Original Article

The effects of multi-strain probiotic compound on symptoms and quality-of-life in patients with irritable bowel syndrome: A randomized placebo-controlled trial

Ahmad Shavakhi, Mohammad Minakari, Somaye Farzamnia, Mohammad Saleh Peykar, Golshan Taghipour, Azadeh Tayebi, Huriyeh Hashemi, Sara Shavakhi[1]

Department of Internal Medicine, and [1]Medical Students' Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Evidence has shown beneficial effects of probiotics in the treatment of irritable bowel syndrome (IBS); however, there is still a lack of data in this regard. We evaluated the efficacy of a multi-strain probiotic compound on IBS symptoms and quality-of-life (QOL).

Materials and Methods: Adult IBS patients ($n = 132$) were randomized to receive a probiotic compound containing seven bacteria species including *Lactobacillus* strains, *Bifidobacterium strains* and *Streptococcus thermophiles* or similar placebo, twice daily after a meal for 14 consecutive days. Improvement of IBS symptoms was assessed in categories of abdominal pain and distension and improvement of bowel habit. Improvement in patients QOL was assessed by the IBS-QOL instrument. Patients were evaluated for symptoms and QOL at baseline and then 1 month after completion of the treatment.

Results: After treatment, there was a decrease in abdominal pain and distension severity in both probiotic and the placebo groups ($P < 0.001$), but there was no difference between the two groups in this regard ($P > 0.05$). Improvement in bowel habit was observed in 33.3% of the probiotic and 36.5% of the placebo group ($P = 0.910$). There was no significant difference between the two groups in QOL after the treatment ($P > 0.05$).

Conclusions: We found no beneficial effects over placebo for a 2-week treatment with the above mentioned multi-strain probiotic compound in the treatment of IBS. Further, trials are yet required before a clear conclusion in this regards.

Key words: Irritable bowel syndrome, probiotics, therapy

Address for correspondence:
Dr. Somaye Farzamnia, Department of Internal Medicine, Isfahan University of Medical Sciences, Hezar Jarib Street, Isfahan, Post Code: 81746-73461, Iran.
E-mail: dr.farzamnia@yahoo.com

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INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional bowel disorder characterized by abdominal pain/discomfort accompanying with disturbed bowel habits. It is estimated that 3-15% of the general population have IBS world-wide, modestly more prevalent in women than in men.[1] IBS possesses

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a chronic nature and affects patients physically, psychologically and economically and therefore, it is associated with impaired quality-of-life (QOL) and causes a major economic burden.[2]

The pathophysiology of IBS is still not completely understood. Studies have shown that the etiology is most likely multifactorial and abnormal brain-gut interaction, food intolerance; altered microflora, post-infectious or inflammatory changes and genetic and psychological factors contribute to the pathogenesis of IBS.[3,4] Heterogeneous pathophysiology and nature of IBS has a substantial impact on the efficacy of therapies for IBS. Only few therapies have been found to be effective in IBS treatment and treatments are not satisfactory in about half of the patients.[5]

The role of altered gut microbiota in the pathogenesis of IBS is highlighted by evidences showing changes in fecal and mucosa associated microflora, post-infectious IBS phenomenon and the link with intestinal bacterial overgrowth and dysregulation of mucosal immune system. Therefore, investigators have tried to see the effects of alterations in the intestinal microflora on IBS symptoms.[6] In this regard, the role of probiotics for intestinal functions and altered bowel microbiota, found in patients with IBS, has drawn attention toward these agents. Previous studies have shown beneficial effects of probiotics in the treatment of IBS and their safety has also contributed in to their popularity.[7-9] However, the benefits are likely to be strain-specific[10] and *Bifidobacterium infantis* has resulted in significant improvement in almost all IBS symptoms.[9]

Based on some evidence, a mixture of probiotics that contains several species of bacteria could be more effective than a single species of bacteria in the treatment of some gastrointestinal diseases. It is assumed that multi-strain probiotics have synergistic effects that increase their effectiveness.[11,12] However, whether a probiotic mixture is more effective than a single agent in treatment of IBS is remained un-answered yet. Another remained concern is the world-wide generalizability of current studies results. Almost all clinical studies with microbial therapies are carried out with people from developed countries.[7-9] Since, there is a variety in gut flora between different world's regions[13,14] the efficacy of probiotics may be affected by different ethnic groups of patients from different countries. There is no published report about probiotics efficacy on IBS treatment in Iran yet. Moreover, most of the previous studies are limited by small sample size.[15] Considering the above mentioned questions and lack of qualified studies, the purpose of our study was to evaluate the efficacy of a multi-strain probiotic compound, Balance® (Protexin Co., Somerset, UK), in the treatment of Iranian IBS patients. Balance® contains seven species of bacteria including *Lactobacillus* and *Bifidobacterium* species that separately have been shown helpful for treatment of IBS.[9,16] We hypothesized that this probiotic compound would decrease symptoms of IBS and increase the QOL.

MATERIALS AND METHODS

Patients and setting

This randomized placebo-controlled triple-blinded study was conducted on adult patients with IBS referred to gastroenterology clinics of Alzahra University Hospital in Isfahan City (central Iran). IBS was diagnosed by a single gastroenterologist according to the Rome II criteria (reference is needed). Patients with symptoms presented at least for 2 days/week in the preceding 2 weeks were included. Those with any infectious diseases before or during the study that need antibiotic therapy, immune-deficient disease, history of surgery on the gastrointestinal tract and history of using antibiotics or probiotics within 4 weeks before the study were not included. Considering type I error = 0.05, study power = 0.8 and expecting 10 point increase in the QOL score,[17] the study sample size was calculated as 66 cases per group. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences and registered in the U.S. National Institutes of Health Protocol Registration System (available at clinicaltrials.gov NCT01837472). Informed consent was obtained from all patients after full explanation of the study aim and protocol.

Intervention

Patients were randomized into probiotic and placebo groups based on random table list. Patients in the probiotic group received the probiotic compound Balance® (Protexin Co., Somerset, UK), twice daily after a meal for 14 consecutive days. Balance® capsules contain seven bacteria species including *Lactobacillus* strains (*Lactobacillus casei*, *Lactobacillus rhamnosus, Lactobacillus acidophilus* and *Lactobacillus bulgaricus*), *Bifidobacterium* strains (*Bifidobacterium breve* and *Bifidobacterium longum*) and *Streptococcus thermophiles*. Total viable count is 1×10^8 CFU/per capsule. Other Ingredients are Fructo-oligosaccharide as prebiotic, magnesium stearate and hydroxypropyl methyl cellulose. Those in the placebo group received placebo capsules with the same order as probiotic group. No other treatment was prescribed for patients during the study period.

Assessments

Primary outcome of this study was improvement of IBS symptoms that was assessed in categories of

abdominal pain and distension (from 0: No symptom to 3: Severe symptom) and improvement of bowel habit (get worse, no change, get better). Secondary outcome was improvement in patients QOL that was assessed by applying the IBS-QOL instrument. The IBS-QOL is a reliable and valid instrument for the assessment of IBS patients' QOL. It contains 34 items with 5-point response scale (1: No problem to 5: Extreme problem). The total score is converted into 0-100 points for better interpretation.[17] The Persian version of the IBS-QOL with sufficient psychometric properties was used in this study.[18] Patients were evaluated for symptoms and QOL at baseline and then 1 month after completion of the treatment.

Statistical analyses

This study was designed as a triple-blind study and attending physicians, patients, principal investigators as well as data analyzer were all unaware about the treatment arms and drug codes. A third colleague who coded the probiotic and placebo capsules clarified the codes after data analyses. Data were analyzed using the SPSS software for windows version 16.0. Quantitative data and qualitative data were compared between the two groups with independent sample *t*-test and Chi-square/Mann-Whitney U tests, respectively. Paired *t*-test and Wilcoxon test were applied to assess changes in QOL score and symptoms severity within each group, respectively. A *P* value of less than 0.05 was considered as indicating a statistical significant difference in all analyses.

RESULTS

A total of 160 patients were evaluated during the study period. Twenty eight patients were not included owing to unwillingness to participate, receiving antibiotics or probiotics at the time of the study. Thus, 132 patients were randomized into the probiotic and placebo groups. Three patients from the placebo group did not come for follow-up evaluations, not due to drug side effects. Thus, 129 patients completed the trial; 66 patients in the probiotic and 63 ones in the placebo group. Mean age was 36.2 ± 9.3 years and 85 (65.9%) cases were female. The two groups were similar regarding demographic and baseline clinical characteristics [Table 1].

Table 1: Comparison of the two groups with regards to demographic and baseline clinical characteristics

Variables	Probiotic *n*=66	Placebo *n*=63	*P*
Age	36.1±7.9	36.4±10.5	0.852*
Female/male	46 (69.6)/ 20 (28.9)	39 (61.9)/ 24 (38.0)	0.227**
Bowel habit			
Diarrhea predominant	23 (34.8)	19 (30.1)	0.790**
Constipation predominant	30 (45.4)	29 (46.0)	
Alternating bowel habit	13 (19.6)	15 (23.8)	

Data are presented as mean±SD, *n* (%), IBS-QOL: Irritable bowel syndrome-quality-of-life questionnaire, *Independent *t*-test, **Chi-square test

After the treatment period, there was a significant decrease in abdominal pain severity in both the probiotic ($P < 0.001$) and the placebo ($P = 0.001$) groups. There was no difference between the two groups in this regard ($P = 0.558$). Furthermore, distension severity decreased significantly in both probiotic ($P < 0.001$) and the placebo ($P < 0.001$) groups, but no difference was observed between the two groups in this regard ($P = 0.673$). Improvement in bowel habit was observed in 33.3% of the probiotic and 36.5% of the placebo group ($P = 0.910$). With regard to QOL, an improvement was observed in the probiotic ($P = 0.008$), but not in the placebo group ($P = 0.175$); though, there was no significant difference between the two groups in this regard ($P = 0.372$), Table 2. Further analysis in each subgroup of bowel habit did not change these results.

In the probiotic group, three patients experienced mild abdominal pain and nausea at the beginning of therapy, which disappeared by continuing the drug. No specific side-effect was reported in the placebo group.

DISCUSSION

The aim of the present study was to evaluate the efficacy of a multi-strain probiotic compound, which contains seven species of bacteria including *Lactobacillus* and *Bifidobacterium* species in the treatment of Iranian IBS patients. We found no beneficial effects for this probiotic compound over placebo in reliving IBS symptoms. Although there was a statistically significant improvement in QOL score in the probiotic group, this change was not clinically important, which might be due to short duration of the study.

Previous studies on the efficacy of multi-strain probiotic compounds in the treatment of IBS have provided different results. Two small studies by Kim *et al*. on a probiotic compound containing *Bifidobacterium*, *Lactobacillus* and *Streptococcus salivarius* species for 4-8 weeks found beneficial effects of these probiotics over placebo only for bloating and flatulence symptoms.[19,20] Ki Cha *et al*. have evaluated a probiotic mixture containing *Lactobacillus* and *Bifidobacterium* and *S. thermophilus* for 8 weeks and found an overall response rate of 48% versus 12% with placebo; though, it had no significant effect on individual symptoms.[21] The study by Williams *et al*. on a combination of

Table 2: Comparison of the two groups with regards to symptoms and quality-of-life after treatment

Variables	Probiotic *n*=66			Placebo *n*=63		
	Before	After	*P*	Before	After	*P*
Abdominal pain score	1.73±0.86	1.20±0.78	<0.001*	1.52±0.82	1.11±0.88	0.001*
Distension score	1.26±0.86	0.80±0.82	<0.001*	1.29±0.83	0.86±0.82	<0.001*
IBS-QOL total score	33.3±15.2	31.7±14.9	0.008**	35.5±20.1	34.5±20.3	0.175**

Data are presented as mean±SD, *n* (%), IBS-QOL: Irritable bowel syndrome-quality-of-life questionnaire, *Wilcoxon test, **Paired *t*-test

Lactobacillus and *Bifidobacterium* species also found greater improvement in IBS symptom severity and also in QOL compared with placebo over the 8-week intervention period.[22] Two other studies by Kajander *et al*. showed that a probiotic mixture of *Lactobacillus* and *Bifidobacterium* species for 5 months can stabilize the intestinal microbiota and alleviate IBS symptoms.[23,24] In contrast to these reports, the study by Søndergaard on a probiotic fermented milk containing Lactobacillus and Bifidobacterium species has found no special effect over acidified milk for 8 weeks.[25] A similar study by Simrén *et al*. also found no positive effect of such treatment.[26] Our study also found no beneficial effects of multi-strain probiotic over placebo in the treatment of IBS. According to systematic reviews and meta-analyses on this subject, there is a considerable heterogeneity among previous clinical trials regarding study design, which prevent a clear conclusion. Studies are different considering the duration of treatment (2 weeks to 5 months), outcome assessments and the type and amount (drug dose) of intervention. A publication bias toward positive results also should be considered.[9] Future studies should follow Rome Committee recommendations for appropriate design of clinical trials in this field.[27]

There are some limitations for this study. We assessed abdominal pain, the most important IBS symptom for patients as well as other symptoms with a Likert scale. This type of assessment is based on clinical importance of change; however, it might not detect small changes. Therefore, it is better for future studies to apply more comprehensive evaluation of symptoms.[28] Furthermore, the IBS-QOL evaluates QOL of the patient in the preceding 30 days; thus, 1 month was not an appropriate interval for expecting change in QOL and the study needed longer follow-up for evaluation of changes in QOL.

CONCLUSIONS

We found no beneficial effects for a 2-weeks treatment with a multi-strain probiotic compound containing *Lactobacillus* and *Bifidobacterium species* over placebo in the treatment of Iranian IBS patients. Further trials with longer duration of treatment and follow-ups are yet required before a clear conclusion in this regards. Such research should also focus on the type, optimal dose of probiotics and the subgroups of patients who are likely to benefit the most.

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