



# Investigation of the efficacy of synbiotics in the treatment of functional constipation in children: A randomized double-blind placebo-controlled study

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## ABSTRACT

**Background/Aims:** The aim of this study was to demonstrate the efficacy of synbiotic (*Lactobacillus casei*, *L. rhamnosus*, *L. plantarum*, and *Bifidobacterium lactis* and prebiotics [fiber, polydextrose, fructo-oligosaccharides, and galacto-oligosaccharides]) treatment in children with functional constipation.

**Materials and Methods:** This study was performed in patients aged 4-18 years, and the patients were diagnosed to have functional constipation according to the Roma III diagnostic criteria. In this prospective study, the first group received synbiotic and the second group received a placebo. At the end of 4 weeks, patients were questioned about the initial symptoms. Patients who showed improvement in the initial symptoms at the end of the 4-week treatment period were considered to completely benefit from the treatment and those with some improvement in initial symptom were considered to partially benefit from the treatment.

**Results:** The synbiotic and placebo groups comprised 72 and 74 patients, respectively. The mean age in the whole study group was  $9.18 \pm 3.48$  years with a male:female ratio of 1:21. After 4 weeks of treatment, significant improvement was not observed in any of the findings in the placebo group. Conversely, a significant improvement was observed in the weekly number of defecations, abdominal pain, painful defecation, and pediatric Bristol scale ( $p \leq 0.001$ ) in the synbiotic group. Complete benefit from the treatment was achieved in 48 (66.7%) and 21 (28.3%) patients in the synbiotic and placebo groups, respectively, and a significant difference was observed between the groups ( $p \leq 0.001$ ).

**Conclusion:** Our studies have shown that the use of synbiotics in the treatment of functional constipation in children is beneficial.

**Keywords:** Child, functional constipation, synbiotic

## INTRODUCTION

Constipation is one of the most commonly observed gastrointestinal diseases during childhood, and its incidence in the pediatric population has been reported to be approximately 1%-8%. Constipation is the main complaint that causes presentation to outpatient clinics in 3%-5% and 25% cases in general pediatric and pediatric gastroenterology clinics, respectively (1). Currently, the diagnosis of functional constipation is performed using Roma III diagnostic criteria (2). Standard treatment of constipation during childhood is educating the family and child, organizing nutrition and toilet habits in addition to administering laxatives for the regulation of bowel movements (3). The term prebiotics is used to

define foods that are indigestible but fermentable and that support the growth and development of microorganisms that reside in the bowel and are beneficial to the host. Their fermentation by colonic microflora causes bloating and abdominal pain, and their efficacy is decreased with long-term use due to changes in the microflora. Its use is preferred by physicians because of its safety in children despite the abovementioned side effects (4,5). Currently, probiotics, defined as live microorganisms beneficial to human health when taken in recommended adequate amounts, have been increasingly used in gastrointestinal diseases, particularly in the treatment of constipation (6-8). Probiotics have been demonstrated to be effective in many studies,

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particularly in the treatment of constipation in adults (9). Studies with probiotics, for example, with *Bifidobacterium infantis*, have demonstrated to increase the number of defecations and soften stool. However, knowledge on the efficacy and safety of probiotics in children when used in the treatment of childhood constipation is limited, and the studies performed have reached controversial results (9). The aim of this study was to demonstrate the efficacy of 4-week synbiotic [*Lactobacillus casei*, *L. rhamnosus*, *L. plantarum*, and *B. lactis* and prebiotics (fiber, polydextrose, fructo-oligosaccharides, and galacto-oligosaccharides)] treatment in children with functional constipation.

## MATERIALS AND METHODS

This study was performed at the outpatient clinics of pediatric gastroenterology of the University of Akdeniz between December 2015 and May 2016 on patients aged between 4 and 18 years and who had functional constipation. The diagnosis of functional constipation was performed according to the Roma III diagnostic criteria (2). Prior to the study, approval from the local ethics board and informed written and verbal consents from the families were obtained.

### Inclusion Criteria

- > Pediatric patients aged between 4 and 18 years.
- > Patients diagnosed with functional constipation according to the Roma III diagnostic criteria (2).
  - o individuals with weekly number of defecation < 3 and
  - o individuals with at least one of the symptoms stated below:
    - weekly encopresis > 1
    - painful defecation
    - individuals who defecate thick and big amounts of stools and those who defecate in large amounts that obstruct the toilet
    - individuals with the behavior of stopping defecation during defecation
    - individuals who were found to have hard stool during abdominal or rectal examination
- > Children who were diagnosed to have functional constipation according to Rome III criteria in the last 2 months.

### Exclusion Criteria

- Pediatric patients younger than 4 years
- Individuals with one of the following:
  - metabolic and gastrointestinal diseases (such as hypothyroidism and celiac disease)
  - neuropathic diseases (such as spinal cord abnormalities and cerebral palsy)
  - intestinal nervous and muscle diseases (such as Hirschsprung disease, intestinal neuronal dysplasia, intestinal pseudo-obstruction, visceral myopathies, and visceral neuropathy)
  - abnormal abdominal muscle morphology (such as prune belly syndrome, gastroschisis, and Down syndrome)
  - connective tissue disorders (such as scleroderma, systemic lupus erythematosus, Ehlers-Danlos syndrome)

- chronic drug use (such as opioids, phenobarbital, sucralfate, antacids, antihypertensives, anticholinergics, antidepressants, and sympathomimetics)
- Conditions such as heavy-metal poisoning (lead), vitamin D poisoning, botulism, and intolerance to cow's milk protein
- Individuals with constipation due to any of the following organic causes and those who used antibiotics for a period close to enrollment, any drug treatment for constipation prior to enrollment, use of drugs affecting gastrointestinal motility, and children fitting criteria for irritable bowel syndrome (IBS) were excluded from this study.

### Randomization

Patients who were diagnosed with functional constipation at the pediatric gastroenterology outpatient clinic were directed to the pediatric gastroenterology nurse, and drug boxes that were labeled with code numbers only and whose package ingredients were unknown were randomly administered to patients and randomization was ensured.

### Blindness of the Study

Two different types of treatments were used that included synbiotic and placebo as ingredients. Drugs that were completely same in color, smell, taste, and packaging properties but had one of the two different code numbers on them were used. The ingredients of the drugs were unknown to the doctor, nurse, and the patient, and which code number included which ingredient was known to the manufacturer only.

### Study Design

The study was performed prospectively, and synbiotic and placebo treatments were provided to the first and second groups, respectively. The first group received a mixture including  $4 \times 10^9$  colony-forming units of *L. casei*, *L. rhamnosus*, *L. plantarum*, *B. lactis* and prebiotics at a dose of 1996.57 mg (fiber, polydextrose, fructo-oligosaccharides, and galacto-oligosaccharides) as a sachet once a day. The second group received a sachet once a day placebo treatment which had the same properties of color, odor, taste, and packaging as the synbiotic treatment. Also, recommendations of a fibrous diet (20-25 g/d for children aged 4-8 years and 30-35 g/d for children aged 8-16 years) and toilet education were given to patients in both groups in addition to synbiotic or placebo treatment.

Fleet enema (paraffin oil 15-30 mL/y) was performed on patients who presented with complaints of progressive abdominal distention and pain while receiving synbiotic or placebo treatment.

### Evaluation of Response to Treatment

At the end of the 1<sup>st</sup> month, the patients were questioned about initial symptoms, such as weekly number of defecations, abdominal pain, painful defecation, rectal bleeding, behavior of avoiding defecation, stool incontinence (encopresis), and changes in the pediatric Bristol stool scale. Patients with improvement in

the initial symptoms stated above and who had weekly number of defecation  $\geq 3$ , softening in the stool consistency (Bristol  $\geq 4$  points), and weekly encopresis  $\leq 1$  were considered to fully benefit from the treatment. Patients who had improvement in one or more of the symptoms were considered to partially benefit from the treatment. When the data are collected, the group containing the same code number are collected in the same group. The results were compared according to the code numbers. Results were analyzed by a statistician who had no knowledge about the ingredients of any code number, and statistical significance was evaluated in the differences between the two groups. Finally, the ingredients of the code were revealed, and the terms synbiotic and placebo were written in the corresponding areas on the tables and figures.

### Follow-Up

Patients who had benefited from the treatment were followed up for 2 months. Patients whose complaints recurred at the end of the 1<sup>st</sup> and 2<sup>nd</sup> months were accepted to have recurrent disease.

### Outcome Measures

Primary outcome measures were complete benefit by resolution of all complaints of the patient with the 4-week synbiotic treatment.

Secondary outcome measures were frequency of complaints, such as weekly number of defecations, consistency of stools, number of weekly fecal incontinence presence of abdominal pain, painful defecation, rectal bleeding and behavior of avoiding defecation, and incidence of side effects, such as vomiting and diarrhea, at the end of the 4-week treatment.

### Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc.; Chicago, IL, USA) version 15.0 package program and Microsoft Office Excel version 2010. Comparison of data was performed using Mann-Whitney U test, chi-square test, and Fisher exact test. Numerical variables were expressed as mean $\pm$ standard deviation, and categorical variables were expressed as number and percentage in descriptive analysis of data. The level of significance was accepted as  $p < 0.05$ .

### RESULTS

A total of 163 patients were diagnosed with functional constipation in this study. Eight patients were excluded because they refused to participate in the study. The treatment method in the remaining 155 patients was randomly selected and administered double-blinded, and the synbiotic and placebo groups comprised 77 and 78 patients, respectively. However, five patients in the synbiotic group and four in the placebo group were excluded from the study because they did not complete the study. Thus, the synbiotic and placebo groups finally comprised 72 and 74 patients, respectively. The flowchart of the patients is shown in Figure 1. In this study, no differences were

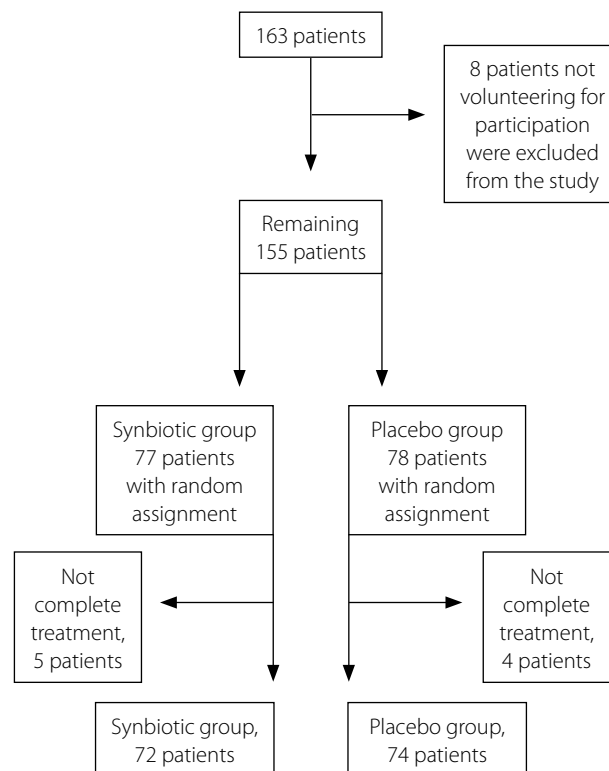


Figure 1. Patient flowchart

Table 1. Demographic properties and frequency of initial symptoms in the two groups

Parameters	Placebo	Synbiotic	p
n	74	72	
Age, years	9.06 $\pm$ 3.49	9.31 $\pm$ 3.47	0.416 <sup>1</sup>
Sex (M/F)	34/40	32/40	0.855
The number of stools per week*, n, %	71 (95.9)	60 (96.9)	0.561 <sup>2</sup>
Abdominal pain, n, %	52 (70.3)	50 (69.4)	0.913
Painful defecation, n, %	34 (45.9)	38 (52.7)	0.367
Fecal retention behavior, n, %	38 (51.4)	29 (40.3)	0.521
Rectal bleeding, n, %	16 (21.6)	14 (19.4)	0.179
The number of fecal soiling per week **, n, %	23 (31.1)	24 (33.3)	0.179
Pediatric Bristol stool scale number***, n, %	73 (98.6)	70 (97.2)	0.617 <sup>2</sup>

<sup>1</sup>Mann-Whitney U test, <sup>2</sup>Fisher's Exact Test, Chi-square test was applied to others

\*Those weekly stool count  $\leq 2$ , \*\*The number of fecal soiling per week  $\geq 2$  ones, \*\*\*Pediatric Bristol stool scale  $\leq 3$  number ones

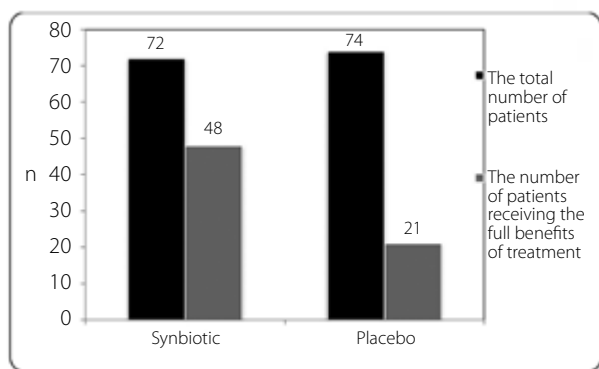
found between the groups in the findings at presentation, age, and gender distribution, and this is demonstrated in Table 1. The mean age of the whole study group was 9.18 $\pm$ 3.48 years with a male:female ratio of 1:21. The most commonly observed symptoms among the symptoms of presentation were, in descending order, stool softening or positive pediatric Bristol stool scale (Bristol points  $\leq 3$ , 97.9%) and abdominal pain (69.8%). No resolution was observed in any findings after 4 weeks of

**Table 2.** Symptoms of functional constipation before and after 4 weeks of treatment, by study group. Values are numbers of patients with each complaint

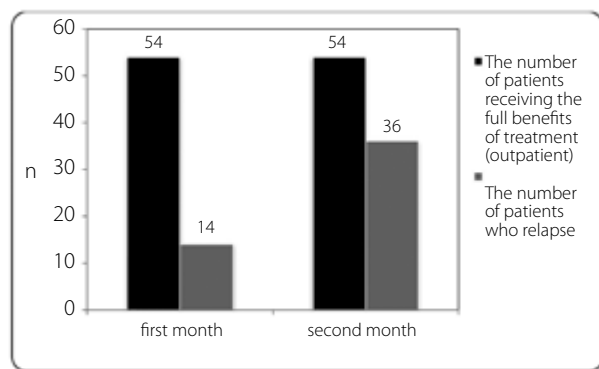
Symptoms	Placebo			Synbiotic		
	Before	After	p <sup>1</sup>	Before	After	p <sup>1</sup>
The number of stools per week*, n, %	71 (95.9)	61 (82.4)	0.583	60 (96.9)	26 (36.1)	<0.001
Abdominal pain, n, %	52 (70.3)	41 (55.4)	0.382	50 (69.4)	4 (5.5)	<0.001
Painful defecation, n, %	34 (45.9)	27 (36.4)	0.207	38 (52.7)	16 (22.2)	<0.001
Rectal bleeding, n, %	16 (21.6)	14 (18.9)	0.193	14 (19.4)	11 (15.2)	0.172
Fecal retention behavior, n, %	38 (51.4)	34 (45.9)	0.316	29 (40.3)	23 (31.9)	0.251
The number of fecal soiling per week**, n, %	23 (31.1)	19 (25.6)	0.413	24 (33.3)	17 (23.6)	0.168
Pediatric Bristol stool scale number***, n, %	73 (98.6)	64 (86.5)	0.193	70 (97.2)	11 (15.3)	<0.001

<sup>1</sup>Chi-square test

\*Those weekly stool count ≤ 2 (before), Those weekly stool count >3 (after) \*\* The number of fecal soiling per week ≥ 2 ones (before), The number of fecal soiling per week ≤ 1 ones (after) \*\*\*Pediatric Bristol stool scale ≤ 3 number ones (before), Pediatric Bristol stool scale ≥ 4 number ones (after)



**Figure 2.** Comparison of groups according to the benefits from the treatment (1. chi-square test)



**Figure 3.** Comparison of recurrence in the 1<sup>st</sup> and 2<sup>nd</sup> months following the end of treatment among fully benefited patients in the whole series (who were able to be followed up) (1. chi-square test)

treatment in the placebo group. On the other hand, weekly number of defecations, abdominal pain, painful defecation, and pediatric Bristol scale or stool softening were significantly improved ( $p \leq 0.001$ ) in the synbiotic group. However, no significant resolution was observed in weekly encopresis ( $p = 0.168$ ), behavior of avoiding defecation ( $p = 0.251$ ), and rectal bleeding ( $p = 0.172$ ) in the synbiotic group (Table 2). Complete benefit from the treatment was achieved in 48 (66.7%) and 21 (28.3%)

patients in the synbiotic and placebo groups, respectively, and a significant difference was observed between the two groups ( $p \leq 0.001$ ) (Figure 2). Follow-up of the patients after the end of the treatment in the whole series (54 of a total of 69 patients whose symptoms improved were followed up for 2 months) disclosed recurrence of symptoms in 14 (25.9%) and 36 (66.7%) patients in the 1<sup>st</sup> and 2<sup>nd</sup> months, respectively, and the recurrence rate was found to be significantly increased with increased duration of follow-up ( $p \leq 0.001$ ) (Figure 3).

Nevertheless, patients compliant with recommendations of diet and toilet education constituted 23% of all patients and 28% of patients who benefited from the study, and the efficacy in response to treatment was not assessed because it was not administered by a sufficient number of patients.

In addition, no side effects of the drugs, such as vomiting and diarrhea, were observed in any of the patients who used synbiotic or placebo.

Fleet enema was performed on five patients in the synbiotic group and four patients in placebo group due to complaints of abdominal distention and pain.

### DISCUSSION

The number of double-blinded and placebo-controlled studies on probiotics use in acute and chronic constipation (in the absence of IBS) in childhood is very few.

Coccorullo et al. (10) performed their study consecutively on 44 babies. They administered the babies *L. reuteri* (DSM1938) and placebo, and similar to our results, they found an increase in the frequency of stools, although there was no change in other symptoms of constipation. Suspensions including bifidobacteria, lactobacillus, and propionibacterium were found to be beneficial for defecation in variable degrees in other uncontrolled studies or studies performed using combined treatment with probiotics and other agents (11).

Tabbers et al. (12) performed their study on 20 patients aged between 3 and 16 years and observed that when *B. breve* was administered in a single daily dose for 4 weeks, it increased the stool frequency, softened the stool consistency, and alleviated abdominal pain which was consistent with our findings; however, contrary to our results, they found decreased fecal incontinence episodes in children with functional constipation. Tabbers et al. (13) also performed a placebo-controlled study in which they administered a mixture of fermented milk that included *B. lactis* DN-173 010 twice daily for 3 weeks to 160 children aged 3-16 years in a multicenter trial performed in Holland and Poland. They observed an increase in stool frequency in the group in which a mixture of fermented milk including *B. lactis* DN-173 010 was used. This was consistent with the finding of increased weekly number of defecation in our study.

Twenty patients aged 4-16 years were administered a mixture of *Bifidobacteria* spp. (*B. bifidum*, *B. infantis*, and *B. longum*) and *Lactobacilli* spp. (*L. casei*, *L. plantarum*, and *L. rhamnosus*) in a nonrandomized and uncontrolled study performed in children with more than one kind of probiotics mixture. Similar to our study, increased stool frequency and improved abdominal pain were observed; however, unlike our results, they did not find any change in stool consistency, and observed improvement in encopresis frequency (14).

Similar to our results, a significant improvement in the stool consistency, stool encopresis, and abdominal pain was noted in a randomized, controlled study performed using synbiotic composed of a mixture of *L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, and *B. infantis* and fructo-oligosaccharides and a mixture of liquid paraffin and placebo (15).

Saneian et al. (16) performed their study on 60 children ages 2-14 years and compared a mixture of synbiotic and mineral oil including *L. sporogenes* and mineral oil-only in a single daily dose for 2 months. Increased stool frequency was observed in both the groups at the end of the treatment, and the increase was higher in the synbiotic and mineral oil group. Hard and very hard stools, incomplete evacuation, and stool encopresis were decreased in both the groups, and this decrease was higher in the synbiotic and mineral oil groups. No side effects were observed in any of the patients. Consistent with our results, they found that the synbiotic containing *L. sporogenes* and mineral oil mixture was effective in the treatment of symptoms in constipation in children.

*L. rhamnosus* GG was used in the double-blinded and placebo-controlled study performed by Banaszkiwicz and Szajewska (17) in children with functional constipation. Weekly number of spontaneous defecation without compulsion was evaluated in those children included in that study, and no significant difference was found between the groups of placebo and probiotics. In our study, however, we observed significant increase in weekly number of defecation in the group receiving synbiotic.

The effects of *L. casei rhamnosus* Lcr35 and magnesium oxide were analyzed in a comparative study from Taiwan in children with chronic constipation. Increase in the frequency of stools, decrease in abdominal pain, and necessity of glycerin enema use were observed to be in higher rates in the probiotics group. No difference was found in the hard stools and appetite between the groups in that study with a limited number of patients (18). We found similar results in our study, with increased weekly number of defecation and reduced abdominal pain; however, unlike their study, we observed softening of stool (improvement in pediatric Bristol scale).

In this present study, no side effects such as vomiting and diarrhea were observed in any of our patients. This result is compatible with the literature finding of safe use of probiotics (19).

The results of this present study are compatible with the literature. The number of patients in the synbiotic group benefited from the treatment was observed to be significantly higher compared with the placebo group. However, at the end of the treatment, complaints were found to recur with increased duration without treatment in the whole series.

In conclusion, our studies have shown that the use of synbiotic in the treatment of functional constipation in children is beneficial. However, because of the recurrence of the disease at the end of treatment, further studies are needed for the determination of the duration of treatment of synbiotic.

**Ethics Committee Approval:** Ethics committee approval was received for this study from Akdeniz University Ethical Committee for Clinical Studies (Decision Date: 11.11.2015/Decision No: 323).

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

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - A.B., R.A.; Design - A.B., R.A., A.A.; Supervision - A.Y., R.A.; Resource - A.B., A.Y.; Materials - A.B., A.Y., A.A.; Data Collection&/or Processing - A.B., A.Y.; Analysis and/or Interpretation - A.B., R.R.A., A.A.; Literature Search - A.B., R.A.; Writing - A.B.; Critical Reviews - A.B., R.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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