

Probiotic for irritable bowel syndrome in pediatric patients: a randomized controlled clinical trial

Hamidreza Kianifar¹, Seyed Ali Jafari¹, Mohammadali Kiani¹, Hamid Ahanchian², Seyed Vahid Ghasemi³, Zubin Grover⁴, Leili Zarif Mahmoodi⁵, Rita Bagherian⁶, Maryam Khalesi⁷

¹ MD, Associate Professor, Department of Pediatric Gastroenterology, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran

² MD, Associate Professor, Department of Pediatric Immunology and Allergy, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran

³ MD, Pediatrician, Department of Pediatrics, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran

⁴ MD, Associate Professor, Queensland Children's Medical Research Institute, Royal Children's Hospital, Brisbane, Queensland, Australia

⁵ Ph.D., Faculty Member, Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

⁶ MD, Faculty Member, Department of Pediatric Gastroenterology, Tehran University of Medical Sciences, Tehran, Iran

⁷ MD, Assistant Professor, Department of Pediatrics, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran

Type of article: Original

Abstract

Background: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder in children. Recently, probiotics have been suggested as a treatment option for gastrointestinal disorders. The most effective species and the most appropriate doses are still unknown.

Objective: The aim of this study was to assess the effects of Lactobacillus GG (LGG) for treating IBS in pediatric patients.

Methods: In a controlled, double blind, randomized trial, patients with IBS diagnosed by Rome III criteria from August 2012 to September 2012 at Dr. Sheikh Hospital, Mashhad University of Medical Sciences, Iran, were assigned to one of two groups, i.e., intervention and control groups. For four weeks, the intervention group received a probiotic in capsule form that contained LGG at a concentration of 1×10^{10} cfu/ml bacteria. For the same period, the control group received a placebo capsule that had the same shape and color but only contained inulin, which also was present in the LGG capsules. The primary outcome was any change in the severity of the patients' pain, and we used a five-point Likert scale to evaluate the severity of their pain. Secondary outcomes were changes of the functional scale, stool patterns, and associated problems.

Results: Fifty-two patients participated in the study, and 26 patients were assigned randomly to each of the two groups. The severity of the patients' pain decreased significantly in the intervention group after one, two, three, and four weeks of treatment, as indicated by P-values of 0.01, 0.00, 0.00, and 0.00, respectively. Also, there was significant improvement in the functional scale after two weeks of treatment (P-value ≤ 0.00).

Conclusion: Lactobacillus GG at a concentration of 1×10^{10} cfu/ml for a period of four weeks can lessen the severity of the patients' pain and improve the functional scale in patients with irritable bowel syndrome. Probiotics can have therapeutic effects for IBS patients.

Trial registration: The trial is registered at the Iranian Registry of Clinical Trials (<http://www.ircr.ir/>) with IRCT

Corresponding author:

Assistant Professor Dr. Maryam Khalesi, Department of Pediatrics, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Tel: +98.5138012469, +98.9151037242, Fax: +98.5138417451, E-mail: khalesim@mums.ac.ir

Received: June 11, 2015, Accepted: August 12, 2015, Published: September 16, 2015

iThenticate screening: August 03, 2015, English editing: September 03, 2015, Quality control: September 12, 2015

© 2015 The Authors. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

registration number: IRCT201205219825N1.

Funding: All phases of this study were supported by Mashhad University of Medical Sciences, Iran.

Keywords: irritable bowel syndrome, children, probiotics

1. Introduction

Irritable bowel syndrome (IBS) is a chronic disturbance of the gastrointestinal function, and it is common in children, affecting their quality of life due to anxiety, frequent visits to a physician, and not being able to go to school. IBS has different presenting symptoms in patients, such as cramping, bloating, diarrhea, constipation, or alternating diarrhea and constipation. The Rome III criteria were used based on the Bristol Stool Form Scale for the clinical diagnosis of IBS. According to the Rome III criteria, patients with IBS subdivide on their stool form into one of four subgroups, i.e., IBS with constipation, IBS with diarrhea, mixed IBS, and unsubtyped IBS. Multiple etiological factors have been suggested for IBS, including psychosocial factors, malfermentation of food residues, altered gastrointestinal motility, and changes in the intestinal microflora. Also, compared to healthy people, patients with IBS have a great homogeneity in the fecal microflora that involves decreased levels of lactobacilli, bifidobacteria, and coliforms (1-5).

IBS should be treated based on the predominant symptoms of patients; reports have indicated that several different types of medical treatments and agents have been used for IBS patients, including antacids, laxatives, anti-diarrhea medications, antispasmodics, and antidepressants. According to recent studies, probiotics are live microorganisms that can be proposed as considerable treatment modalities for different gastrointestinal problems in children. It has been suggested that these microorganisms can reduce the symptoms of IBS. Probiotics have multiple beneficial effects in the gastrointestinal tract, such as increasing the mass of bacterial microflora, especially lactobacilli strains; decreasing bacterial overgrowth; inducing the intestinal mucosal barrier; and normalizing the motility of the digestive tract. Also, they can regulate the balance between the pro- and anti-inflammatory cytokines. Due to these beneficial effects, probiotics have been suggested as a therapeutic option for IBS. Although some probiotic strains have been reported to be clinically more efficient than placebos in treating adults with IBS, only limited data are available regarding the beneficial effects of probiotics in children with IBS. The goal of this study was to assess the effects of the probiotic *Lactobacillus GG* (LGG) on the symptoms of children with IBS (6-10).

2. Material and Methods

2.1. Trial design

This double-blind, randomized controlled trial study was conducted at Dr. Sheikh Hospital, Mashhad University of Medical Sciences, Iran, from August 2012 to September 2012.

2.2. Participants

The inclusion criteria were patients whose ages ranged from 4 to 18 years old who had active symptoms of abdominal pain for at least two weeks before the beginning of the study and had been diagnosed with IBS by a pediatric gastroenterologist. This diagnosis must have been made on the basis of Rome III criteria and other differential diagnoses must have been excluded by laboratory evaluation, abdominal ultrasound, radiographic imaging, endoscopy, and breath hydrogen testing, if needed. Patients were excluded if they were taking any drugs or had underlying diseases (cardiac disease, renal disease, asthma, failure to thrive, cystic fibrosis).

2.3. Interventions

Both the probiotic and the placebo were provided in capsule form. The capsules contained either LGG with a concentration of 1×10^{10} cfu/ml bacteria or a placebo. The placebo was inulin, which also was present in the LGG capsules. All of the randomized patients took one capsule of the probiotic or one capsule of the placebo twice per day for a period of four weeks. The two types of capsules were the same size and the same color, and they tasted the same.

2.4. Outcomes

As a part of the primary evaluations, dietetic histories, including assessment of fiber intake, were taken. No changes in dietetic habits were allowed during the study period. The same physician recorded the pre-trial and post-trial measures, initially and weekly thereafter for one month. The evaluated measures included the severity of pain, functional changes (disruption of social activities, need to see a doctor, use of medications, days of absence from school), and variables that could induce abdominal pain (e.g., gastroenteritis, abdominal pathologies, and life

events). A five-point Likert scale was used for to specify the severity of the pain (0 = very mild, 1= mild, 2 = moderate, 3 = severe, 4 = very severe), and a three-point Likert scale was used for functional changes (1= decrease, 2 = no change, 3 = increase). Changes of the functional scale, stool patterns from baseline to the end of the treatment period, and associated problems (headaches, limb pains, and sleep problems) were considered as secondary outcomes.

2.5. Sample size

Twenty-six patients were included in each group (probiotic and placebo groups) based on the calculation of sample size with $\alpha = 0.5$, $\beta = 0.19$ and an estimated standard deviation of 1.0 within the groups.

2.6. Randomization

Patients were assigned randomly to one of two groups (probiotic and placebo groups). Randomization was done with a computer-generated list using a permuted block design.

2.7. Blinding

Investigators and patients alike were blinded to the type of treatment.

2.8. Statistical methods

SPSS version 11.5 (SPSS Inc., Chicago, Illinois, USA) was used to analyze the data. The results for the two groups were compared using the independent sample t-test for age, Fisher's exact test for gender, and the Mann-Whitney U test for the type of IBS. Changes in abdominal pain and functional scale before and after treatment were compared by the Wilcoxon rank-sum test. P values less than 0.05 were considered to be statistically significant.

2.9. Research ethics

The protocol for this study was approved by the Ethics Committee of Mashhad University. Patients could withdraw from the treatment at any time for any reason, including treatment intolerance, experience of any side effect, or personal preference. Informed consent was obtained from the patients and their parents.

3. Results

Initially, 60 patients were assigned randomly to one of the two groups (probiotics and placebo groups). Five patients were excluded due to lack of follow up in placebo and probiotic groups. Three patients were excluded because other problems cause them to take antibiotics during the study. There was no complication leading to drug discontinuation. Thus, 52 children were evaluated in this trial. The mean age of patients was 7.1 ± 0.3 years. Forty-eight percent of patients were females, and 52% were males. The most common type of IBS was alternating between constipation and diarrhea. There were no significant differences in age, gender, or the type of IBS between the two groups. The main characteristics of two groups are summarized in Table 1.

Table 1. Main characteristics of the two groups (probiotic and placebo groups)

Variables		Groups		P-value
		Placebo	Probiotic	
Age (Mean \pm SD)		7.3 \pm 0.5	6.8 \pm 0.4	
Gender (Female/Male)		13/13	12/14	
Type of IBS	Mostly diarrhea	4	5	0.4 (T-student test)
	Mostly constipation	6	6	0.3 (Fisher's exact test)
	Alternative constipation and diarrhea	16	15	0.8 (Mann-Whitney U test)

Although no significant difference was obtained regarding the baseline pain severity scales between the two groups, a statistically significant difference was observed from one week after the treatment. The functional scale was improved significantly after two weeks of treatment in the probiotic group. Stool consistency was not significantly different between the two groups (Table 2). There was no significant change in associated problems (headache, limb pain, and sleep problems) between the two groups during the study ($P > 0.1$). The LGG was well tolerated, and no adverse effects were reported.

Table 2. Outcome measures at baseline, one, two, three, and four weeks after the initiation of treatment in the two groups (placebo and probiotic)

Outcome measures		Pain Severity Scale	Functional Scale	Defecation rate/week (Mean)	Stool consistency			
					Firm with groove (%)	Firm (%)	Pasty (%)	Loose (%)
Probiotic	Pre T*	2.5±0.9	-	2.3±0.1	35.7	57.1	0	7.1
	1 week after T*	1.5±1.0	2.0±0.5	2.4±0.1	0	83	0	16.6
	2 weeks after T*	1.2±1.1	2.3±0.6	2.3±0.6	14.2	57.1	14.2	14.2
	3 weeks after T*	1.0±0.9	2.4±0.5	2.5±0.1	14.2	87.5	0	0
	4 weeks after T*	0.8±0.9	2.4±0.5	2.5±0.1	8.3	75	0	16.6
Placebo	Pre T*	2.7±0.8	-	3.1±0.5	23.0	57.9	19.2	0
	1 week after T*	1.8±0.6	1.9±0.3	3.1±0.1	0	64	36	0
	2 weeks after T*	1.9±0.8	2.0±0.5	2.8±0.1	7.6	50	38.4	3.8
	3 weeks after T*	1.8±0.6	2.0±0.4	3.1±0.1	7.6	50	42.3	0
	4 weeks after T*	1.5±0.8	1.9±0.4	2.8±0.1	7.6	53.8	38.4	0
P-value**	Pre T*	0.4	-	0.01	0.8			
	1 week after T*	0.01	0.1	0.00	0.4			
	2 weeks after T*	0.00	0.00	0.01	0.8			
	3 weeks after T*	0.00	0.00	0.01	0.6			
	4 weeks after T*	0.00	0.00	0.1	0.3			

*T: Treatment; **Wilcoxon rank-sum test

4. Discussion

Despite various risk factors suggested for IBS, such as psychosocial factors, altered GI motility, malfermentation of food residues, and alterations of the intestinal microflora, the exact etiology of IBS is not clear. In an earlier study, high homogeneity of the fecal flora with a decrease in lactobacilli, coliforms, and bifidobacteria was reported for IBS patients compared with healthy controls (11). Administering probiotics to IBS patients is beneficial in raising the group of advantageous bacteria in the digestive system, diminishing bacterial overgrowth in the small bowel, and improving the balance between the pro- and anti-inflammatory cytokines. Strengthening of the intestinal mucosal barrier and regulating the motility of the GI tract and visceral sensitivity also have been proposed as beneficial effects of probiotics. Also, it has been reported that several lactobacilli strains are influential in attacks of intestinal pain through the induction of the expression of μ -opioid and cannabinoid receptors in the intestinal epithelial cells (8).

Controversial results have been obtained by different studies that have evaluated the efficacy of probiotics for reducing the symptoms of IBS. Regardless of the differences in their probiotic regimens, some studies have shown that the probiotics had significant effects in reducing the abdominal distention, flatulence, and the hypersensitivity to distension in IBS patients, but there were no significant improvements in any of the other symptoms (12-14). One study concluded that probiotics provided no significant efficacy in improving the symptoms of IBS that were evaluated (15). Some other studies only have shown noteworthy reductions in the frequency of pain attacks, but there was no reduction in the severity of the pain (9) or in the composite score of all of the symptoms, i.e., abdominal pain, flatulence, distension, and borborygmi (16). The results of our study indicated that, in the group that received the probiotic, there was a significant reduction in the severity of the pain as well as a decrease in the number of pain attacks. The conflicting results of the various studies may be attributable to the investigation of different species of probiotics, the dosages used, the duration of the treatment, and differences in the assessments of the outcomes. To assess the most appropriate dosage of the probiotic *Bifidobacterium infantis* (*B. infantis*), Whorwell et al. compared the efficacy of different dosages, i.e., 1×10^6 , 1×10^8 , and 1×10^{10} cfu/mL, in improving the symptoms of IBS patients after four weeks. The results of their study indicated that, among the three dosages tested, the dosage of 1×10^8 cfu/mL of *B. infantis* was the most effective in managing abdominal pain, bloating, bowel impairment, straining, incomplete evacuation, and flatulence among IBS patients (17).

In our study, the LGG dosage of 1×10^{10} cfu/ml resulted in a significant reduction in the severity of the patients' pain severity and a reduction in the number of pain attacks in children with IBS. However, in another study that used the same dosage of LGG that we used, it was concluded that there was no significant reduction in the symptoms of IBS

in the children (5). However, another study that used an LGG dosage of 3×10^9 cfu/ml reported results similar to ours regarding the significant reduction of the number of pain attacks (9). It is interesting to note that the concentration of the probiotic used in their study was only 30% of the concentration that we used, but the results were the same. When the efficacy of a mixture of probiotics was evaluated, i.e., LGG, *Lactobacillus rhamnosus* LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii* JS with the total amount of bacteria in the range of $8-9 \times 10^9$ cfu/ml with an equal amount of each strain, a significant improvement of the total symptom score was observed (16). Based on our review of the literature, probiotics have been used to treat IBS patients for periods of time that ranged from one week to six months. Most of the studies in which there was agreement about the effectiveness of probiotics for patients with IBS indicated that the beneficial effects were evident after four weeks of treatment, especially in reducing abdominal distention (5, 9, 13, 16). In our study, the pain severity score was the first outcome measure to show improvement, and it occurred after just one week of treatment. Subsequently, we observed improvements in the functional score after two weeks and a reduction in the number of pain attacks after four weeks. Most of the previous studies have indicated that there were no complications associated with the administration of the probiotics, and our findings were in agreement with those studies. Considering the high prevalence of IBS and the safety of this treatment strategy, even a slight improvement in the symptoms could be significant (16-20).

There were some limitations in this study. First, the probiotic was administered for only four weeks, and patients were assessed only during this period. Thus, we were unable to determine whether there might have been significantly different results by the prolonged use of the probiotic by the patients accompanied by a prolonged follow-up period. Also, potential rare side effects could have gone undetected in this clinical trial because of the small number of patients. To obtain a more comprehensive evaluation of the effects of probiotics on IBS, we suggest long-term treatment and long-term follow up with larger groups of patients.

5. Conclusions

The results of this study supported the therapeutic effects of LGG for IBS patients. The indications were that the administration of LGG decreased the pain severity score and improved the patients' functional scores. We suggest further studies to determine the most effective species, the most appropriate doses, and to clarify whether a combination of probiotics would be better than using a single species.

Acknowledgments:

We thank the staff of the Clinical Research Development Center at Ghaem Hospital for their assistance in this completing this study and preparing the manuscript. This study, which was based on the research conducted for a medical student's thesis, was supported by a grant from the Vice Chancellor for Research at the Mashhad University of Medical Sciences; the approval number was 2661.

Trial registration:

The trial is registered at the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with IRCT registration number: IRCT201205219825N1.

Funding:

All phases of this study were supported by Mashhad University of Medical Sciences, Iran.

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References

- 1) Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointest Liver Dis.* 2006; 15(3): 237-41. PMID: 17013448
- 2) Ersryd A, Posserud I, Abrahamsson H, Simren M. Subtyping the irritable bowel syndrome by predominant bowel habit: Rome II versus Rome III. *Aliment Pharmacol Ther.* 2007; 26(6): 953-61. doi: 10.1111/j.1365-2036.2007.03422.x. PMID: 17767480

- 3) Singh P, Staller K, Barshop K, Dai E, Newman J, Yoon S, et al. Patients with irritable bowel syndrome-diarrhea have lower disease-specific quality of life than irritable bowel syndrome-constipation. *World J Gastroenterol.* 2015; 21(26): 8103-9. doi: 10.3748/wjg.v21.i26.8103. PMID: 26185382, PMCID: PMC4499353
- 4) Iovino P, Tremolattera F, Boccia G, Miele E, Ruju FM, Staiano A. Irritable bowel syndrome in childhood: visceral hypersensitivity and psychosocial aspects. *Neurogastroenterol Motil.* 2009; 21(9): 940-e74. doi: 10.1111/j.1365-2982.2009.01303.x. PMID: 19368655
- 5) Khalesi M. How probiotic reduce symptoms of irritable bowel syndrome?. *International Journal of Pediatrics.* 2014; 2(2.1): 29.
- 6) Jafari SA, Ahanchian H, Kiani MA, Khakshour A, Noorbakhsh Z, Zamani E, et al. Synbiotic for prevention of antibiotic-associated diarrhea in children: a randomized clinical trial. *International Journal of Pediatrics.* 2014; 2(1): 55-62.
- 7) Enck P, Junne F, Klosterhalfen S, Zipfel S, Martens U. Therapy options in irritable bowel syndrome. *Eur J Gastroenterol Hepatol.* 2010; 22(12): 1402-11. doi: 10.1097/MEG.0b013e3283405a17. PMID: 21389791
- 8) Dai C, Zheng CQ, Jiang M, Ma XY, Jiang LJ. Probiotics and irritable bowel syndrome. *World J Gastroenterol.* 2013; 19(36): 5973-80. doi: 10.3748/wjg.v19.i36.5973. PMID: 24106397, PMCID: PMC3785618
- 9) Gawronska A, Dziechciarz P, Horvath A, Szajewska H. A randomized double-blind placebo-controlled trial of Lactobacillus GG for abdominal pain disorders in children. *Aliment Pharmacol Ther.* 2007; 25(2): 177-84. doi: 10.1111/j.1365-2036.2006.03175.x. PMID: 17229242
- 10) Lazaraki G, Chatzimavroudis G, Katsinelos P. Recent advances in pharmacological treatment of irritable bowel syndrome. *World J Gastroenterol.* 2014; 20(27): 8867-85. doi: 10.3748/wjg.v20.i27.8867. PMID: 25083060, PMCID: PMC4112893
- 11) Guandalini S, Magazzu G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. *JPGN.* 2010; 51(1): 24-30. doi: 10.1097/MPG.0b013e3181ca4d95. PMID: 20453678
- 12) Martens U, Enck P, Zieseniss E. Probiotic treatment of irritable bowel syndrome in children. *Ger Med Sci.* 2010; 8: Doc07. doi: 10.3205/000096. PMID: 20234804, PMCID: PMC2839254
- 13) Kim HJ, Camilleri M, McKinzie S, Lempke MB, Burton DD, Thomforde GM, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* 2003; 17(7): 895-904. PMID: 12656692
- 14) Bucci C, Tremolattera F, Gallotta S, Fortunato A, Cappello C, Ciacci C, et al. A pilot study on the effect of a symbiotic mixture in irritable bowel syndrome: an open-label, partially controlled, 6-month extension of a previously published trial. *Tech Coloproctol.* 2013; 18(4): 345-53. doi: 10.1007/s10151-013-1055-2. PMID: 23922211
- 15) Dai C, Guandalini S, Zhao DH, Jiang M. Antinociceptive effect of VSL#3 on visceral hypersensitivity in a rat model of irritable bowel syndrome: a possible action through nitric oxide pathway and enhance barrier function. *Mol Cell Biochem.* 2012; 362(1-2): 43-53. doi: 10.1007/s11010-011-1126-5. PMID: 22020749
- 16) Niv E, Naftali T, Hallak R, Vaisman N. The efficacy of Lactobacillus reuteri ATCC 55730 in the treatment of patients with irritable bowel syndrome--a double blind, placebo-controlled, randomized study. *Clin Nutr.* 2005; 24(6): 925-31. doi: 10.1016/j.clnu.2005.06.001. PMID: 16051399
- 17) Kajander K, Hatakka K, Poussa T, Farkkila M, Korpela R. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther.* 2005; 22(5): 387-94. doi: 10.1111/j.1365-2036.2005.02579.x. PMID: 16128676
- 18) Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. *Am J Gastroenterol.* 2006; 101(7): 1581-90. doi: 10.1111/j.1572-0241.2006.00734.x. PMID: 16863564
- 19) Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: Lactobacillus rhamnosus GG for abdominal pain-related functional gastrointestinal disorders in childhood. *Aliment Pharmacol Ther.* 2011; 33(12): 1302-10. doi: 10.1111/j.1365-2036.2011.04665.x. PMID: 21507030.
- 20) Madden JA, Hunter JO. A review of the role of the gut microflora in irritable bowel syndrome and the effects of probiotics. *Br J Nutr.* 2002; 88 Suppl 1: S67-72. doi: 10.1079/BJN2002631. PMID: 12215182