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Lactobacillus probiotics for treating functional dyspepsia in children

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Abstract

Background Functional dyspepsia is a common gastrointestinal disorder in school-aged children, though, there is no reliable treatment. Probiotics are live microorganisms administered in adequate amounts to confer beneficial health effects on the host. Although definitive evidence is lacking, several studies have found probiotics to be effective for relieving symptoms of dyspepsia, particularly abdominal pain and bloating.

Objective To determine the efficacy of lactobacillus probiotics for treating functional dyspepsia in children.

Method A double-blind, randomized controlled trial was done from April to June 2012 in five schools in the Pakpak Bharat Regency, North Sumatera. A total of 116 children who fulfilled the Rome III criteria for functional dyspepsia were randomized into 2 groups to receive either lactobacillus probiotics or placebo for 2 weeks. All patients received a diary to record symptoms and frequency of pain daily. The primary outcome for treatment was defined to be no pain at the end of the intervention.

Results The probiotics and placebo groups were not significantly different in recovery from functional dyspepsia (29.3% *vs.* 13.8%, respectively; P=0.432). However, compared to the placebo group, the probiotics group had significantly reduced frequency of pain (P=0.0001), but no significant differences in pain severity (P=0.08) or pain duration (P 0.091).

Conclusion There are no significant differences in recovery from functional dyspepsia, pain severity, or pain duration between the probiotics and placebo groups. However, the probiotics group has significantly reduced frequency of pain compared to that of the placebo group. **[Paediatr Indones. 2016;56:37-42.]**

Keywords: *Lactobacillus, functional dyspepsia, children*

Dyspepsia is a clinical condition associated with a complex of upper abdominal symptoms including upper centered discomfort or pain, a feeling of abdominal fullness, early satiety, abdominal distention, bloating, belching, and nausea.[1] The majority of dyspepsia is functional dyspepsia, mostly due to the disruption of gastrointestinal function.[2] Functional dyspepsia (FD) is a common disorder in school-aged children.[3] Its prevalence varies between 3.5% and 27% of school-aged children.[3,4] Although benign, FD is frequently associated with anxiety, school absenteeism, and frequent physician visits.[5]

Probiotics are live microorganisms administered in adequate amounts, which confer a beneficial health effect on the host. The probiotics' mechanisms of action include antimicrobial substance production, competitive exclusion of pathogen binding, competition for nutrients, and modulation of the immune system.[6] Probiotics are effective in relieving symptoms of dyspepsia, particularly abdominal pain and bloating,

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but limited data from children are avalaible.[7] The aim of this study was to determine the efficacy of *Lactobacillus* probiotics compared to placebo for treating functional dyspepsia in children.

Methods

We conducted a randomized, double-blind, placebo-controlled trial from April to June 2012, in students from primary and junior high schools in Salak, Pakpak Bharat Regency, North Sumatera. Our inclusion criteria were students aged 7 to 14 years, with functional dyspepsia. The diagnostic criteria for FD, according to Rome III criteria, were a history of pain for at least once per week for at least 2 months before diagnosis, consisting of (i) pain or discomfort in the upper abdomen, (ii) no evidence that dyspepsia was relieved by defecation or associated with the onset of a change in stool frequency, and (iii) no evidence of an inflammatory, anatomic, metabolic, or neoplastic process.[8] Students were excluded if we found alarm symptoms including involuntary weight loss, deceleration of linear growth, significant vomiting (bilious or protracted), chronic diarrhea, unexplained fever, abnormal stool, dysmenorrhea, or organomegaly on physical examination. This study was approved by the Health Research Ethics Committee of the University of Sumatera Utara Medical School, Medan.

History-taking was done by questionnaires followed by a full review. Potentially eligible subjects underwent physical examinations and anthropometric measurements. We randomized subjects with a random number table to receive either probiotics (*Lactobacillus rhamnosus* 1.9 x 10^9 colony-forming units (CFU) and *Lactobacillus acidophilus* 0.1 x 10^9 CFU) or placebo (saccharum lactis), orally, once daily for 2 weeks. All subjects in our study received a daily diary to record frequency, duration,and severity of pain, drug use and school absenteeism, as well as abdominal discomfort during 2 weeks of treatment. For the assessment of pain severity, we used a numeric rating scale (NRS) for self-assessment. The NRS was a 10 cm (100 mm) scale with markings at 1 cm intervals from 0 to 10. Zero denoted no pain, 1 to 3 denoted mild pain, 4 to 6 denoted moderate pain, and 7 to 10 denoted severe pain (excruciating pain).[9] The patient was asked to identify the mark on the scale that corresponded to his/her degree of pain . The primary outcome was considered to be no pain (score of 0 on the numeric rating scale) at the end of the intervention. The secondary outcomes were improvements defined as a change in frequency, duration, and severity of pain, use of medication, school absenteeism, and abdominal discomfort at the end of the 2nd week of treatment.

Data processing was performed by *SPSS version 15.0* software. The Chi-square test was used to determine differences between the probiotic and placebo groups. Independent T-test was used to determine differences in frequency, duration, and severity of pain between the probiotic and placebo groups. Severity of pain was measured using a numeric rating scale (NRS). Results were considered to be statistically significant for P values < 0.05 and 95% confidence intervals (CI). All analyses were performed on an intention-to-treat basis.

Results

After an initial screening of 958 children, 124 were considered to be eligible for participation, but 8 children were excluded due to lack of parental consent or refusal to take the treatment. Of the 116 children enrolled in the study, 58 received probiotics and 58 received placebo. There were no withdrawals or dropouts. The study outline is shown in **Figure 1**. Characteristics and distribution of subjects in both groups are shown in **Table 1.** Mean age, gender, weight, height, and pain characteristics were similiar in the two groups.

Table 2 shows the treatment success, frequency, duration and severity of pain at 2 weeks after treatment. Overall, 25 of the 116 (21.5%) participants reported treatment success. The probiotics group had higher treatment success than the placebo group, but the difference was not significant [29.3% *vs* 13.8%, respectively; (P=0.432)]. The frequency of pain at 2 weeks was significantly reduced in the probiotics group compared to the placebo group (P<0.0001), however, there was no significant difference in pain duration between the groups. Mean post-treatment pain severity was mild in both groups, with 1.6 (SD 1.14) NRS in the probiotics group and 2.4 (SD 2.79) NRS in the placebo group, but the difference was not significant (P=0.08).

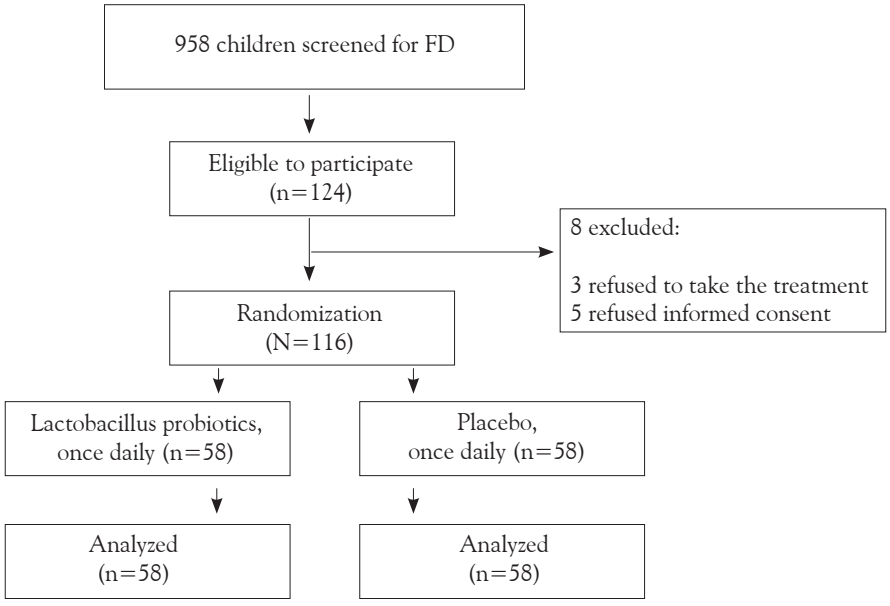

Figure 1. Study profile

Table 1. Baseline characteristics of subjects

Characteristics	Lactobacillus group (n=58)	Placebo group (n=58)
Gender, n (%)		
Male	31 (53.5)	22 (37.9)
Female	27 (48.6)	36 (62.1)
Mean age (SD), years	11.1 (2.17)	11.0 (2.16)
Mean weight (SD), kg	29.3 (7.56)	28.4 (7.47)
Mean height (SD), cm	138.0 (12.30)	136.2 (12.00)
Nutritional status, n (%)		
Underweight	17 (29.3)	24 (41.4)
Normoweight	41 (70.7)	34 (58.6)
Mean frequency of pain (SD), times/week	2.7 (0.72)	2.7 (0.66)
Frequency of pain, n(%)		
≤ 2 times/week	22 (37.9)	24 (41.38)
>2 times/week	36 (62.1)	34 (58.62)
Mean duration of pain (SD), minutes	12.4 (6.50)	13.1 (7.30)
Duration of pain, n(%)		
10 minutes	50 (86.2)	49 (84.48)
30 minutes	8 (13.8)	9 (15.52)
60 minutes	0	0
Mean severity of pain (SD), NRS	2.7 (0.72)	2.7 (0.66)
Severity of pain, n(%)		
Mild pain (1-3)	56 (96.5)	50 (86.2)
Moderate pain (4-6)	2 (3.5)	8 (13.8)
Severe pain (7-10), n(%)	0	0
Use of drug treatment for abdominal pain, n (%)	13 (22.4)	13 (22.7)
School absenteeism because of abdominal pain, n (%)	9 (15.5)	13 (22.7)
Abdominal discomfort, n (%)	47 (81.0)	48 (82.8)

Table 3 shows that abdominal discomfort, use of medication, and school absenteeism due to abdominal pain at 2 weeks after treatment were not significantly different between the groups.

Table 2. Treatment success, as well as pain frequency, duration, and severity at 2 weeks after treatment

Outcomes	Lactobacillus group (n=58)	Placebo group (n=58)	95% CI of differences	P value
Treatment success, n (%)	17 (29.3)	8 (13.8)	-0.325 to 7.333	0.432†
Mean frequency of pain (SD), times/week	1.08 (0.540)	2.0 (0.96)	1.260 to 0.601	0.0001•
Mean duration of pain (SD), minutes	8.4 (7.45)	10.7 (7.46)	-4.849 to 0.367	0.091•
Mean severity of pain (SD), NRS	1.6 (1.14)	2.4 (2.79)	-1.575 to 0.092	0.08•

†Chi-square test, • Independent T-test, NRS= numeric rating scale

Table 3. Abdominal discomfort, use of medication, and school absenteeism at 2 weeks after treatment

Outcomes	Lactobacillus group (n=58)	Placebo group (n=58)	95% CI of differences	P value
Abdominal discomfort, n (%)	18 (31)	29 (50)	-0.237 to 2.213	0.578
Use of medication, n (%)	4 (6.9)	8 (13.8)	-1.050 to 1.312	0.543
School absenteeism, n (%)	1 (1.7)	5 (8.6)	-1.011 to 1.188	0.914

Discussion

In our study, 958 children were screened for FD. Of these, 124 (12.94%) children were eligible to participate. The mean age of all subjects was 11 years. We included children aged 7 to 14 years based on the high prevalence of FD in school-aged children, and the rare occurrence of organic or pathological disorders being the underlying cause of dyspepsia in school-aged children.[3] A US study reported that 12.5 to 15% of children aged 4 to 18 years referred to a tertiary care center because of abdominal pain were diagnosed with FD.[2]

We found no significant differences between *l*actobacillus in treating functional dyspepsia over the placebo group, in terms of treatment success, pain duration and severity. However, the frequency of pain at 2 weeks of treatment was significantly reduced in the probiotics group compared to the placebo group. We used probiotics containing *Lactobacillus sp (Lactobacillus rhamnosus* 1.9 x 10^9 CFU and *Lactobacillus acidophilus* 0.1 x 10^9 CFU), given orally, once daily, for 2 weeks. We chose this probiotic because *Lactobacillus sp* have the ability to stimulate immunity, affect migration motoric and intestinal transit time, increase the pain threshold, and reduce stress-induced hypersensitivity.[10] Moreover, *Lactobacillus sp* have a wide range of doses, ranging from 1 x 10^7 CFU to 1.8 x10^9 CFU per day, with a duration of 1 to 10 weeks, and are relatively safe to use.[11,12] However, an optimal dose of *Lactobacillus* has not been recommended.[11] We used a placebo control group in the study, which is considered an essential requirement for interventional studies of functional gastrointestinal disorders. However, we cannot exclude the placebo effect that has ranged from 10% to 70% for FD in previous studies.[13] The placebo effect may be responsible for the lack of obvious effect from the *Lactobacillus* treatment. Our study was school-based, and we found the intensity of pain in our subjects to be mostly mild. As such, a placebo effect may also explain the lack of differences between groups.

Clinical trials on probiotics to reduce functional abdominal pain disorders (FAPD) have been limited, and several studies did not use dyspepsia functional as specific diagnosis.[14-16] One trial assessed the effect of *Lactobacillus rhamnosus* GG (LGG) in pediatric patients with FAPD [FD, irritable bowel syndrome (IBS) and functional abdominal pain (FAP)] who were given LGG 3 x 10^9 CFU, twice daily for 4 weeks. The LGG appeared to moderately increase treatment success, particularly among children with IBS.[14] Another clinical trial assessed the effect of LGG for relieving symptoms in children with recurrent abdominal pain (IBS and FAP). Children with IBS were given 3 x 10^9 CFU LGG for 8 weeks and subsequently found to have significantly reduced frequency and severity of abdominal pain.[15] In contrast, a US study assessed

the effect of LGG to improve symptoms in children with IBS and found that LGG was not superior to placebo in the treatment of abdominal pain, but may have helped relieve symptoms such as perceived abdominal distention.[16]

For the assessment of pain severity, we used a numeric rating scale (NRS) for self-assessment. The NRS is a 10 cm (100 mm) scale with markings at 1 cm intervals from 0 to 10. Zero denotes "no pain" and 10 denotes "excruciating pain."[15] The patient was asked to identify the mark on the scale that corresponded to his/her degree of pain. We chose this scale based on age, as this NRS was found to be effective in children at least 7 years of age.[17] The use of self-assessed outcome measures is recommended, however, it is noteworthy that currently no measures for the functional gastrointestinal disorders are sufficiently validated to be unequivocally recommended as the primary outcome measure.[13]

All patients in our study received a diary to record symptoms and characteristics of daily pain, medication use and school absenteeism. As recommended, we also used diaries to measure outcomes and minimize recall bias.[17] We used diaries to measure outcomes and minimize recall bias. The validity of paper diary records is sometimes questioned.[18] The problems with paper diaries include poor adherence to daily recording with some subjects filling them up right before their routine visit. Electronic diaries would be a more reliable recording method.[13,18]

We found that the probiotics were well-tolerated and no adverse effects were reported. The adverse effects of probiotics are typically mild, such as flatulence or mild abdominal discomfort, and usually self-limited.[19,20] Sepsis may occur in severely ill or immunocompromised hosts or children with short-gut syndrome, so it is prudent to avoid probiotics in these patients.[21]

Several factors may explain the lack of obvious effect of lactobacillus, such as wrong selection of the probiotic strain, too short a treatment duration, or an inadequate dose.[11] Another limitation of this study was that probiotic cultures were not performed before treatment.

In conclusion, probiotics and placebo are not significantly different for recovery of functional dyspepsia in children. However, the probiotics group has significantly reduced frequency of pain.

Conflict of interest

None declared.

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