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Efficacy of synbiotic, probiotic, and prebiotic treatments for irritable bowel syndrome in children: A randomized controlled trial

BOWEL

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Original Article

ABSTRACT

Background/Aims: Irritable bowel syndrome (IBS) is an important health problem that presents serious social burdens and high costs. Our study investigated the efficacy of synbiotic (*Bifidobacterium lactis* B94 with inulin), probiotic (*B. lactis* B94), and prebiotic (inulin) treatment for IBS in a pediatric age group.

Materials and Methods: This study was randomized, double-blind, controlled, and prospective in design and included 71 children between the ages of 4 and 16 years who were diagnosed with IBS according to the Rome III criteria. The first group received synbiotic treatment [5×10^9 colony forming units (CFU) of *B. lactis* B94 and 900 mg inulin]; the second group received probiotic treatment (5×10^9 CFU *B. lactis* B94), and the third group received prebiotic treatment (900 mg inulin) twice daily for 4 weeks.

Results: Probiotic treatment improved belching–abdominal fullness (p<0.001), bloating after meals (p=0.016), and constipation (p=0.031), and synbiotic treatment improved belching–abdominal fullness (p=<0.001), bloating after meals (p=0.004), constipation (p=0.021), and mucus in the feces (p=0.021). The synbiotic group had a significantly higher percentage of patients with full recovery than the prebiotic group (39.1% vs. 12.5%, p=0.036).

Conclusion: Administration of synbiotics and probiotics resulted in significant improvements in initial complaints when compared to prebiotics. Additionally, there was a significantly higher number of patients with full recovery from IBS symptoms in the synbiotic group than in the prebiotic group. Therefore, the twice daily administration of synbiotics is suggested for the treatment of children with IBS.

Keywords: *Bifidobacterium lactis* B94, irritable bowel syndrome, synbiotic, probiotic, child

INTRODUCTION

Irritable bowel syndrome (IBS) is an important health problem that presents serious social burdens and high costs. IBS is a functional gastrointestinal disorder that presents with alterations in bowel habits. Although microscopic inflammation has been identified in some cases, the underlying cause of IBS has yet to be determined (1). The diagnosis of IBS can be made using the Rome III diagnostic criteria.

Based on the stool form, IBS can be subclassified as diarrhea-predominant, constipation-predominant, variable, or unclassified forms (2).

Recently, new aspects on the pathophysiology of IBS have been studied, including changes in bowel motility, intestinal bacteria overproduction (3), microscopic inflammation (1), visceral hypersensitivity (4), and changes in the brain-bowel axis (5). These investigative approaches have provided the groundwork for the use of probiotics in the treatment of IBS (6). Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (7). Prebiotics are carbohydrates that pass through the small intestine without being digested; when they reach the colon, they stimulate the growth and function of beneficial bacteria, particularly bifidobacteria and lactobacilli. Inulin is a prebiotic made of chicory extract, and it consists of long-chain fructooligosaccharides (8). Galactooligosaccharides, fructooligosaccharides, inulin, and ß-glucans are the main types of prebiotics, and all are nutrients for probiotics (9).

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The efficacy of probiotics as a treatment for bowel disorders depends on their type, the way they are prepared, their dosage, and the route of administration (10). Probiotics help protect the bowel epithelium by enhancing intercellular tight junctions and stimulating mucus production. In addition, they have antioxidant properties and alter intestinal microflora. Probiotics compete with pathogens for attachment to the intestinal mucosa, they increase bacteriocin production, and they produce organic acids, which decrease luminal pH (11).

The etiology of IBS has not been fully elucidated. Therefore, new studies examining the efficacy and safety of different probiotics and synbiotics for the treatment of IBS in different age groups are necessary. In the current study, we investigated the efficacy of synbiotic (*B. lactis* B94 with inulin), probiotic (*B. lactis* B94), and prebiotic (inulin) treatments for IBS in children.

MATERIALS AND METHODS

This study included children between the ages of 4 and 16 years who were diagnosed with IBS according to the Rome III criteria in the Akdeniz University Pediatric Gastroenterology outpatient clinic between September 2014 and May 2015. Ethics committee approval was received for this study from the ethics committee of Akdeniz University School of Medicine, Clinical Research Ethics Committee (issue date, 19/11/2014; decision no. 506) and families of children gave written informed consent.

Randomization

Patients diagnosed with IBS at the outpatient clinics of pediatric gastroenterology of this hospital were directed to the pediatric gastroenterology nurse and drug boxes that were labeled with code numbers only. The package ingredients were unknown and were randomly given to the patients, thus randomization was provided.

Blindness of the study

Three different types of treatment were used including synbiotics, probiotics, and prebiotics as ingredients Blindness was provided by administration of one of the three packages with completely same color, odor, taste and package properties with a label on the package stating one of the three different code numbers. The ingredients of the package were unknown to the doctor, nurse and patient but only the manufacturer knew which code number included which drug.

Study design

This study was prospectively performed. Synbiotic treatment (5×10^9 CFU *B. lactis* B94 and 900 mg inulin) was applied in the first group (Maflor® sachet, Mamsel; Turkey); probiotic treatment (5×10^9 CFU *B. lactis*, which had the same color, smell, taste, and package properties with the symbiotic treatment) was applied in the second group; and prebiotic treatment (900 mg of inulin only) was applied in the third group.

Evaluation of treatment response

Changes in the initial symptoms, such as postprandial swelling, belching-abdominal distension, mucoid defecation, difficulty in defecation, feeling of incomplete defecation, and urgent defecation were questioned at the end of one month. Individuals with improvement in all the presenting symptoms stated above at the end of treatment for one month were accepted as 'fully benefited'. Individuals who had resolution in one or several of the symptoms were accepted as 'partially benefited'. During data collection, data including the same code number were collected in the same group. The results were compared according to the code numbers. Data was analyzed by a statistician who had no information on which code number included what, and the statistical significance between the groups were compared. Finally, the ingredients of the code were learned and corresponding names of synbiotic or placebo were written into the tables and figures.

Endpoint criteria

The primary endpoint criterion was complete benefit of the patient with resolution of all present complaints with synbiotic or probiotic treatment for 4 weeks.

The secondary endpoint criterion was resolution at the end of the 4-week treatment of one or more of the symptoms such as postprandial swelling, belching-abdominal distension, mucoid defecation, difficulty in defecation, feeling of incomplete defecation, and urgent defecation.

Evaluation of safety

The frequency of side effects such as diarrhea, vomiting, constipation, and abdominal pain that were not present initially was evaluated.

Statistical analysis

Statistical analysis of the data was performed using SPSS version 15.0 (SPSS Inc.; Chicago, IL, USA). The Chi-square test and Kruskal-Wallis test were used to compare the data. For descriptive statistical analysis, mean and standard deviation were reported for numerical variables while counts and percentages were used for categorical variables. Values of $p<0.05$ were accepted as significant.

RESULTS

During the study period, 83 children were diagnosed with IBS. Seven patients were not enrolled in the study because they refused to participate. The remaining 76 patients were randomized into three groups and received double-blinded treatment. Five patients were excluded from the study because they could not complete their treatment. A flow chart of the patients is shown in Figure 1. In the whole study group (71 patients in all), the most common subtype was constipation-predominant IBS, the mean age was 10.88±4.38 years (with an age range from 4 to 16 years), and the female:male ratio was 1:1. The synbiotic group contained 23 patients, the probiotic group contained 24

patients, and the prebiotic group contained 24 patients. There was no significant difference between the groups with respect to initial complaints, IBS subgroups, age, and sex distribution (Table 1). With regards to initial complaints, the most common complaint was sudden urge to defecate (47; 66.2%) followed by bloating after meals (46; 64.8%) and belching (46; 64.8%). The least common complaint was mucus in the stool (30; 42.3%). In the whole study group, abdominal pain was experienced daily by 19 patients (27%), once a week by 24 patients (34%), and at least 3 days per month by 28 patients (39%).

At the end of the 4-week treatment, the numbers of patients with symptoms were compared (Table 2). No significant improvement in any of the initial complaints were found in the prebiotic group. In the probiotic group, the most significant improvement was observed in belching–abdominal fullness ($p<0.001$), while there were also significant improvements in bloating after meals ($p=0.016$) and difficulty with defecation ($p=0.031$). In the synbiotic group, the most significant improvement was in belching–abdominal fullness ($p<0.001$), while there were also significant improvements in bloating after meals ($p=0.004$), difficulty with defecation ($p=0.021$), and mucus in the stool ($p=0.021$). Full recovery was observed in nine patients (39.1%) in the synbiotic group, seven patients (29.2%) in the probiotic group, and three patients (12.5%) in the prebiotic group. When the groups were compared with each other with regards to full recovery, there were no significant differences between the prebiotic and probiotic groups ($p=0.155$) or between the probiotic and synbiotic groups ($p=0.471$). However, there was a significant difference in the number of patients who fully recovered between the prebiotic and synbiotic groups ($p=0.036$). Post-treatment results by subgroups in all three groups were similar to the results of the overall

Table 1. Demographic properties and initial symptom frequency in the three groups

Parameters	Prebiotic	Probiotic	Synbiotic	p
N	24	24	23	
Age, years	12.33±4.65	10.20±3.78	10.08±4.49	0.118*
Sex (M, F)	12, 12	10, 14	11, 12	0.835**
IBS subtype, n (%)				
Diarrhea-predominant	6 (25.0)	7 (29.2)	6 (26.0)	0.945**
Constipation-predominant	11 (45.8)	10 (41.7)	10 (43.5)	0.958**
Variable type	3 (12.5)	4 (16.7)	3 (13.0)	0.904**
Unclassified	4 (16.6)	3 (12.5)	4 (17.3)	0.881**
Bloating after meals, n (%)	12 (50.0)	18 (75.0)	16 (69.6)	0.163**
Belching–abdominal fullness, n (%)	13 (54.2)	18 (75.0)	15 (65.2)	0.319**
Mucus in stool, n (%)	8 (33.33)	10 (41.7)	12 (52.2)	0.424**
Difficulty with defecation, n (%)	15 (62.5)	17 (70.8)	13 (56.52)	0.592**
Feeling of being unable to completely empty at bowel movements, n (%)	14 (58.3)	15 (62.5)	11 (47.)	0.581**
Sudden urge to have bowel movements, n (%)	16 (66.7)	16 (66.7)	15 (65.2)	0.993**

*Kruskal-Wallis test was used.
**Chi-square test was used.

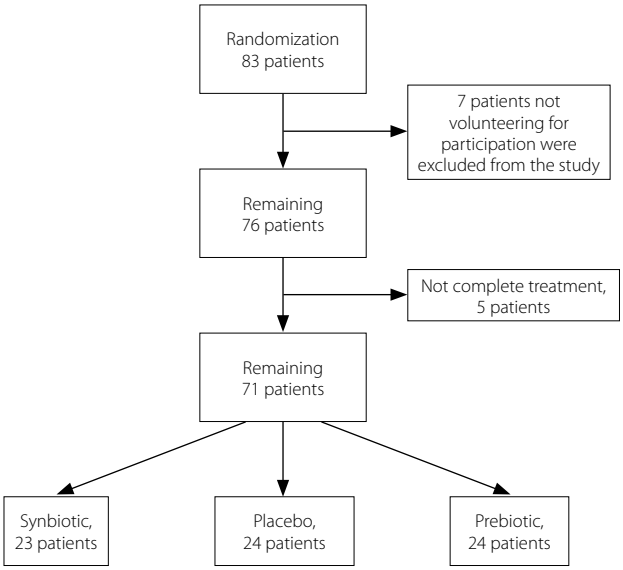

Figure 2. Patient flow chart

Table 2. Symptoms of IBS before and after 4 weeks of treatment by study group. Values are percentages of patients with each complaint

Complaint	Prebiotic (n=24)			Probiotic (n=24)			Synbiotic (n=23)		
	Before	After	p*	Before	After	p*	Before	After	p*
Bloating after meals, %	50	50	1.000	75	45	0.016	69.6	30.4	0.004
Belching–abdominal fullness, %	54.2	45.8	0.250	75	25	<0.001	65.2	13	<0.001
Mucus in stool, %	33.3	29.2	1.000	41.7	37.5	1.000	52.2	17.4	0.021
Difficulty with defecation, %	62.5	50	0.250	70.8	45.8	0.031	56.5	21.7	0.021
Feeling of being unable to completely empty at bowel movements, %	58.3	41.7	0.125	62.5	45.8	0.125	47.8	26	0.063
Sudden urge to defecate, %	66.7	62.5	1.000	66.7	54.2	0.250	65.2	56.5	0.500

*Chi-square test was used.

groups and were statistically similar with the results of the overall groups given above. In addition, no side effects such as diarrhea, constipation, and abdominal pain developing after the treatment in any of the synbiotic, probiotic, and prebiotic groups were encountered.

DISCUSSION

There have been several clinical studies, including randomized controlled trials, regarding various subtypes of *B. lactis* and IBS. These studies mainly used probiotic mixtures, were conducted in adults, and examined changes in symptoms. Placebo-controlled studies have shown that patients using various probiotic mixtures (including *B. lactis*) have a significantly greater number of improvements in stool consistency (12,13) and in IBS symptoms such as abdominal pain (12,14,15) satisfaction with bowel habits, quality of life (14), and fullness (13,15) than those in the control groups. Furthermore, these studies have shown that a significantly greater number of patients in the probiotic groups had full recovery when compared to the placebo groups (12,13). Patients taking probiotics did not have any significant increases in intestinal microbiota or changes in levels of the inflammatory marker C-reactive protein (15). Another study reported that patients taking a probiotic mixture containing *B. lactis* and those taking placebo had similar improvements in gastrointestinal symptoms after 8 weeks (16). One controlled study observed that a group taking synbiotic yogurt (including *B. lactis* Bb12 and acacia fiber) had significant improvements and recovery in the initial symptoms of constipation-predominant and diarrhea-predominant IBS than did those taking standard yogurt as a control (17). Another study found that patients taking milk containing *B. lactis* (DN-173 010) had significant recovery in abdominal fullness and gastrointestinal passage time than did those in a control group (18). Altogether, these studies indicate that the use of probiotics and synbiotics containing *B. lactis* leads to significant improvements in the initial symptoms of IBS.

To our knowledge, there is no information regarding the utilization of *B. lactis* B94 in IBS in the literature. According to a recent review and the latest probiotic and prebiotic guidelines published by the World Gastroenterology Organization, *B. infantis* is the only recommended *Bifidobacterium* species used in IBS treatment (19). Studies on bifidobacteria generally use probiotic mixtures, and few studies used bifidobacteria alone (12,18). In our study, we used *B. lactis* B94 as a probiotic and inulin as a prebiotic for the treatment of IBS to investigate the efficacy of synbiotic, probiotic, and prebiotic treatments for IBS. We observed a significantly greater number of patients with full recovery in the synbiotic group than in the prebiotic group. Although there was also improvement in the probiotic group, the number of patients with full recovery was not significantly different than that of the prebiotic group. Significant improvement was observed in belching–abdominal fullness and bloating after meals in the probiotic and synbiotic groups. Similarly, difficulty with defecation improved significantly in the probiotic and synbiotic groups while mucus in the stool improved significantly only in the synbiotic group.

Fewer studies examined the effect of prebiotics than those of probiotics in IBS. One prebiotic study that compared transgalactooligosaccharides to placebo observed that prebiotics altered the fecal microbiota and increased the amount of bifidobacteria (20). Randomized controlled trials of patients using fructooligosaccharides and galactooligosaccharides, at varying doses between 3.5 and 20 g for 4–12 weeks, revealed improvements in IBS symptoms such as gas passage and fullness (21-24). In our study, we used 900 mg of inulin and this did not lead to an improvement in any of the initial complaints. However, further studies are necessary to determine the effective dosage of probiotics in IBS treatment. One placebo-controlled study found that patients who used synbiotics made of inulin, resistant starch, and a probiotic mixture had a better life quality score, shorter rectosigmoid passage time, and decreased distention and gas passage than those in the placebo group (25). In a similar study, there were significant improvements in weakness, un-wellness, dyspepsia/distention, and complaints related to colitis in the synbiotic group (26). We found similar results in the synbiotic group in our study.

No side effects were encountered associated with the use of *B. lactis* B19, as was the case in the previously performed studies with *B. lactis* B19 in our country (27,28).

A major limitation of our study was that it was done in a tertiary health care center. This caused the study to be conducted with relatively more complex patients. Also, the number of the IBS groups (more than one) produced a limitation in clear-cut evaluation of the results.

In conclusion, administration of synbiotics and probiotics resulted in significant improvements in initial complaints when compared to prebiotics. Additionally, when compared to the prebiotic group, there was a significantly higher number of patients with full recovery from IBS symptoms in the synbiotic group. Therefore, twice-a-day administration of synbiotics (5×10^9 *B. lactis* B94 and 900 mg of inulin) is suggested for the treatment of children with IBS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Akdeniz University School of Medicine (Issue date: 19/11/2014; Decision no: 506).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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