin, a non-systemic antibiotic which acts by suppressing bacterial gene expression and probiotics (VSL#3) by modulating the gut microbiota were found in amelioration of disease symptoms during literature search. **Aim**: This study was carried out to compare effects of probiotics and rifaximin when given in IBS-D patients. **Methodology:** It was an open-label, parallel group, prospective, randomized and comparative study, in 88 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 NRS scale for pain intensity, IBS-SSS for pain frequency, BSFS for stool character and stool frequency at baseline, 2weeks, 4weeks and 6weeks after treatment. **Results:** Both rifaximin and VSL#3 were found to be effective in reducing pain and stool parameters after treatment. Reduction in NRS score was seen in 63% and 45%(p=0.014) of patients at 6 weeks, in IBS-SSS score was seen in 63% and 54%(p=0.147) of patients at 6 weeks, in Likert scale was seen in 49% and 47%(p=0.138) of patients at 6 weeks, in BSFS for stool character was seen in 28% and 26%(p=0.418) of patients at 6 weeks and for stool frequency was seen in 71% and 57%(p=0.078) of patients at 6 weeks, in rifaximin and VSL#3 respectively. **Conclusion:** VSL#3 was found to be non-inferior with rifaximin in the patients of IBS-D.

KEYWORDS: VSL#3, Rifaximin, BSFS, IBS-SSS, NRS.

INTRODUCTION

Irritable bowel syndrome (IBS) is considered as one of the commonly presenting functional gastrointestinal disorders[1] characterized by abdominal pain or discomfort, which is relieved by defecation or the passage of gas. It is associated with changes in stool frequency and consistency, without physical, endoscopic abnormalities or laboratory findings indicating organic disease.[2] According to Rome IV criteria, IBS is classified into four subtypes: IBS-C, IBS-D. IBS-M and IBS-U.[3] Among the four subtypes, Indian population has much higher incidence of diarrhea predominant IBS (1.5%) compared to IBS constipation (0.3%).[4] Patients with diarrhea predominant IBS, typically, present with pain in abdomen associated with frequent loose stools and cramping, urgency which is not relieved by defecation,[5] all of which cause a significant impact on patient's quality of life (QoL) due to physical suffering and psychological co-morbidities.[6]

The etio-pathogenesis of IBS remains largely enigmatic with a number of possible factors, such as diet, psychological features, genetic factors, post infectious IBS, hypothalamic-pituitary-adrenal axis (HPA) dysfunction, serotonin dysregulation, immune activation and visceral hypersensitivity caused by dysbiosis i.e abnormal alteration in gut microbiota.[7] This imbalance plays an important role in the development of symptoms like accumulation of gas in the intestine resulting in bloating and flatulence which leads to abdominal pain or discomfort as well as altering the innate immune reaction leading to motor and intestinal barrier dysfunction resulting in diarrhea.[8]

As IBS is multifactorial in nature, currently there is no single management strategy available which is universally adapted. The treatment goal in IBS-D patients is to reduce their overall symptoms and efforts should be made to eliminate or decrease the patient's primary symptoms.[9] Various pharmacological agents like antidiarrheal agents (loperamide), opoid receptor agonists and antagoninsts (Eluxadoline), anti-depressants (TCA's and SSRI's) have been used, but the recurrence of symptoms during treatment free period and serious side effects associated with some drugs are an important concern. As dysbiosis is the mainstay for causing gastric symptoms of abdominal pain and diarrhea, so antibiotics and probiotics have been proposed as a possible treatment option for IBS. Rifaximin is a rifamycin derivative which inhibits bacterial protein synthesis by binding to RpoB irreversibly and altering bacterial gene expression. Due to its low systemic absorption and broad spectrum

antimicrobial activity it is an ideal agent for gastrointestinal diseases like IBS-D by reducing visceral hypersensitivity (abdominal pain) and decreasing colonic transit (diarrhea). It is poorly absorbed in the digestive tract, so has poor bioavailability with enhanced fecal concentrations which reduces its systemic toxicity, resulting in reduced number of serious side effects.[10] VSL#3, a specific probiotic combination, is a patented probiotic preparation containing eight different strains of bacteria's and has been revealed effective in IBS patients for reducing bloating and other abdominal symptoms.[11]

With this background, the present study was conducted to compare the efficacy of both the drugs in patients with diarrhea predominant irritable bowel syndrome, by assessing the improvement in abdominal pain and stool character and frequency parameters, as no such study has been done till now comparing the two drugs in IBS-D.

MATERIAL AND METHODS

Study design and patient population

The present study was conducted as an open labelled, parallel group, prospective, randomized, comparative clinical study which was done in accordance with the principles of Good Clinical Practice (GCP) and Declaration of Helsinki. The study was approved by Institutional Ethics Committee (IEC). The study included 88 patients who were initially screened as per predefined inclusion and exclusion criteria The eligible patients were randomly divided into two study groups i.e. Group 1 and Group 2 with the help of computer generated random numbers. All patients were followed up for a period of six weeks. During the study, patients were not permitted to take any non-study drugs. An informed consent was obtained from all patients enrolled for the study and the study was approved by Institutional Ethics Committee (IEC).

Inclusion criteria included- Patients aged between 18 years to 60 years of either gender fulfilling ROME Criteria IV of IBS.

Recurrent abdominal pain, on an average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria.

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

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

Exclusion criteria included- i) Severe systemic disease or diabetes mellitus or hyperthyroidism ii) Other disorders which mimic irritable bowel syndrome symptoms (lactose and fructose intolerance, celiac disease, ulcerative colitis and Crohn's disease) iii) Patient of IBS already on treatment with antibiotics, antidiarrheal agents, spasmolytics or probiotics during the last two weeks iv) Pregnant and lactating females v) Any previous bowel resection surgery. The eligible patients, after screening, were randomly allocated to two treatment groups.

Drug treatment- Each study group received either tablet Rifaximin (550mg) twice daily or tablet VSL#3 (112.5 billion bacteria/tablet) twice daily for a period of 2 weeks with follow up at 4 and 6 weeks after treatment.

Primary End Points

1. Relief in abdominal pain by using.

i) Numeric Rating Scale (NRS) for pain intensity

ii) IBS-symptom severity scale (IBS- SSS) for pain frequency

iii) Likert scale for pain association with bowel movement.

2. Reduction in stool frequency and improvement in its consistency/character by using- Bristol Stool Form Scale (BSFS).

Study Procedure

A detailed patient information sheet was provided to the patients. Only those participants who were willing to give written informed consent were enrolled in the study. The details of all participants were recorded in the case report form (CRF). At baseline, routine investigations such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), thyroid function tests (TFT), random blood sugar estimation (RBS) were recorded in all the patients of either group before drug administration. Baseline parameters were recorded on first visit by using scales for abdominal pain – (i) Numeric Rating Scale (NRS) for intensity of pain, (ii) an item derived from IBS Symptom Severity Scale (IBS-SSS) for frequency of pain, (iii) 5-point likert scale for relationship with bowel movement and Bristol Stool form Scale for stool character and frequency. The patients were followed up at the end of 1week, 2 weeks, 4 weeks and 6 weeks.

Statistical Analyses

For all descriptive and analytical analysis, Statistical Package for Social Sciences (SPSS) Version 23 was used. Data was expressed as Mean ± SEM, number (%) depending on nature of data, p-value < 0.05 was considered significant. The intra-group outcomes of NRS, IBS-SSS, five point likert scale, BSFS were compiled and analyzed using paired "t" test. Inter-group analysis between 2 groups for the above mentioned parameters were compiled and analyzed using independent paired "t" test.

RESULTS

A total of 88 patients were screened for the study, 12 patients were excluded for not fulfilling inclusion criteria and 4 patients refused to give informed consent. After exclusion, 72 patients were enrolled in the study and underwent randomization into groups. Thirty seven patients were randomly assigned to rifaximin group and 35 to VSL#3 (**Figure 1**). Demographic and baseline characteristics were generally comparable among the study population (**Table-1**). The mean age of the patients was 36.28 ± 2.34 and 33.19 ± 2.56 years in Group 1 and 2, respectively. Male patients were 56.3% in rifaximin group and 64.0% in VSL#3 group. The median duration of diarrhea-predominant irritable bowel syndrome was 4 years in rifaximin group and 5 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 estimation (RBS) were recorded and the values of all parameters were within normal range in patients of both the treatment groups.

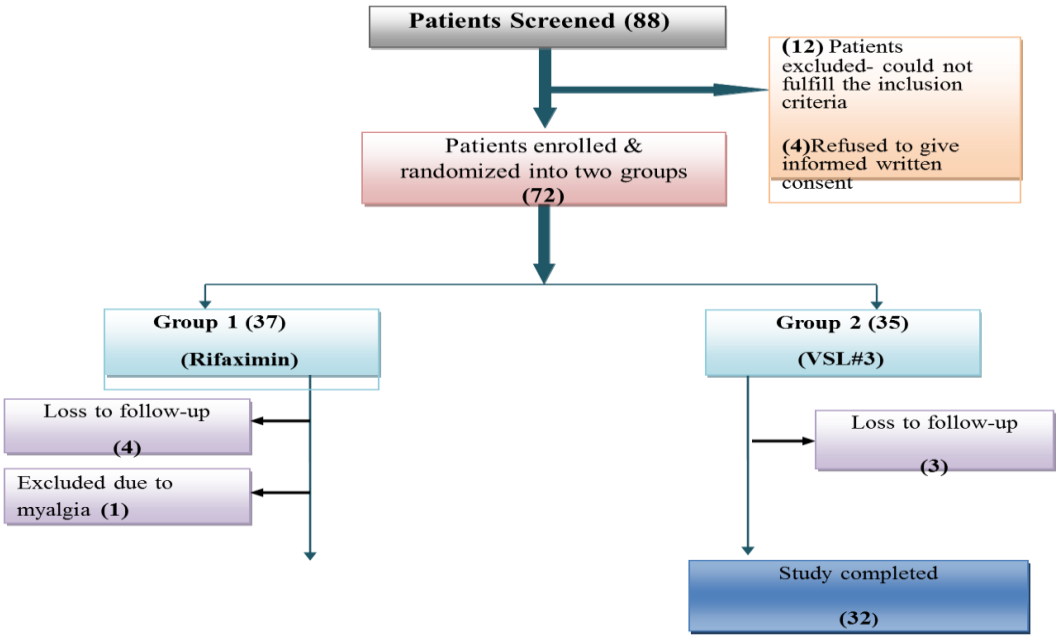

Figure 1: Enrollment of study population.

Table 1: Baseline Characteristics Of Study Population.

Variables		**Group 1 (n=32) Rifaximin**	**Group 2 (n=32) VSL#3**	**'p' value***
Age (years)		36.28 ± 2.34	33.19 ± 2.56	N.S
Sex	Male	56.3%	64.0%	N.S
	Female	43.7%	36.0%	
Marital Status	Married	65.6%	68.8%	N.S
	Unmarried	34.4%	31.3%	
Education	Illiterate	21.9%	21.9%	N.S
	High school	28.1%	34.4%	
	Graduate	40.6%	37.5%	
History of drug allergy		None	None	-
Duration of IBS		4 years	5 years	N.S

***N.S – non significant**

Assessment of Abdominal Pain[12]

All the parameters were evaluated at baseline (before drug administration) and then at the end of 1, 2, 4 and 6 weeks after treatment.

a) Abdominal Pain Intensity

Figure 2, In **Group 1**, baseline score was **7.5 ± 0.29** which reduced to **3.72 ± 0.34** and **2.81 ± 0.39** at 2 and 6 weeks in 51% and 63% of patients respectively. Similarly, in **Group 2,** reduction in NRS score was highly statistically significant ($p < 0.0001$) from baseline score of **7.69 ± 0.27** to **3.78 ± 0.27** and **4.22 ± 0.39** at 2 and 6 weeks in 51% and 45 % patients respectively.

On intergroup analysis, rifaximin showed statistical significance in reducing pain at 6 weeks as compared to VSL#3 with **p=0.014**.

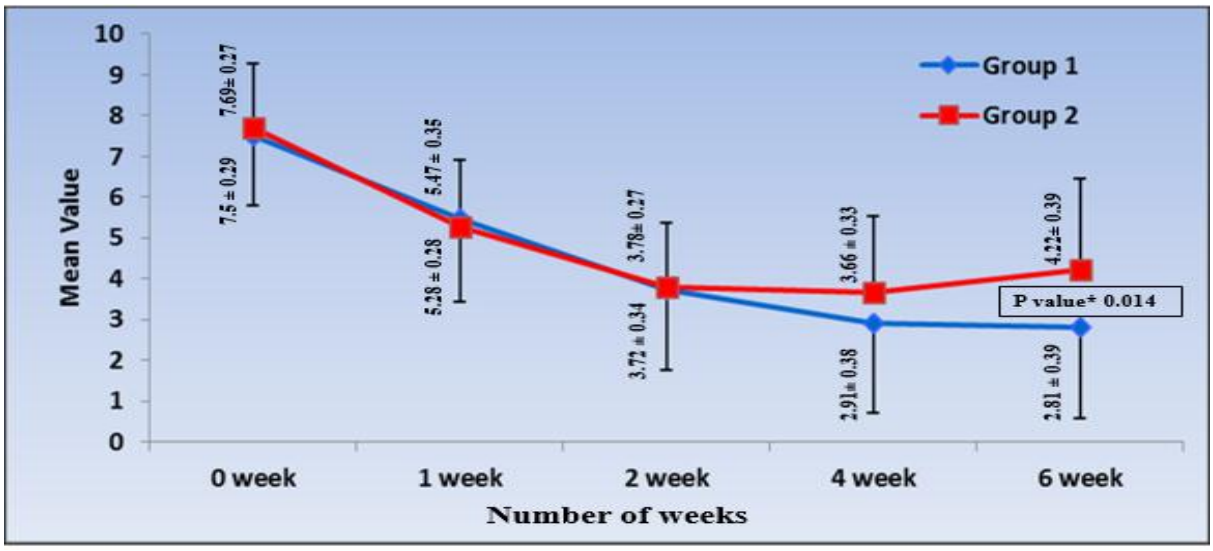

Figure 2: Comparison of changes in pain intensity by using Numeric Rating Scale Score (NRS), Rifaximin showed significant improvement in pain intensity at 6 weeks as compared to VSL#3 (p= 0.014).

b) Abdominal Pain frequency

Figure 3, In **Group 1,** baseline score was **7.81 ± 0.33** which reduced to **3.66±0.34** and **2.88 ± 0.25** at 2 and 6 weeks in **53%** and **63%** of patients respectively. Similarly, in **Group 2,** reduction in IBS-SSS score was highly statistically significant ($p < 0.0001$) from baseline score of **8.03 ± 0.30** to **3.75±0.23** and **3.72 ± 0.37** at 2 and 6 weeks in **53%** and **54%** of patients respectively. On intergroup analysis, both drug treatments were comparable after 6 weeks of treatment.

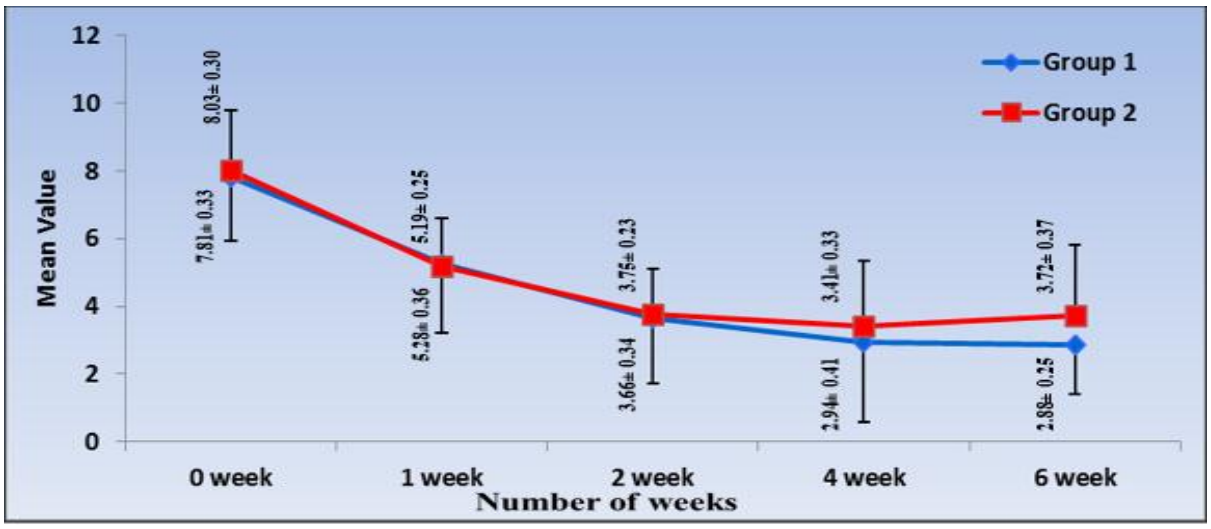

Figure 3: Comparison of changes in pain frequency by using IBS-Symptom severity scale (IBS-SSS) score.

c) Abdominal pain association with bowel movement

Figure 4, In **Group 1,** baseline score was **1.88 ± 0.16** which increased to **1.88 ± 0.16** and **3.38 ± 0.16** at 2 and 6 weeks in **44%** and **49%** of patients respectively. Similarly, in **Group 2** increase in Likert scale was highly statistically significant from baseline score of **1.75 ± 0.11** to **2.81 ± 0.14** and **3.31 ± 0.16** at 2 and 6 weeks in 50% and 47% of patients. On intergroup analysis, both the drug treatments were comparable at 2 weeks as well as during follow up.

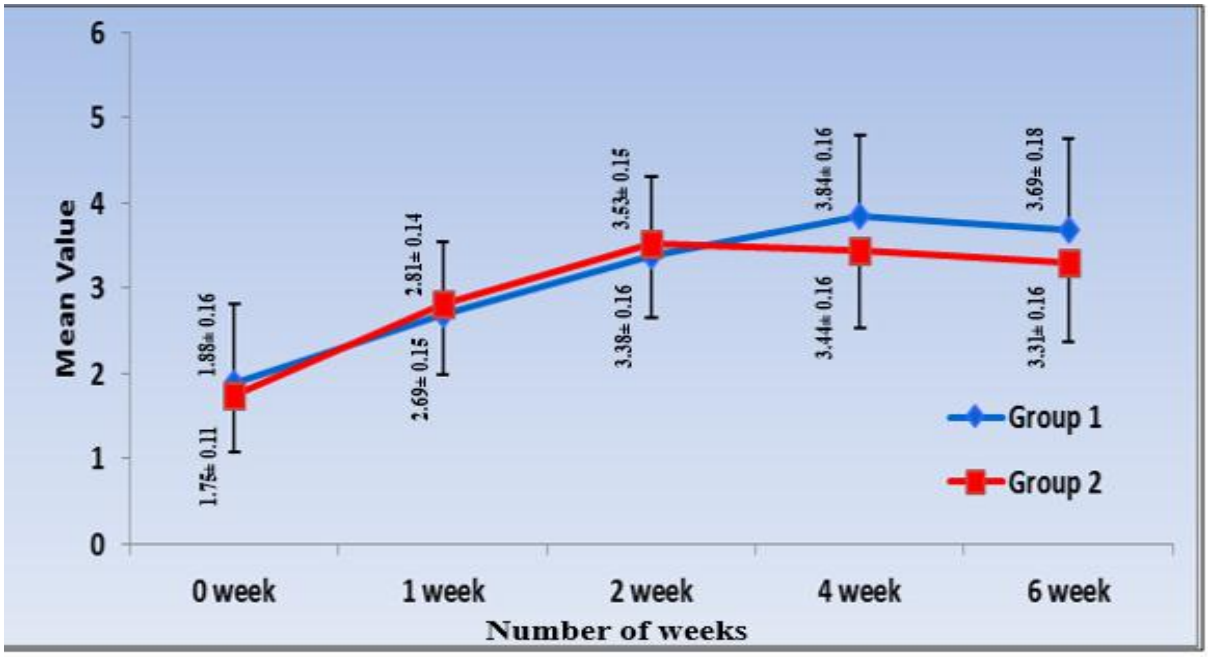

Figure 4: Comparison of changes in abdominal pain association with bowel movement by using 5-point Likert scale score.

Assessment of Diarrhea[13]

All the parameters were evaluated at baseline (before drug administration) and then at the end of 1, 2, 4 and 6 weeks after treatment.

a) Stool character

Figure 5, In **Group I,** baseline score was **6.62 ± 0.08** which decreased to **4.88 ± 0.08** and **4.78 ± 0.17** at 2 and 6 weeks in 27% and 28% of patients respectively. Similarly, in **Group 2** decrease in BSFS for stool character was highly statistically significant from baseline score of **6.78 ± 0.07** to **4.75 ± 0.10** and **5.00 ± 0.20** at 2 and 6 weeks in 30% and 26% of patients respectively. On intergroup analysis, both the drug treatments were comparable at 2 weeks as well as during follow up.

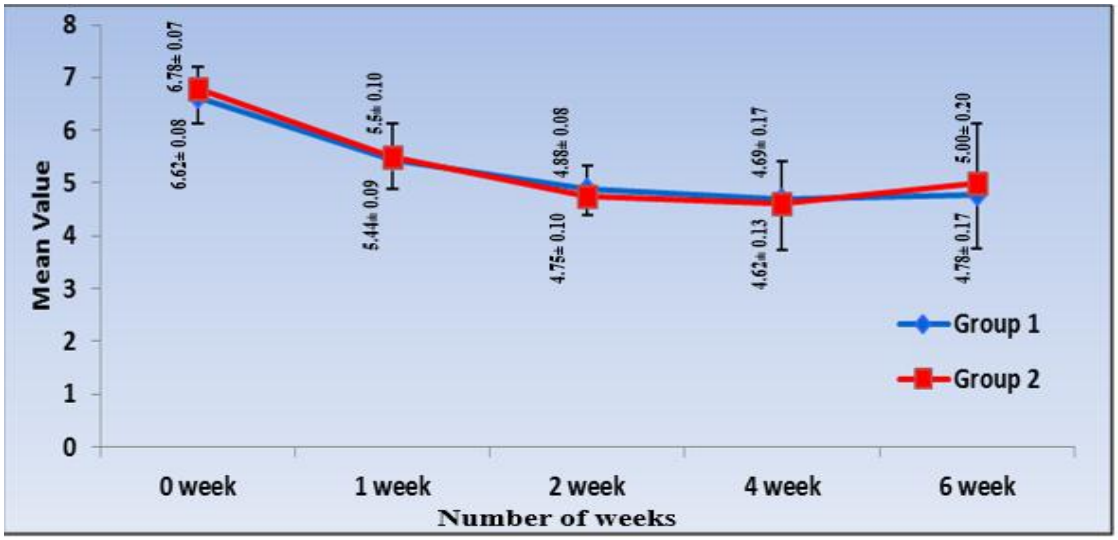

Figure 5: Comparison of changes in stool character by using BSFS.

b) Stool frequency

Figure 6, In **Group I,** baseline score was **2.28 ± 0.08** which decreased to **1.00 ± 0.10** and **0.66 ± 0.14** at 2 and 6 weeks in 56% and 71% of patients respectively. Similarly, in **Group 2** decrease in BSFS for stool frequency was highly statistically significant from baseline score of **2.44 ± 0.08** to **1.62 ± 0.08** and **1.06 ± 0.17** at 6 weeks in 66% and 57% of patients respectively. On intergroup analysis, both the drug treatments were comparable at 2 weeks as well as during follow up.

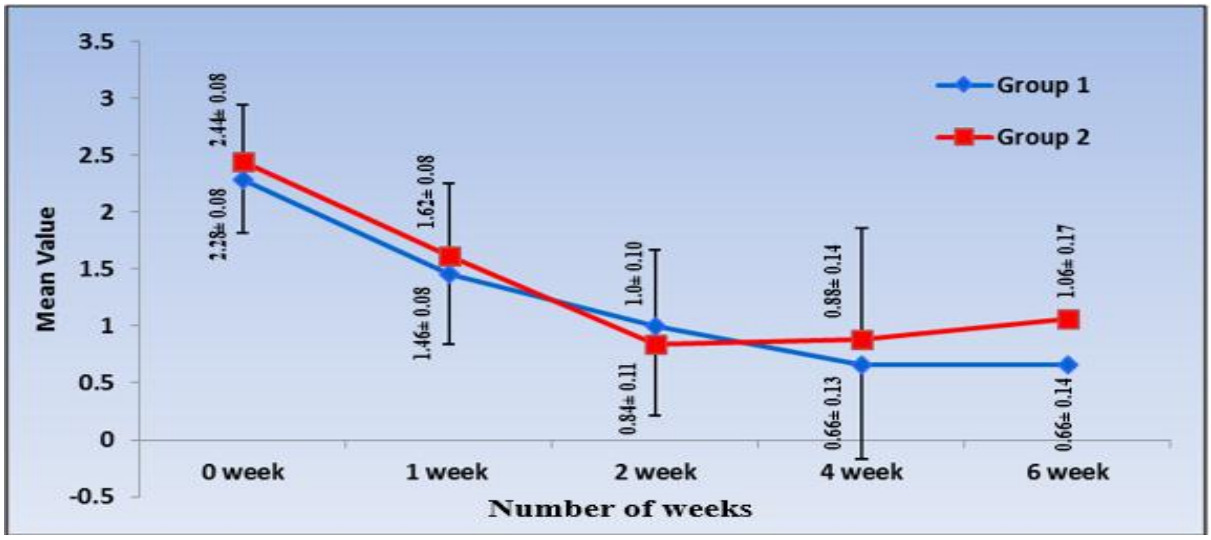

Figure 6: Comparison of changes in stool frequency by using BSFS.

DISCUSSION

The Rome IV Committee has redefined IBS on the basis of abdominal and bowel symptoms that occur with sufficient frequency in affected patients, in 2016.[7] IBS has been strictly

attributed to dysbiosis in the GIT, which entails increase in pathogenic bacteria responsible for the disease symptoms.[7] Treating IBS is important because the bothersome symptoms have a potential impact on patients health-related quality of life, resulting in decreased work productivity and increased use of health resources.[14] Both rifaximin and VSL#3 have proven to be effective in patients of IBS-D in various individual studies, but till date no study has been carried out to compare the efficacy of both these drugs in patients of IBS-D, In the present study, tablet Rifaximin 550mg BD and VSL#3 1 tablet BD was given to group 1 and group 2 respectively, for a period of 14 days and patients were followed up at 4 and 6 weeks. Both the study drugs were found to be efficacious by amelioration of most displeasing symptoms i.e abdominal pain and diarrhea. Rifaximin and VSL#3 caused significant improvement in both pain and stool parameters at 4 and 6 weeks as compared to baseline values. Rifaximin was found to be better in reducing pain parameters while VSL#3 was found to be better in improving stool character and frequency at the end of 6 weeks. Rifaximin (63% patients) showed statistically significant reduction in NRS score at 6 weeks in comparison with VSL#3 (52% patients) in reducing pain intensity, while pain frequency and association with bowel movement showed non-significant difference in both the groups at 4 and 6 weeks of treatment. The improvement in pain parameters was on expected lines as rifaximin and VSL#3 play an important role in decreasing inflammation and less release of mast cells by modulating the dysbiotic microbiota, as activation of mast cells in proximity to nerves in the colonic mucosa is responsible for alteration in nociceptive visceral sensory nerve function and causes stimulation of pain episodes and hypersensitivity. The study results were consistent with those of a study by Lembo et al, who carried out a study in 636 patients to assess abdominal pain with rifaximin and 56.8% had abdominal pain response with weekly decrease (improvement) in responders mean 10- point NRS score from baseline.[15] Another study, showed similar results with VSL#3, wherein the mean of abdominal pain duration by using IBS-SSS significantly decreased from baseline score of 37.50 to 19 after treatment.[16]

Along with pain, both the drugs were also effective in improving stool character and frequency i.e loose stools associated with irritable bowel syndrome on a predefined BSFS Scale. The improvement was seen as early as at 1 week which continued during the follow up period. VSL#3 showed greater improvement in stool character at week 4 whereas improvement in stool frequency was observed at 2 weeks i.e during treatment period. This improvement may be due to the fact that the de-conjugation of bile acids by pathogenic bacteria is responsible for mucosal inflammation and colonic water secretion and both the study drugs helps in reducing frequency of diarrheal episodes by inhibiting pathogenic

bacteria. At the end of 6 weeks i.e during follow up period rifaximin showed better improvement as few patients in VSL#3 showed relapse in the symptoms. The antibiotic effect of rifaximin is the presumed mechanism for its sustained beneficial effects in patients with IBS.[14] This study results were found similar to two identically designed, placebo-controlled studies where in 5-point scale for stool consistency was assessed with rifaximin and there was significant relief in greater number of patients during the primary evaluation period than in the placebo group.[14] Consistent results were found with those of a study conducted by Michail S et al, in which diarrhea subscale scores in gastro intestinal symptom rating scale (GSRS-IBS) were decreased significantly over the 8 weeks of treatment period with VSL#3. Another study evaluated 25 diarrhea predominant IBS patients for 8 weeks and found non-significant decrease in stool consistency and frequency from baseline after treatment with VSL#3.[11] The findings of the present study with VSL#3 showed better improvement in BSFS score and this difference can be attributed to the fact that less number of patients were evaluated in the above mentioned study.

The limitation of the present study is that number of patients included for drug therapy were less in both the groups, our study results could be better if more number of patients were enrolled for the treatment.

CONCLUSION

Both rifaximin and probiotic (VSL#3) have shown their efficacy in decreasing abdominal pain and diarrhea in the patients of IBS-D. Rifaximin was found to be superior than VSL#3 in improving pain parameters whereas VSL#3 was found to be superior than rifaximin in improving stool parameters. Both rifaximin and probiotic can be used in patients of diarrhea predominant irritable bowel syndrome as per physician's preference and patient's satisfaction.

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