A Double Blind Randomized Clinical Trail: Comparing Lactobacillus plantarum 299v with Placebo in treating irritable bowel syndrome patients

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Abstract

Irritable bowel syndrome (IBS) is a gastrointestinal disease of intestinal mobility. IBS present with variable clinical symptoms making the treatment difficult. IBS is quiet prevalent around the globe with different frequency. Differences in frequency and gender is due to diet habit. It is less frequent where diary product and vegetable are frequently consumed as compared to those who consumed meat. Lactobacillus plantarum 299v (L. plantarum 299v) is the most widely studied strain in the IBS patients. It is resistant to the actions of intestinal acids and bile, colonizes the human colonic mucosa and is non-pathogenic in nature. The efficacy of Lactobacillus plantarum 299v L is different in different study. The present study was designed to find the efficacy of Lactobacillus plantarum 299v in comparison to placebo in randomized control trial.

Method

One hundred and ninety patients were assessed for eligibility 46 among them were excluded from the study and twenty four declined to participate in the study. One hundred and twenty patient of IBS was grouped in two different groups. The one was treated with Lactobacillus plantarum 299v and the other was treated with placebo. Symptoms of IBS, like abdominal pain, bloating and complete rectal emptying was noted and interpreted among the groups.

Results

There was no statistically significant difference in relieving abdominal pain, bloating, rectal emptying in Lactobacillus plantarum 299v treated group and placebo treated group.

Conclusion

This randomized control trail of Lactobacillus plantarum 299v fail to show signicant efficacy in IBS treatment as compared to placebo.

Introduction

Irritable bowel syndrome (IBS) is a gastrointestinal disease characterized by altered intestinal motility, affecting about 11% of the world's population[1]. The prevalence of IBS among different countries varies such as in Pakistan it is 13.34%, Iran 7.13%, China 11.5%, United States of America 20.4%, United Kingdom 21.65% and in Japan 14.04%[2]. This variation in the prevalence of this most common functional disorder is attributed to the wide clinical spectrum and the different criteria used for the diagnosis of this disorder.

IBS patients usually present with a complex of symptoms which is difficult to treat[3]. These symptoms have a negative impact on the patient's value of life. The patients suffer from severe depression with tendency of suicide. Treating patients usually involves surgeries and invasive measures [4, 5] .The efficacy of the up-to-date treatment modalities for IBS is low mainly because of the heterogeneous nature of the disease pathophysiology includes hypersensitive viscera's, altered gut motility, distorted interactions of

brain with gut, intolerance to specific foods, altered intestinal permeability and inflammatory changes in the gut[6]. More recently the role of enteric infections and intestinal inflammation along with the implications of changing gut flora has been proposed in the pathogenesis of IBS[7]. Based on these facts it was suggested that the IBS patients may have bacterial overgrowth and the eradication or altering the gut flora may improve symptoms in these subset of patients[8, 9].

To improve immunize the patients against environmental opportunistic, probiotics are used. These probiotics are usually live or attenuated bacteria or bacterial metabolites [10]. How probiotics improves the symptoms of IBS patients is still to be understood, but few concepts have been postulated with evidences. As enteric flora is thought to play some role in the disease pathogenesis[11], gut functions improves with changes in gut flora attributed to probiotics[7]. In post-infectious IBS the disease course is altered by the antibacterial and antiviral effects possessed by many probiotic organisms[12]. Anti-inflammatory actions of probiotics on the gut's mucosal surface may decrease the firing of enteric neurons, mediated by the immune system, resulting in lesser stimulus and response cycles between the gut's mucosa and brain[13]. The probiotics are considered to play a role in transforming short chain fatty acids from the undigested carbohydrates, which in turn have its influence on intestinal handling of its contents by acting as nutrients for the enteric cells[14].

Lactobacillus plantarum 299v (L. plantarum 299v) is the most widely studied strain in the IBS patients. It is resistant to the actions of intestinal acids and bile, colonizes the human colonic mucosa and is non-pathogenic in nature[15]. While adhere to the colonic mucosal layer it reduces the inflammation by its antimicrobial activity against many potential pathogens importantly gram negative bacteria which contains endotoxins[16]. The synthesis and seceretion of the interleukin-10 from the macrophages and the T-cells of the inflamed colon is increased by the L.Plantarum which has got beneficial immnuomodulatory activity[17]. The lowering of the colonic pH by small chain fatty acids helps in controlling the growth of the microbes in the gut, L.Plantarum increases the concentration of carboxylic, acetic and propionic acids in the feces[16].

The results from the previous international trails were very encouraging regarding the safety and the efficacy of the probiotics use in IBS. The aim of the present study was to assess the efficacy L. Plantarum 299v against in local population suffering from IBS with improved study design and larger sample size.

Materials And Methods

Study population

The patients were recruited through the outpatient clinic of Gastroenterology and Hepatology Department of the Lady Reading Hospital, Peshawar. All the adult patients of either gender fulfilling the Rome III criteria for IBS, willing to participate and committed for follow up throughout the study period were enrolled in the study. The patients having history of major abdominal surgery, organic intestinal disease or chronic infectious disease like HIV or tuberculosis were excluded from the study. The pregnant and the

female breastfeeding their babies or anyone with current use of antibiotics were also not included in the study population.

Study Design

This was a double blind placebo-controlled study, conducted for six (6) months. Approval of the study was taken from the Institutional Research and Ethics Board reference number 31/IREB/PGMI/LRH. After fulfilling the inclusion criteria for the study and signing the informed consent form the randomization was started by lottery method and then patients were alternatively allotted to either of the two groups. All the patients received probiotics (L. Plantarum 299v) or placebo for four (4) weeks and had three follow up visits after the baseline investigation. The baseline and the first follow up after two weeks of the treatment were face to face. The second follow up, at the end of the treatment and the last one which was after four (4) weeks of finishing the treatment, were telephonic.

Study product:

The study drug containing 5x1010 cfu of L.Plantarum 299v and the placebo containing micro-crystalline cellulose powder, both were packed in the similar packing by the manufacturers (Genetex Pharma PVT Limited). The study drug was labeled A and the placebo as B, it was disclosed at the end of the study.

Re-assessments and compiling results

Two end point assessments was noted and interpreted. Daily frequency of abdominal pain was considered as primary end point. The secondary end points were improvement in the severity of abdominal pain, severity of the bloating and feeling of partial rectal emptying. Both the primary and the secondary end points were gauged on the visual analogue scale from zero (0) to ten (10), 0 being normal and 10 being very severe. In each visit the patients were examined thoroughly and all the parameters were noted along with the medication compliance. The patients were advised to avoid any change their dietary habits and intake of medicine regularly in the study period.

Statistical Analysis

The data was collected and SPSS version 19 I.L Chicago was used to analyze the data.

Results

One hundred and ninety patients were assessed for eligibility 46 among them were excluded from the study and twenty four declined to participate in the study (Figure 1). One hundred and twenty participant meet the criteria to participate in the study with 60 participant in each group. In the follow up period 5 participant in L.Plantarum group and 7 in the placebo group discontinued the study. Mean age of participant in the L.Plantarum group was 37.53 ± 9.02 and the placebo group was 34.40 ±11.23 (p value = 0.652). The male to female ratio in the L.Plantarum group was 34: 21 and it was 29:24 in the placebo

group (p value = 0.412). In both the groups the majority of the patients were having mixed type IBS with no statistically significant difference were observed among the groups. Table 1.

The primary end point was frequency of abdominal pain per day, although mean frequency was decreased from baseline at the end of therapy but no statistically significant difference were observed among the two groups (2.7 vs 3.4, p value = 0.744). There were no difference in frequency of abdominal pain among the two groups in any follow up assessment (Figure 2).

In the end point assessment for the abdominal pain between the two groups no statistically significant difference was observed. The mean scores for the severity of bloating were not significantly improved among the groups from the baseline in the entire study period. A complaint of feeling incomplete rectal emptying was improved from baseline to secondary end point with no statistically significant difference between L.Plantarum and the placebo group (3.6 vs4.1, p value = 0.211).

Discussion

In this study we included all subtypes of IBS fulfilling the Rome III criteria. Although most trials has been done in IBS-D regarding probiotics microbiological studies indicate that changes in microbiota occurs in all IBS subtypes. Therefore all patients meeting Rome III criteria were included in the study. In the present study most of the patients were male as compared to other trials where approx 2/3 of population was female. The reason for male predominant complain of IBS as compared to female unlikely reported in European countries; that IBS is less prevalent in female as compared to male in Asian countries [18]. In our study there was no significant difference in treatment and placebo group in relieving IBS symptoms. This is in contrast to a recent Indian study, a population that shows the same demographics as Pakistan[6, 19]. However this may be due to different eating behavior in India where a high percentage were pure vegetarians and half the population was consuming yogurt daily. This might have confounded the results as in that study relief in abdominal pain was more significant in vegetarian group as compared to non-vegetarians. Furthermore yogurt is also rich in probiotics other than L. Bacillus which may be responsible for better results. This is in contrast to our population which is not strictly vegetarian. The result of the study is suggestive of partial interaction of the luminal content and the strain with enhancement of the other probiotic strain.

In study done by Nobaek S et al administration of L. plantarum with known probiotic properties decreased pain and flatulence in patients with IBS [5]. The study is little biased because intake of fermented product was 59% in L.Plantarum group as compared to placebo group which was 73%, which may be source of other Probiotic strain other than L bacillus. Furthermore it is ambiguous in that medications for IBS like fiber supplementation and antispasmodics were controlled or not. The information about bloating among L.Plantarum group and placebo control group in 12 month follow up assessment is also not reported [5, 20].

Treatment of colonic fermentation in untreated IBS patients by L bacillus found no significant difference between control and L.Plantarum group. They assessed symptoms daily by validated composite score

and 24 hour indirect calorimetry for fermentation. Breath hydrogen was determine three hour later after intake 20 ml lactulose. There was no significant difference between median symptom score (8 vs 8.5), median maximum rate of gas production (0.92 ml/min vs 0.55 ml/min) and median hydrogen production (208.2 ml/24 hr vs 189.7 ml/24hr in l .bacillus group vs placebo[19, 21].

Largest RCT in this regard was done by Stevenson C Et al in Cape Town South Africa which included 81 patients. These patients were treated with either L. plantarum 299 v at a dosage of 5 × 109 cfu per capsule for 12 weeks or placebo. No significant difference in abdominal pain relief was observed among the L.Plantarum and placebo group and control group. Similarly no significant difference in QoL- IBS scores between the groups were observed [19, 22]. However significant improvement in abdominal pain scores during the study was observed with an average of 251.55 to 197.90 ($P < 0.0001$) indicating a large placebo effect. They responded well to both probiotic therapy and placebo which is also the case in our study. Our study was similar in design to this study with even larger no of patients thus validating the results of aforementioned study. There is high degree variability in clinical outcomes in many IBS clinical trials. The cause of such a placebo effect could be due to the fact that patients with IBS have complex pathophysiology with many features interacting with each other. Furthermore patients with IBS are usually anxious to be treated and may respond to any alteration in therapy, even if that alteration is placebo.

Conclusion

This randomized trail failed to show any significant improvement in the IBS symptoms by the use of L. Plantarum as compared to placebo.

Declarations

Ethics approval and consent to participate:

The study was conducted according to Helsinki deceleration and approved by Institutional Research and Ethic Board of Lady Reading Hospital Peshawar (Ref.No. 31/IREB/PGMI/LRH). Written inform consent were obtained from participant.

Consent for publication

Not Applicable

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Moeen-ul-haq and Muhammad Kamran Hassan conceptualized the study idea Moeen-ul-haq and Fazl Ullah and Ahmad Nawaz Babar performed study; Anwar Ullah drafted the manuscript. All authors read and approved the final manuscript.

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Tables

Characteristics	L.Plantarum (n=55)	Placebo (n=53)	P Value
Age (yrs)	37.53 ± 9.02	34.40± 11.23	NS
Men/Women	34/21	29/24	NS
IBS Type			
IBS-D	18	15	NS
IBS-C	16	12	NS
IBS-M	21	26	NS

Table 1: Baseline Characteristics of Patients Population

End Points	Baseline		After 2 weeks of therapy		End of therapy		4 weeks After therapy	
	L.Plantarum	Placebo	L.Plantarum	Placebo	L.Plantarum	Placebo	L.Plantarum	Placebo
Frequency of abdominal pain	8.71	7.84	5.3	4.8	2.7	3.4	5.54	6.69
Abdominal pain severity	8	7	4.8	4.4	2.9	3.7	4.1	4.5
Severity of Bloating	4.3	5.2	4.1	4.2	4	4.4	4.13	3.98
Feeling of incomplete rectal emptying	7.8	7.5	4.3	4.6	3.6	4.1	1.21	0.98

Table 2: Comparison of Primary and Secondary End Points Between the two Groups

After 4 weeks of therapy frequency of abdominal pain had no significant difference in L.Plantarum vs placebo group (5.54 vs 6.69 p=0.15) as compared to the baseline (8.71 vs 7.84). Similarly in the severity of bloating (4.13 vs 3.98 p = 0.34) and the feeling of incomplete rectal emptying (1.21 vs 0.98 p=0.19) the difference in the both the groups was not significant.

Figures

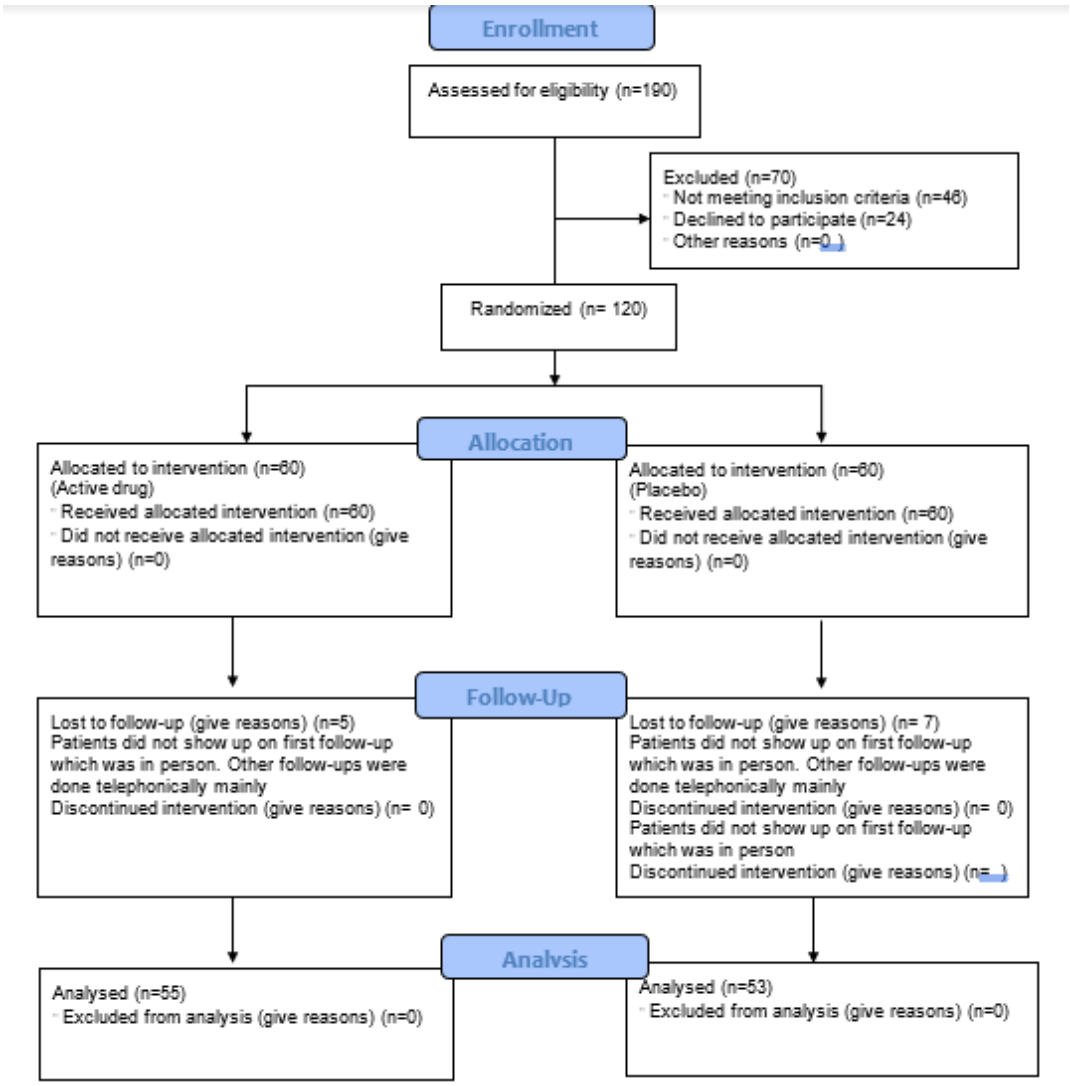

Figure 1

Flow diagram of recruitment of participants

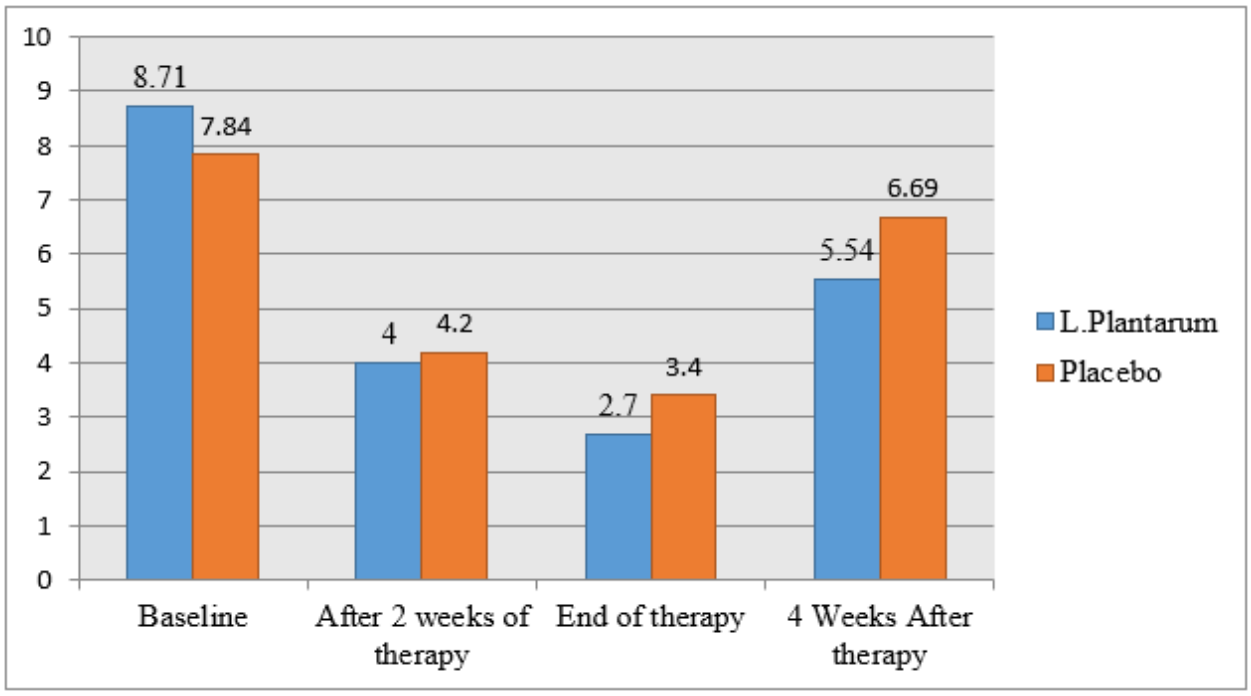

Figure 2

Mean Frequency of abdominal pain per day

Supplementary Files

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- CONSORT2010FlowDiagramLplantarum.docx
- CONSORT2010Checklist.doc