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Effect of Multispecies Probiotic Supplementation on Irritable Bowel Syndrome

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Authors' contributions

This work was carried out in collaboration between both authors. Author SYA designed the study. Author MA performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Both authors managed the analyses of the study. Author MA managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a common, chronic and sometimes disabling functional disorder of the gastrointestinal system and its treatment remains as health problem. Thus the aim of this study was to evaluate the Effect of multispecies probiotic supplementation, as a novel and Controversial therapeutic method on Irritable bowel syndrome.
Materials and Methods: In this randomized double blind Placebo-controlled clinical trial, 60 patients with IBS were enrolled. The patients were divided randomly into two groups. Patients in intervention group received two 500 mg probiotic capsules (Familact®) and in control group, received two 500 mg placebo capsules daily for 30 consecutive days. The symptoms and quality of life were measured and compared at the beginning and just after the end of study for each case.
Results: Results showed the mean score of Abdominal pain after 1 month of treatment in the probiotic group was significantly lower than the control group (1.76 ± 2.04 vs. 2.88 ± 2.25, P=0.049, respectively). While, other symptoms and quality of life did not change significantly (P>0.05). Furthermore, defecation habit and global symptoms improvement was similar after intervention in both groups and we did not observe significant differences in these items (P>0.05).

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Conclusion: The results of this study showed the beneficial effects of multispecies probiotic supplementation in controlling IBS patients' abdominal pain. thus it can be prescribed as a therapeutic option in addition to standard therapy and significantly lead to better control of this symptom in the short term.

Keywords: Irritable bowel syndrome; multispecies probiotic; abdominal pain; IBS symptoms; quality of life.

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic and sometimes disabling functional disorder of the gastrointestinal tract characterized by abdominal pain and/or discomfort along with an altered bowel habits in absence of any structural abnormality. Further than pain and discomfort and that alteration, it has some other symptoms such as bloating and flatulence, fecal urgency, sense of incomplete evacuation, dyspepsia, nausea, vomiting, and heartburn [1,2]. Worldwide, the quality of life decreases in IBS patients and induces high health costs in Asian countries as well as Western populations [3,4]. The prevalence of IBS is increasing and total prevalence is between "6.53% to 15.02%" [5,6]. The pathophysiology of IBS is not well understood; however, it is considered as a multifactorial disorder with different etiologies like genetic factors, alteration in gastrointestinal motor activity, visceral hypersensitivity, dysregulation in brain-gut axis, psychological disturbance, gut immune activation and mucosal inflammation, bile acid malabsorption and gut dysbiosis. Many recent studies suggest that alteration in gut flora plays a pathologic role by overgrowth or inducing intestinal micro inflammation [2,7,8]. In order to solve this issue and readjust gut flora, antibiotics, pre and probiotics are employed. This theory has led to growing interests in running many recent studies focused on beneficial effects of probiotics on the improvement of IBS symptoms, and several recent meta-analyses have reported that probiotics contain specific strains which improve the symptoms of IBS especially abdominal pain [9,10]. While, some other studies did not find correlation between improvement of gastrointestinal symptoms and probiotic ingestion in patients with IBS [11]. Therefore, recent interests have focused on finding the best agents such as pro and prebiotics to reach acceptable effects in IBS patients. In addition, because disruption of gut microbial balance may aggravate the quality of life in IBS, supplementation with multispecies probiotic may help resolve symptoms in IBS patients. To the best of our knowledge, there is insufficient prospective study about the efficacy of multispecies probiotic on treating symptoms in IBS patients especially in Iran. However, the need for further studies has been emphasized in many previous trials. Therefore, this study was designed to evaluate clinical efficacy of multispecies probiotic supplementation on IBS symptoms.

2. MATERIALS AND METHODS

2.1 Study Design and Target Group

This prospective randomized double blind placebo-controlled clinical trial was conducted in the Internal Medicine department of Qom Ayatollah Golpaygani Hospital, center of Iran from April 2019 to June 2019. The quality of life and symptoms healing parameters of IBS patients receiving multispecies probiotic supplementation (intervention group) were compared to patients receiving placebo capsule (control group). The study received ethics approval from the Ethics Committee of Qom Islamic Azad University (IR.IAU. QOM.REC.1397.042) on November 2018, and all participants signed the written informed consent. This trial has also registered on the Iranian registry of clinical trials (IRCT) affiliated to the world health organization registry network and international clinical trials registry platform (ICTRP) with IRCTID: IRCT20181231042191N1. Inclusion criteria consisted of patients referred to internal medicine department with a diagnosis of IBS based on Rome II criteria (abdominal pain or any digestive discomfort for at least 3 months during the last year(not necessarily consecutive), along with two of the three following items: relieving pain after defecation, starting symptoms associated with change in frequency of defecation, starting symptoms associated with consistency of stool), signed an informed consent form to participate in the study and age older than 18. Exclusion criteria consisted of patients with history of any organic bowel disease or chronic digestive disorder, history of major gastrointestinal surgery, chronic

consumption of antibiotics, corticosteroids and immunosuppressive drugs, use of drugs affecting gastrointestinal motility such as metoclopramide, cisapride, domperidone, narcotics, especially opioid derivatives, laxatives, anticathartics, and any other drugs that are effective in the treatment of IBS (the list is given to the patient), severe psychological and behavioral disorders, food allergy, incidence of acute gastrointestinal disease during the trial, such as acute gastroenteritis or acute gastrointestinal bleeding, major changes in the diet or lifestyle during the study, incidence of any side effects due to probiotic supplementation and dissatisfaction to continue participation in the study. We also excluded patients with incomplete data.

2.2 Participants

The study flowchart is shown in Fig. 1. Sixty patients with IBS, who had been diagnosed by gastroenterologist based on our inclusion and exclusion criteria were enrolled in this study.

The participants were randomly allocated in two groups using a block randomization procedure with matched subjects in each block based on sex and age. Fifty-two patients completed the study; 25 in intervention group and 27 in control group.

Patients were especially advised to avoid the use of antibiotics during the trial as it can deactivate probiotics. About the diet we also informed the patients that there is no need to change the type and volume of food intake during the study period; as we wanted just to evaluate the pure effects of multispecies probiotics.

Complications of probiotics are rare, however, patients were advised to stop using it and inform researchers if any skin rashes, itching, coughing, and any distressing persistent digestive discomfort occurred. The aims of the study were explained to all participants who entered the study. As the trial is double blind, all patients received reassurance and essential explanations of the nature of the disorder at the beginning of the study.

Patients in the intervention group received two 500 mg probiotic capsules (Familact®) and in the control group received two 500 mg placebo capsules, daily for 30 consecutive days. Familact® contains *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Streptococcus thermophilus* and Fructooligosaccharides (FOS). The count of this product is 10^9 CFU. Placebo capsules had the same shape and packaging to probiotic capsules. Packages of the products were coded two types by the company; one code for the original drug and one code for the placebo. Each of the two randomly divided groups received a type of drug code. The codes were kept secret from patients and researchers and announced to researchers at the end of the clinical trial. At the beginning of the study, and just at the end of the study (30 days after starting the treatment), patients were evaluated for symptoms and quality of life based on standard questionnaires.

2.3 Instruments

IBS symptom questionnaires: IBS related symptoms were checked by two questionnaires at the beginning and end of the clinical trial. At the beginning Patients were asked to choose a number from 0 to 10 for showing the intensity of their abdominal pain, abdominal discomfort and abdominal bloating. 0 reflects absence or no intensity of the symptom and 10 reflects the highest intensity for that symptom. Patients also were asked to choose I have/I don't have for nausea and heartburn. At the end of our study abdominal pain, abdominal discomfort and abdominal bloating were checked just as the beginning point. We asked patients if their nausea and heartburn got better, worse or didn't change. We also asked about change of their defecation habit in terms of frequency and consistency (better/ no change/worse) and if they had global IBS symptoms improvement or not.

Validity and reliability of our questionnaires were confirmed by standard methods.

IBS-QOL (Persian version): IBS-QOL questionnaire is a 34-item instrument developed and validated for measurement of health-related quality of life in non-subtyped IBS patients. Andrae DA et al. (2013) showed that IBS-QOL has high value of Cronbach's Coefficient α ($\alpha = 0.963$). Moreover, in terms of test-retest reliability, the Andrae DA et al. demonstrated good levels for the IBS-QOL total score (reliability threshold of around 0.7) [12]. Validity and reliability of Persian version of IBS-QOL-34 have been analyzed and confirmed in several studies; For example, Masaeli et al. (2013) showed total reliability of 0.95 using Cronbach's alpha and appropriate content and

concurrent validity for Persian version of IBS-QOL-34 [13].

2.4 Data Analysis

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using SPSS version 24 software (SPSS Inc., Chicago, IL, USA). To compare qualitative variables between groups Chi-square test was performed. The normal distribution of all studied parameters was checked with Kolmogorov-Smirnov test. Student's t-test and paired t-test were used for variables which were distributed in a normal way, besides Mann-Whitney and Wilcoxon test were performed for variables that have not normal distribution. The two tailed p-value < 0.05 were considered significant.

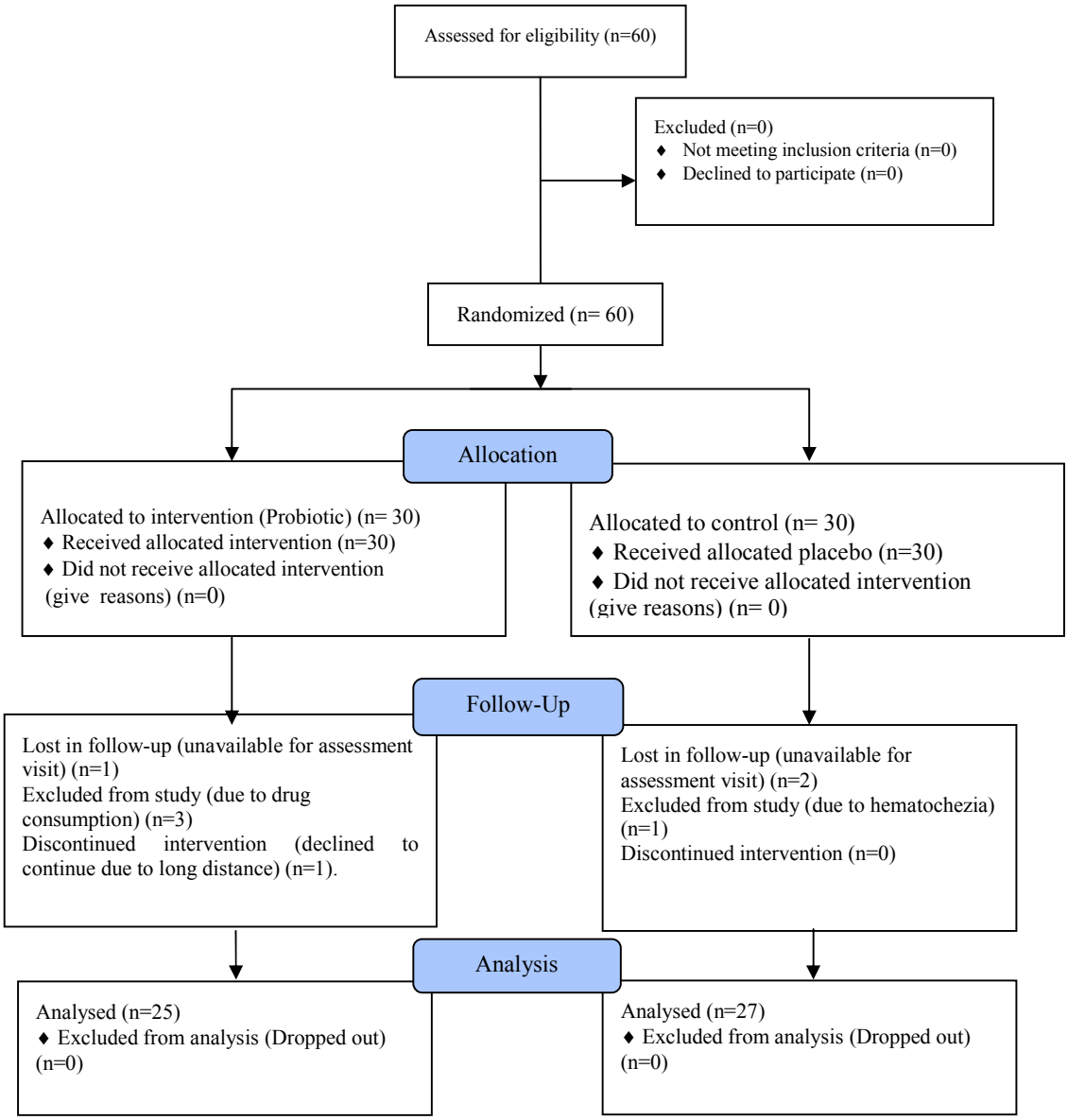

Fig. 1. Study flowchart (Consort format)

3. RESULTS

Demographic features in age (P=0.613), sex (P=0.609) and educational levels (P=0.408) in both groups were similar (Table 1). Moreover, IBS type did not differ between probiotic and control group (P=0.976). Eight patients were dropped out and finally, 52 patients completed the study. Before intervention, studied variables including symptoms such as abdominal pain (P=0.399), abdominal discomfort (P=0.375), bloating (P=0.449), heartburn (P=0.957) and nausea (P=0.627) (Table 1) and IBS-QOL total score and subtypes (P>0.05) (Table 2) did not differ between the groups.

Results showed that the mean score of Abdominal pain after one month of treatment in the probiotic group was significantly lower than the control group (1.76 ± 2.04 vs. 2.88 ± 2.25, P=0.049, respectively). While, other symptoms did not change significantly (P>0.05). Furthermore, defecation habit and global improvement was similar after intervention in both groups and we did not observe significant differences in these items (P>0.05). (Table 1) Moreover, IBS-QOL total score decreased significantly in both groups (P<0.05), while this reduction in total score and subtypes score was not significantly different between control and probiotic groups (P>0.05). (Table 2).

4. DISCUSSION

Probiotics provide health benefits through different mechanism to their host. They significantly modify the intestinal microbiota [14]. Multispecies probiotics may have different beneficial effects on IBS symptoms due to particular act of each species on the gastrointestinal tract, and may have a synergistic effect [15]. Although several studies have demonstrated the efficacy of probiotics in improvement of IBS symptoms [16-19], their conclusions vary because of different types of study design, inadequate sample size, and use of various probiotic strains. On the other hand, less study focused on the effect of

Table 1. Studied variables during different periods of time in both control and probiotic groups

Variables	Groups		Placebo (n=27)	Probiotic (n=25)	P-value
Age (year)			31.44 ± 7.6	31.2 ±12.3	0.613
Sex (male)			17 (63 %)	14 (56 %)	0.609
Education level	Illiterate and elementary		3 (11.1 %)	3 (12 %)	0.408
	Diploma and less		4 (14.8 %)	8 (32 %)	
	Undergraduate and Bachelor		6 (22.2 %)	6 (24 %)	
	Master's and Ph.D.		14 (51.9 %)	8 (32 %)	
IBS type	IBS-M		8 (29.6 %)	7 (28 %)	0.976
	IBS-D		10 (37 %)	10 (40 %)	
	IBS-C		9 (33.3 %)	8 (32 %)	
Abdominal pain	Before intervention		4.22 ± 2.33	4.84 ± 2.9	0.399
	After intervention		2.88 ± 2.25	1.76 ± 2.04	0.049
Abdominal discomfort	Before intervention		5 ± 2.77	4.28 ± 3.02	0.375
	After intervention		3.37 ± 2	2.52 ± 2.25	0.156
Bloating	Before intervention		5.74 ± 2.63	6.28 ± 2.46	0.449
	After intervention		4.92 ± 2.49	4.4 ± 2	0.621
Heartburn	Before intervention		11 (40.7 %)	10 (40 %)	0.957
	After intervention	Without change	5 (18.5 %)	3 (12 %)	0.513
		Improved	6 (22.2 %)	9 (36 %)	
Nausea	Before intervention		8 (29.6 %)	9 (36 %)	0.627
	After intervention	Without change	4 (18.4 %)	5 (20 %)	0.559
		Improved	2 (7.4 %)	2 (8 %)	
		Deterioration	2 (7.4 %)	0	
Defecation habit	Improved		14 (51.9 %)	17 (68 %)	0.179
	Without change		10 (37 %)	8 (32 %)	
	Deterioration		3 (11.1 %)	0	
Global improvement	No		15 (55.6 %)	10 (40 %)	0.262
	Yes		12 (44.4 %)	15 (60 %)	

Table 2. IBS-QOL in both control and probiotic groups before and after intervention

IBS-QOL / Groups		Placebo (n=27)	Probiotic (n=25)	P-value
Before intervention	Dysphoria	34.36 ± 22.83	30.33 ± 18.89	0.493
	Social Reaction	25 ± 24.51	25.5 ± 20.08	0.936
	Health Worry	43.82 ±22.94	47.66 ±22.5	0.546
	Body Image	21.06 ±20.07	19 ±16.58	0.689
	Relationships	40.74 ±20.32	37.33 ±14.85	0.496
	Food Avoidance	41.04 ±20.79	37.66 ±21.39	0.566
	Sexual	17.59 ±24.82	11.5 ±19.73	0.327
	Interference with Activity	33.64 ±14.56	30.66 ±18.97	0.527
	Total score	32.57 ±17.17	30.17 ±14.55	0.591
After intervention	Dysphoria	22.63 ±13.79	22.11 ±13.08	0.889
	Social Reaction	22.22 ±16.29	20.25 ±14.9	0.652
	Health Worry	29.93 ±19.51	31 ±19.62	0.846
	Body Image	18.28 ±15.49	14 ±16.66	0.341
	Relationships	32.71 ±14.6	33 ±17.59	0.95
	Food Avoidance	29.32 ±22.21	29.66 ±17.36	0.951
	Sexual	14.35 ±21.56	8 ±14.82	0.184
	Interference with Activity	25.77 ±16.05	25.66 ±16.03	0.981
	Total score	24.26 ±11.82	23.14 ±11.23	0.729

multispecies probiotic on controlling IBS symptoms. Therefore, given the controversies in IBS pathophysiology and lack of sufficient evidence for gastrointestinal tract microbiota abnormalities in patients with IBS, additional randomized clinical trials with appropriate endpoints with different probiotic species are needed to evaluate to which extent probiotics help in the management of IBS symptoms.

The aim of this study was to evaluate the effects of multispecies probiotic supplementation on different aspects of irritable bowel syndrome. According to our results, multispecies probiotic supplementation was significantly superior to placebo in reduction of the severity of abdominal pain; however, the severity of other symptoms, global improvement and quality of life based on IBS-QOL34 did not differ from control group.

In a randomized, double-blind, placebo-controlled trial performed in 2014 reported that multispecies probiotics are effective in IBS patients by improving abdominal pain/discomfort and bloating and induce the alterations in the composition of intestinal microbiota (*B. lactis*, *L. rhamnosus*, and *S. thermophilus* had increased significantly) [20]. Another study performed in 2016 showed that multispecies probiotic supplementations are effective in IBS-C subjects in improving abdominal pain, abdominal discomfort, bloating and induce a different assessment in the composition of intestinal microbiota [21]. However, we did not observe significant differences in the terms of abdominal discomfort and bloating, but we found that abdominal pain decreased significantly in multispecies probiotic group as compared to placebo. These differences obtained from ours as compared to other studies may be due to different sample size, different probiotics, differences in race, geographic location and demographic features.

Yoon H et al. showed that 4-week administration of multispecies probiotic mixture significantly increased the fecal concentration of most probiotic strains and improved diarrhea-symptom scores in IBS patients. However, they reported no significant improvement in other global symptom score or any other symptoms like pain/discomfort, bloating/gas and constipation over time [22]. Although, we did not evaluate the fecal concentration of probiotic strains, but we found that defecation habit improved 68 % in probiotic group (while improvement was 51.9 % in placebo group). However, this difference was not statistically significant, but improvement ratio was higher in intervention group and in larger sample size, we may observe reliable significance.

A study performed by Farhad Pourfarzi et al. demonstrated that adding probiotic yogurt to the IBS patients' diet leads to improvement of symptoms such as abdominal pain and flatulence. However, they did not find a significant difference between two groups in the response to treat for other symptoms including vomiting, epigastric pain, and bowel habit [23]. The results of this study for abdominal pain improvement after receiving probiotic was similar to our study, while, we did not find significant changes in flatulence.

In another study performed by Shavakhi A et al. found no beneficial effects over 2-week treatment with multi-strain probiotic compound comparing to placebo in IBS patients. Abdominal pain and distension decreased and bowel habits improved in both (improvement in the bowel habit was 33.3% in group probiotic and 36.5% in placebo group); and there was no significant difference between intervention and control group. Moreover, they did not find significant difference between the two groups in quality-of-life after the treatment [24]. While, we found that abdominal pain decreased significantly in the probiotic group, although, we did not find significant changes in the terms of quality-of-life or any other symptoms (similar to Shavakhi A et al. study).

Our study has some limitations. The duration of study was short. Maybe longer time of treatment with multispecies probiotic supplementation could have different and better effects on some symptoms and the quality of patients' lives. In addition, we did not check the duration patients' abdominal pain could remain improved after completion probiotic consumption. Next limitation was the assessment of fecal concentration of probiotic strains. Perhaps assessment of fecal concentration especially if we had greater sample size would have revealed more useful information especially about specific actions of each species.

5. CONCLUSIONS

The results of the current study showed the beneficial effects of multispecies probiotic supplementation in improvement of IBS patients' abdominal pain. Thus, it can be prescribed as a therapeutic option in addition to standard therapy and significantly lead to better control of this symptom in the short term.

CONSENT AND ETHICAL APPROVAL

The study received ethics approval from the Ethics Committee of Qom Islamic Azad University (IR.IAU.QOM.REC.1397.042) on November 2018, and all participants signed the written informed consent.

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COMPETING INTERESTS

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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