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Original Article

Efficacy and immunologic effects of a synbiotic in children with functional abdominal pain

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ABSTRACT

Background: The objective of this study was to examine the efficacy of a synbiotic in addressing recurrent abdominal pain in children, including functional abdominal pain, and to assess its impact on serum levels of pro-inflammatory and anti-inflammatory cytokines.

Methods: We included 80 patients diagnosed with Functional Abdominal Pain Not Otherwise Specified according to the Rome IV criteria and divided the sample into two groups: the synbiotic group (Lactobacillus helveticus, Lactobacillus casei, Bifidobacterium lactis, chicory inulin) (Group 1) and the placebo group (Group 2). We inquired about pre-intervention and post-intervention symptoms in both groups and measured their blood cytokine levels. All statistical analyses were performed using SPSS 23 for Windows.

Results: The 80 patients with functional abdominal pain had a mean age of 11.48 ± 3.86 years. The groups were compared for the severity of symptoms before and after the intervention, and no statistical difference was found ($p>0.05$). There was no significant difference between the synbiotic group and the placebo group in terms of pre-intervention serum pro-inflammatory or anti-inflammatory cytokine levels (TNF α, IFN γ, IL-10, TGF β, IL-13), and no statistically significant difference was determined after 8 weeks of synbiotic or placebo administration ($p>0.05$). A comparison was made of pre-treatment and post-treatment cytokine levels in each group. The most significant finding was the substantial increase in IL-13 levels post-treatment in the synbiotic group ($p < 0.001$).

Conclusion: In the present study, no differences were found between the symbiotic and placebo groups with regard to functional abdominal pain symptoms or serum cytokine levels. However, a significant increase in IL-13 levels was detected after treatment in the symbiotic group. There is a need for further research on the optimal dosage and duration of synbiotic application, the type of probiotic that should be administered, and its effect on cytokine levels in functional gastrointestinal diseases.

Keywords: functional gastrointestinal diseases, synbiotics, cytokines

INTRODUCTION

Functional abdominal pain (FAP) is a common condition in children that is diagnosed after a thorough medical assessment when the symptoms cannot be attributed to any other medical condition. The pathology of functional gastrointestinal diseases (FGID) associated with abdominal pain in children is yet to be clarified.[1] The subtypes of FAP, defined by the Rome IV criteria, include conditions such as irritable bowel syndrome (IBS), functional dyspepsia (FD), abdominal migraine, and functional abdominal pain not-otherwise specified (FAPNOS), each of which requires a customized diagnostic and therapeutic strategy.[2] Previous research has reported various causes to explain the symptoms of FGIDs associated with abdominal pain, like altered gut motility, visceral hypersensitivity, abnormal gut-

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brain axis interactions, gut flora, psychosocial discomfort, and immune system activation.[3-5]

Following a study that revealed bacterial overgrowth in some patients with IBS, the idea that altered bacterial flora influences the development of IBS symptoms has gained attention.[6] Another research indicated a higher prevalence of abnormal bacterial fermentation among children with IBS or functional abdominal pain compared to healthy controls.[7]

Given the effects of gut microbiota on the maturation of the gastrointestinal epithelium, providing a mucosal barrier, visceral hypersensitivity, intestinal immune response, and gut motility, it is believed to play a key role in the pathogenesis of FGIDs. In this regard, probiotics, prebiotics, and synbiotics play a crucial role in gut microbiota and dysbiosis. There are numerous studies on the effects of probiotics, prebiotics, and synbiotics on gut microbiota and their use in gastrointestinal and non-gastrointestinal diseases.[6,8,9] Examining the studies on the effect of probiotics on FGIDs, we see that the body of research is limited and mostly focuses on adults with IBS, and there is no clear consensus on which microorganism should be administered in what dose and for how long, which suggests further research.[10-13]

The present trial aimed to observe the effects of treatments that support the microbiota on symptoms and serum pro-inflammatory and anti-inflammatory cytokine levels in patients with functional abdominal pain.

MATERIALS AND METHODS

The study population comprised patients aged 6 to 18 years who presented to the outpatient clinic for Paediatric Gastroenterology, Hepatology and Nutrition at a tertiary care centre with complaints of recurrent abdominal pain. Using the Rome IV criteria, the patients were diagnosed with FAPNOS, and patients with alarm symptoms of recurrent abdominal pain were excluded.[2]

Exclusion criteria:

1. Presence of another organic cause that could lead to abdominal pain
2. Antibiotic use in the last two months
3. Having another chronic disease involving other systems, including the gastrointestinal tract

The study was designed as a randomized, double-blind, placebo-controlled trial. Informed consent was obtained from study participants and their families. Synbiotic or placebo products, in exactly the same shape and size, and coded by the manufacturer, were randomly distributed to the patients by the head nurse, who was also blinded to the products' contents. The patients received either a synbiotic-containing capsule or a placebo orally once a day for 8 weeks. At the end of eight weeks, we checked the product codes and formed two groups: Group 1, the synbiotic group (n=39), and Group 2, the placebo group (n=41).

Each capsule of the synbiotic product was a Mamsel Maflor® plus capsule containing *Lactobacillus helveticus (L.helveticus), Lactobacillus casei (L.casei), Bifidobacterium lactis (B.lactis), chicory inulin* 100 mg: in total 7x 10^9 CFU of active probiotics. The placebo capsules had no active ingredient, with the same package and form as provided by the manufacturer.

We contacted the patients in both groups by phone weekly to discuss the continuity of their treatment, their clinical status, and any symptoms they were experiencing. We asked the patients to show the location of the abdominal pain, and these locations were recorded. We also asked the patients to keep records regarding their pain each week of treatment for 8 weeks. These records included pain frequency (more than twice a week, twice a week, once a week, or no pain), pain severity (0 = absent, 1=mild, 2=moderate, 3=severe), school absenteeism due to pain, the number of days of absence, and limitations in daily activities due to pain. Pre-treatment data were obtained from records kept for one month before admission, including pain frequency (weekly), pain severity (0=absent, 1=mild, 2=moderate, 3=severe), school absenteeism due to pain, number of days of absence, and limitations in daily activities due to pain. At the end of the eighth week, the patients were examined again in the pediatric gastroenterology outpatient clinic, and they were asked to evaluate the success of the treatment with a score from 1 to 100, and these scores were recorded with the joint decision of the parents.

We took blood samples to measure serum levels of pro-inflammatory cytokines (TNF-α, IFN-γ) and anti-inflammatory cytokines (IL-10, TGF β, IL-13) at the beginning and end of the study. TNF α, IFN γ, IL-10, TGF β, and IL-13 plasma levels were measured in the Immunology Laboratory of our faculty; TNF α, IFN γ, IL-10, TGF β levels were measured using a *Boster Human ELISA* kit, and IL-13

levels using a *Bioscience Human ELISA* kit, all separately and according to the manufacturer's instructions. Optical density values were measured at *450 nm* wavelength, *620 nm* reference wavelength, using an *ELISA microplate* reader *(Sunrise Remote/ Touch Screen, Tecan, Austria)*. We created linear correlations with the results and the standard concentration values, and evaluated the results with separate calibration curves for each cytokine.

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki of 1975. Approval number was 2014-16/6.

Statistical analysis

We investigated the correlations between the variables using the SPSS 23 statistics software for Windows. We examined the differences between the frequencies of categorical variables using the Chi-square test. We tested the data for normal distribution using the Shapiro-Wilk test. For continuous variables, the differences between the two groups were evaluated using Student's t-test. Differences between the two groups were evaluated using Student's t-test for continuous variables and the Mann-Whitney U test for data that did not fit a normal distribution. G*Power 3.1 statistical program was used for power analysis. The analysis of continuous variables was conducted employing the Wilcoxon signed-rank test for paired data. For all analyses, the significance level was set at $p<0.05$.

RESULTS

Eighty patients with functional abdominal pain were included in the study. The patients had a mean age of 11.48±3.86 years, and 57.5% (n=46) of the patients were female and 42.5% (n=34) were male. The most common localization of abdominal pain was periumbilical, occurring in 78.8% of cases (n=63). We also analyzed factors that affect patients' daily lives, including pain frequency, pain severity, absenteeism from school, the number of days of absence, and limitations in daily activities. Pain frequency was more than twice a week in 61.2% (n=49) of patients, twice a week in 17.5% (n=14) of patients, and once a week in 21.2% (n=17) of patients. Pain severity was moderate for 65% (n=52) of the patients, mild for 20% (n=16), and severe for 15% (n=12).

Thirty-nine (48.8%) of the patients were in the synbiotic group (Group 1) and 41 (51.2%) in the placebo group (Group 2). We found no difference between the groups in terms of the distribution of sex, age, or weight-for-height z-scores, and pain location did not differ significantly between the groups (p>0.05) (Table 1). Considering the factors affecting daily life before treatment, such as pain frequency, pain severity, absenteeism from school, the number of days of absence, and limitations in daily activities, we observed no significant difference between the groups ($p > 0.05$) (Table 2). Pre-treatment IL-13, IL-10, IFN-γ, TGF-β, and TNF-α serum levels again did not differ significantly between the groups (p>0.05) (Table 2).

After 8 weeks of treatment, complete recovery (100%) was achieved in 64.1% (n=25) of patients in Group 1 and 43.9% (n=18) of patients in Group 2, with no statistically significant difference (p>0.05). The reduction in complaints was higher in Group 1 compared to Group 2, with a borderline statistically significant difference (p=0.05) (Table 3). Unresponsiveness to treatment was observed in 12.5% (n=5) of patients in Group 1 and 13.8% (n=8) in Group 2, though without a statistically significant difference (p>0.05) (Table 3).

Considering the factors affecting daily life after treatment, such as pain frequency, pain severity, absenteeism from school, the number of days of absence, and limitations in daily activities, we observed no significant difference between the groups ($p > 0.05$) (Table 4). Finally, there was no significant difference between the groups in terms of post-treatment IL-13, IL-10, IFN-γ, TGF-β, and TNF-α serum levels (p>0.05) (Table 4). A comparison was made of pre-treatment and post-treatment cytokine levels in each group (Table 5). The most significant finding was the substantial increase in IL-13 levels post-treatment in Group 1 ($p < 0.001$). Although IFN γ levels decreased after treatment in both Group 1 and Group 2, this decrease was much more pronounced in Group 1 than in Group 2, respectively, (p<0.001),(p=0.010).

Table 1. Sex, age, weight, height, characteristics and location of abdominal pain of the groups

	Group 1 (n=39)	Group 2 (n=41)	p
Female*	53.8 (21)	61 (25)	0.519#
Age (years)	11.90±3.92	11.09±3.80	0.352€
Weight Z score	0.11±1.20	-0.13±0.96	0.301€
Hight Z score	-0.34±1.44	-0.17±1.21	0.593€
Location of abdominal pain*			
Periumlical	74.4 (29)	82.9 (34)	0.595#
Epigastric	20.5 (8)	12.2 (5)	
Hypogastric	5.1 (2)	4.9 (2)	

*% (n)
#ki-kare test, €student-t test

Table 2. Characteristics of pre-treatment abdominal pain and serum cytokine levels by groups			
Before treatment	**Group 1, n=39**	**Group 2, n=41**	**p**
Pain frequency*			
Once a week	12.8 (5)	29.3 (12)	0.127#
Twice a week	15.4 (6)	19.5 (8)	
More than twice a week	71.8 (28)	51.2 (21)	
Intensity of pain*			
Mild	15.4 (6)	24.4 (10)	0.226#
Moderate	74.3 (29)	56.1 (23)	
Severe	10.3 (4)	19.5 (8)	
School absenteeism*	30.8 (12)	41.5 (17)	0.320#
Days of absence from school in the last 1 month	0 (0-1)	0 (0-1)	0.505±
Restriction in daily activity*	71.8 (28)	75.6 (31)	0.698#
Cytokine levels (pg/ml)			
IL-13	0.42 (0.31-0.96)	0.61 (0.36-1.23)	0.179±
IL-10	5.4 (4.7-7.7)	6.1 (5.3-8.7)	0.112±
IFN-γ	0.9 (0.1-2.8)	0.3 (0.1-2.3)	0.542±
TGF-β	648 (584-738)	651 (586-738)	0.900±
TNF-α	0.1 (0.1-2.3)	0.1 (0.1-0.15)	0.360±

The data are presented as median (25%-75%)
*% (n) # ki-kare test ±Mann-Whitney U test

Table 3. Comparison of treatment results by groups			
Treatment response	**Group 1, n=39**	**Group 2, n=41**	**p**
Complete improvement in symptoms*	64.1 (25)	43.9 (18)	0.070#
Rate of reduction in symptoms (%)	100 (70-100)	80 (40-100)	0.054±
Non-response to treatment*	12.8 (5)	19.5 (8)	0.417#

The data are presented as median (25%-75%)
*% (n) # ki-kare test ±Mann-Whitney U test

DISCUSSION

This prospective, randomized, double-blind, placebo-controlled trial investigated the clinical and immunological effects of a synbiotic (*Lactobacillus helveticus, Lactobacillus casei, Bifidobacterium lactis, and chicory inulin)* in patients with functional abdominal pain. Considering the microbiota and their effects on gastrointestinal immunity, probiotics and synbiotics are still being investigated for the treatment of various gastrointestinal diseases.[14] In our trial, we observed similarities between the study group and placebo group in terms of age, sex, anthropometric measurements, cytokine levels at admission, and complaints.

There are a handful of randomized, double-blind, placebo-controlled trials examining the effects of probiotics and synbiotics on the symptoms of children with functional gastrointestinal diseases. When the Rome IV criteria are applied to children diagnosed with recurrent abdominal pain, IBS constitutes the most common diagnosis, with a rate of up to 45%.[15] The majority of research on probiotics and synbiotics has been focused on IBS, with a paucity of studies conducted on functional abdominal pain. A meta-analysis was conducted in order to evaluate the efficacy of probiotics in treating IBS in children. The analysis revealed that probiotics, particularly mixtures of *L. rhamnosus GG*, *VSL#3,* and three *bifidobacteria* strains, were associated with improvement in abdominal pain seen in IBS.[16]

In their recent position statement on the utilisation of probiotics for the treatment of paediatric gastrointestinal disorders, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, 2023) includes a weak recommendation for *L. rhamnosus*

Table 4. Characteristics of post-treatment abdominal pain and serum cytokine levels by groups			
After treatment	**Group 1, n=39**	**Group 2, n=41**	**p**
Pain frequency*			
No pain	68.4 (26)	55 (22)	0.246#
Once a week	15.8 (6)	12.5 (5)	
Twice a week	7.9 (4)	7.5 (4)	
More than twice a week	7.9 (3)	25 (10)	
Intensity of pain*			
No pain	68.4 (26)	55 (22)	0.538#
Mild	10.5 (4)	10 (4)	
Moderate	15.8 (7)	22.5 (10)	
Severe	5.3 (2)	12.5 (5)	
School absenteeism*	8.1 (3)	12.5 (5)	0.528#
Days of absence from school in the last 1 month	0 (0-0)	0 (0-0)	0.276±
Restriction in daily activity*	13.2 (5)	22.5 (9)	0.283#
Cytokine levels (pg/ml)			
IL-13	0.77 (0.43-1.62)	0.7 (0.27-1.33)	0.519±
IL-10	5.1 (4.2-6.2)	5 (4.5-6.3)	0.363±
IFN-γ	0.2 (0.1-0.7)	0.2 (0.1-1.3)	0.700±
TGF-β	949 (863-1058)	894 (807-1014.5)	0.164±
TNF-α	0.1 (0.1-3.9)	0.1 (0.1-5.8)	0.755±

The data are presented as median (25%-75%)
*% (n) # ki-kare test ±Mann-Whitney U test

Table 5. Comparison of cytokine levels of the groups before and after treatment				
		Before treatment	**After treatment**	**p***
Group 1	IL-13	0.42 (0.31-0.96)	0.77 (0.43-1.62)	<0.001
	IL-10	5.4 (4.7-7.7)	5.1 (4.2-6.2)	<0.001
	IFN-γ	0.9 (0.1-2.8)	0.2 (0.1-0.7)	<0.001
	TGF-β	648 (584-738)	949 (863-1058)	<0.001
	TNF-α	0.1 (0.1-2.3)	0.1 (0.1-3.9)	0.527
Group 2	IL-13	0.61 (0.36-1.23)	0.7 (0.27-1.33)	0.246
	IL-10	6.1 (5.3-8.7)	5 (4.5-6.3)	<0.001
	IFN-γ	0.3 (0.1-2.3)	0.2 (0.1-1.3)	0.010
	TGF-β	651 (586-738)	894 (807-1014.5)	<0.001
	TNF-α	0.1 (0.1-0.15)	0.1 (0.1-5.8)	0.103

The data are presented as median (25%-75%)
*Wilcoxon Signed Ranks test

GG (1-3 × 10^9 CFU twice daily) to reduce pain in children diagnosed with IBS.[17] A study of 29 paediatric patients with FD treated with *L. reuteri* found a significant reduction in pain.[18] In one randomized, double-blind, placebo-controlled trial in Turkey, children with functional constipation were given a synbiotic containing *L. casei*, *L. rhamnosus*, *L. plantarum*, and *B. lactis*, inulin, and a significant improvement was found in the synbiotic group in terms of abdominal pain, painful defecation, and defecation frequency.[19] A study of 101 children with chronic abdominal pain found that treatment with *L. reuteri DSM 17938* reduced pain days and intensity.[20] However, a contradictory study has been conducted on the efficacy of probiotics in functional abdominal pain. Eftekhari et al.[21] conducted a randomized,

double-blind, placebo-controlled trial on 80 children aged 4-16 years with functional abdominal pain, and by dividing them into two groups, they gave them *L. reuteri* and a placebo for 4 weeks. In contrast to the positive effects of probiotics reported in the preceding studies, this study found that there was no significant difference in complaints between the probiotics and placebo groups at weeks 4.[21] In the present study, no significant difference was observed in functional abdominal pain symptoms between the synbiotic group, which received a treatment containing *L. helveticus, L. casei, B. lactis, chicory inulin,* and the placebo group. This finding indicates that distinct probiotic strains may exert varied effects on functional abdominal pain, and that the dosage and duration of treatment with probiotic or synbiotic preparations may also result in different outcomes. Furthermore, the pathophysiology of different subgroups of functional abdominal pain disorders has not yet been fully elucidated, so the potential for different responses to different treatments with different treatment durations remains unclear.

Numerous studies have shown mucosal inflammation and elevated pro-inflammatory cytokine levels in functional gastrointestinal disorders, mostly in IBS.[22-25] There is limited research that compares intestinal mucosal damage, microbiota changes, and serum levels of pro-inflammatory cytokines in childhood. Zambruni et al.[26] found impaired gut microbiota and elevated serum levels of pro-inflammatory cytokines in children with growth retardation. One trial from China compared fecal flora and serum cytokine levels among infants with and without bronchopulmonary dysplasia (BPD). The authors highlighted a significant increase in proteobacteria and a significant decrease in firmicutes in the fecal flora of infants with BPD compared to controls. These infants also had significantly higher pro-inflammatory cytokine levels (IL1β, IL-6, TNFα) and significantly lower anti-inflammatory cytokine levels (IL-10).[27]

There are some animal trials on this subject. Liu HY et al.[28] used L. reuteri to treat colitis induced by 3% dextran sulfate sodium in mice. The authors demonstrated that this treatment decreased pro-inflammatory cytokine levels (TNF-α, IL-1β, INFγ) in the colon. Wang et al.[29] administered L. casei Zhang to mice with acute liver failure orally and showed decreased production of IL-1β and TNF-α in serum, as well as decreased hepatic inflammation. Considering the literature, studies in this regard are most often concentrated on experimental animals, and human trials have mostly investigated the correlations between changes in gut microbiota and systemic inflammation. In the current trial, we compared serum levels of pro-inflammatory cytokines (TNFα, INFγ), anti-inflammatory cytokines (IL-10, IL-13), and an immunomodulatory cytokine (TGF-β) among children with functional abdominal pain at the time of diagnosis and after treatment, and we revealed no significant difference compared to the placebo group. The synbiotic we applied, containing *Lactobacillus helveticus, Lactobacillus casei, Bifidobacterium lactis, and chicory inulin,* caused no significant change in cytokine levels compared to the placebo group. This could be due to the strain of probiotics or the administered dose.

On the other hand, when comparing the cytokine levels of the probiotic group before and after treatment, we observed a significant increase in the anti-inflammatory cytokine levels of IL-13. Furthermore, it was demonstrated that pro-inflammatory cytokine IFN-γ levels decreased in both the synbiotic and placebo groups; however, this decrease was significantly greater in the synbiotic group. In a rat model of ulcerative colitis, a combination therapy consisting of *L. acidophilus* and Chinese medicine Huan Kui Le suspension was used, and it was demonstrated that the combined intervention resulted in upregulation of IL-13 and TGF-β and downregulation of IFN-γ in colon protein expression levels, as well as enrichment of the microbiota composition toward beneficial bacteria.[30] A recent study using a mouse model of intestinal dysfunction induced by sodium dextran sulfate and broad-spectrum antibiotics has shown that intestinal dysfunction causes muscle and bone loss in conjunction with microbial imbalances. This study shows *Bifidobacterium animalis subsp. lactis A6* can reduce muscle and bone loss by tweaking the gut microbiome and increasing butyrate-producing bacteria. This, in turn, decreases pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β, IL-17) in the blood.[31] The *Lactobacillus* and *Bifidobacterium* strains used in our study are probiotics that have been extensively studied and are known to exhibit promising properties. The changes in the gut microbiota caused by probiotics, prebiotics, synbiotics, and postbiotics, as well as their effects on dysbiosis and various systems, particularly the immune system, continue to be an exciting and promising area of research.

In conclusion, functional abdominal pain is a complex group of diseases with multiple factors, including genetic, environmental, familial, psychosocial, intestinal motility, impaired gut-brain axis, dysregulation of the mucosal immune system, dysbiosis, mucus secretion, and barrier dysfunction. The present study was unable to demonstrate

that the synbiotic preparation used in this study caused any difference in symptoms or serum cytokine levels in comparison with a placebo in functional abdominal pain, a complex disorder. However, the significant increase in IL-13 serum levels in the symbiotic group after treatment is a noteworthy finding, and further research is required to explore its implications for intestinal microbiota and the clinical manifestations of functional abdominal pain.

CONCLUSION

In the present study, no discrepancy was observed between the synbiotic and placebo groups with regard to functional abdominal pain symptoms or serum cytokine levels. Nevertheless, a notable increase in anti-inflammatory cytokine, IL-13 levels was observed in the synbiotic group following treatment when the groups were compared within themselves. Our study leaves an open door for the efficacy of synbiotics in the treatment of functional abdominal pain in children. Therefore, there is a need for more studies on the use of synbiotics with different strains, different doses, and different durations.

Ethical approval

This study has been approved by the Uludag University Faculty of Medicine Clinical Research Ethics Committee (approval date 02.09.2014, number 2014-16/6). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: HAA, TBO, TO, FB, NUS; data collection: HAA, NUS, FB; analysis and interpretation of results: HAA, TO; draft manuscript preparation: HAA, TO, TBO. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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