Meta Analysis

Probiotic Use on Children with Functional Dyspepsia: A Meta-Analysis

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Functional abdominal pain disorders are gastrointestinal disorders with abdominal discomfort, bloating, belching, and colic as the symptoms. Treatment options for functional dyspepsia are limited. Some studies have shown that probiotic supplementation can significantly reduce gastrointestinal symptoms, but data are still limited. Through this meta-analysis, studies published since database inception from January 2011 to December 2020 were included. All of the bias risk was assessed for the all the studies. With 314 participants, his three research papers published between 2016 and 2020 were successfully included in the meta-analysis. The pooled hazard ratio for the symptom improvement outcome of functional dyspepsia was 2.13 (95% CI: 0.79, 5.71), indicating symptom improvement after probiotic administration with Lactobacillus species, with major improvement in severity of pain, the pain frequency and the duration of pain ($p<0.001$). This meta-analysis provides an update from the previous systematic review that probiotic administration may help children with functional dyspepsia.

INTRODUCTION

Functional dyspepsia is part of functional abdominal pain disorders based on Rome IV criteria. The common diagnostic criteria for functional abdominal pain disorders are the presence of abdominal pain that, upon further investigation, cannot be attributed to other disorders. Based on Rome IV, to diagnose a functional dyspepsia, the criteria needed were as follow, 2 or more bothersome symptoms are present for at least 2 months on 4 or more days per month. Unpleasant symptoms include postprandial satiety, early satiety, epigastralgia or a burning sensation unrelated to defecation (1,2). Previous meta-analysis of 58 studies found the prevalence of functional abdominal pain disorder of 13.5% (95.8–15.3). Its prevalence increases in children aged 4–6 years and in early adolescence (1,3). A U.S. survey of 949 mothers found around 1.4% of the children had epigastric pain or discomfort at least once a week, compared with the Childhood Rome III criteria (4). Some studies also show that abdominal pain was associated with anxiety and depression. Abdominal pain can also be very disruptive to a child's daily life and interfere with participation in school, sports, and social activities. Several mechanisms have been described to explain the causes of the symptoms of functional dyspepsia, which include several hypotheses of gastric dysmotility, visceral hypersensitivity, mild inflammation, and genetic predisposition (5).

Treatment options for functional dyspepsia are limited. To date, there are no widely available effective drugs and drug development has been hampered by large placebo effects and lack of adequate validation of endpoints based on the definition of functional dyspepsia. Studies on the effectiveness of probiotics in treating abdominal pain in children are limited. A meta-analysis of three studies analyzed the efficacy of probiotics in treating functional abdominal pain disorders in children showed that children diagnosed with functional abdominal pain

who received LGG supplements had significantly less pain than children who received placebo. However, when each diagnostic subtype was analyzed separately, the only significant response was children with irritable bowel syndrome (IBS). Other groups had similar responses to LGG and placebo (6).

Probiotics are organisms that provide health benefits. Almost all probiotics are isolated from the human microbiome. They are used to increase the number of microbiota and can usually be administered orally (7–9). Probiotic supplementation has been shown to improve symptoms in patients with functional dyspepsia to reduce the inflammation and improve mucosal permeability, but the benefits of probiotics itself still remain controversial (10).

METHODS

In this meta-analytic quantitative study, several national and international databases such as the Cochrane Library, PubMed, Medline, Google Scholar, EBSCO, and national journals were searched with the following basic keywords: digestion; Indigestion, epigastric pain, functional dyspepsia postprandial distress, satiety, upper gastrointestinal symptoms, abdominal pain, epigastric discomfort. The basic keywords were combined with probiotic search terms (AND operator set: *Saccharomyces, Lactobacillus, Bifidobacterium*, Probiotics, Synbiotics, or Prebiotics). RCT search terms (set operator AND; randomized controlled trial, clinical trial, placebo-controlled trial, double-blind RCT). Child search terms (AND operator set: children, childhood, children, teenagers, children under 18). The search was limited to literature published between 2011 and 2020. This study included only Indonesian and English literature with complete documents (full text).

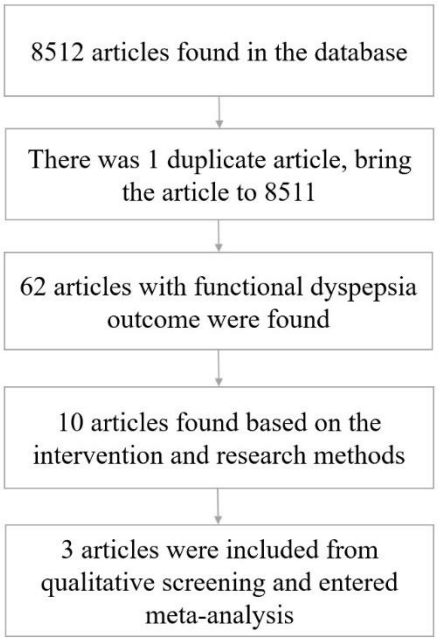

Figure 1. Flowchart of Study

Table 1. Characteristics of the research analyzed

Researcher & year of publication	Ahyani et al. (2016)	Gianetti et al. (2017)	Rahmani et al. (2020)
Location/country	Indonesia (North Sumatra)	Italy (Napoli and Foggia)	Iran
Sample characteristics			
Types of research	Double-blind, placebo-controlled RCT	Double-blind cross over RCT	Double-blind clinical trial
Sample size	116 (58 interventions, 58 controls)	25 (12 interventions, 13 placebo)	29 (16 interventions, 13 placebo)
Age range (years)	7-14	8-16.6	6-16
Average age (years)	11.1 (treatment group) 11.0 (control group)	Median: 11.6 (functional dyspepsia group)	7.3±1.7 (treatment group) 7.7±2.1 (control group)
Administration of probiotics			
Strains	L. acidophilus and L. rhamnosus	Bifidobacterium mix M-63 infantry, M-16V breve, and longum BB536	L. reuteri
Dosage (CFU)	0.1x109 (L. acidophilus) 1.9 x 109 (L. rhamnosus)	3x109 Bifidobacterium longum BB536 109 Bifidobacterium infantis M-63 109 Bifidobacterium breve M-16V	108 (1 probiotic tablet)
Duration (days)	14	42 days (6 weeks)	28 (4 weeks)
Comparator/control	Placebo (saccharum lactis)	placebo	placebo
Rating scale used	Numerical rating scale (NRS)	Functional disability inventory (FDI) (score: 0-60; the higher the score, the lower the QoL)	Wong Baker Faces Pain Rating Scale (WPFPRS)
Mean post-treatment scale scores	NRS Skala scale 1.6 (treatment group) 2.4 (placebo group)		WBFPRS Skala Scale 1.1±1.3 (treatment group) 2.0±1.0 (placebo group)

RCT, randomized controlled trial

RESULTS

The PubMed, Google Scholar, Cochrane, Pediatrica Indonesiana, and EBSCO databases were systematically searched, and 8512 research articles were retrieved. The Mendeley application showed that one article was duplicated, and 8511 articles remained. After manual screening based on title suitability, which examined the outcome of functional dyspepsia, 62 articles remained. Fifty-two articles were excluded after further manual screening based on the intervention and research methods, leaving 10 articles. Seven articles were excluded because they used inappropriate research protocols, were abstracts from a conference, or had no downloadable full text of the article.

All participants were children aged between 6 and 17 years, and the studies were carried out in various geographic areas (two in Asia—Iran and Indonesia; one in Europe—Italy). Two studies used a combination of probiotic strains: one study used a combination of L. acidophilus and L. rhamnosus, and the other used a combination of Bifidobacterium infantis M-63, breve M-16V, and BB536 longum mixtures. One study used the single-strain probiotic L. reuteri. The duration of probiotic administration varied from 14 to 42 days. The flowchart for the study is illustrated in Figure 1.

All articles were eventually screened in-depth, and inclusion criteria, including age, year of publication, and completeness of data and analysis, were applied. Three research articles, which involved 314 participants and were published between 2016 and 2020, were successfully included on the meta-analysis (Table 1).

The results of the analysis of the risk of bias were shown in the Figure 2 and 3.

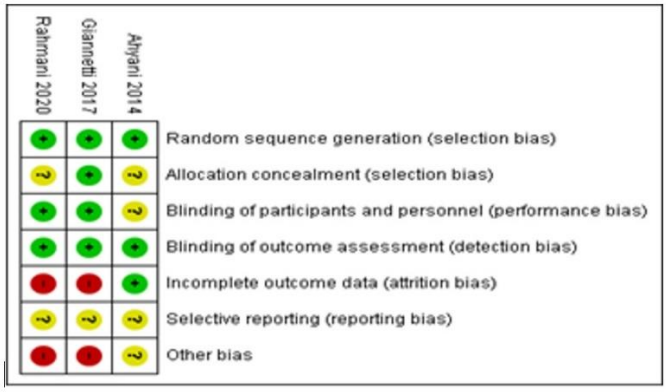

Figure 2. Analysis of Bias

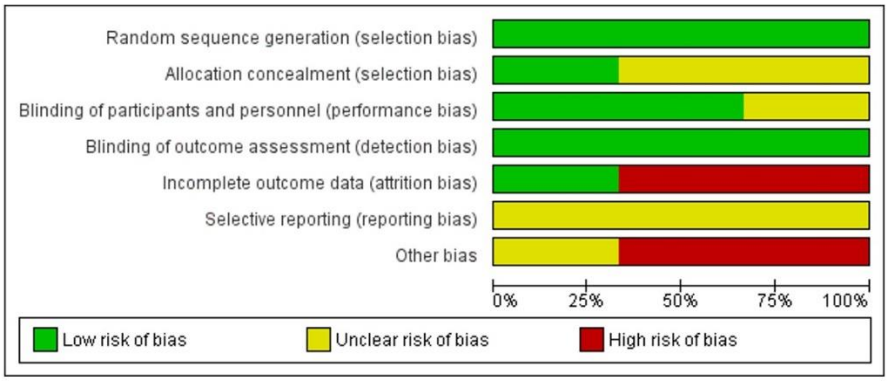

Figure 3. Bias Analysis

All studies compared the administration of probiotics or a combination of probiotics to placebo administration. The pooled risk ratio for the outcome of improving functional dyspepsia symptoms was 2.13 (95% CI: 0.79, 5.71), which indicated an improvement in symptoms after probiotic administration (2.13 times that of placebo administration in reducing functional dyspepsia symptoms in children). The intervention and control groups in

the studies by Giannetti et al. and Rahmani et al. were not balanced, because the functional dyspepsia outcomes in the two studies were included in the subgroup analysis. This widened the confidence interval for the results of the pooled treatment. The results of the forest plots are shown in Figure 4.

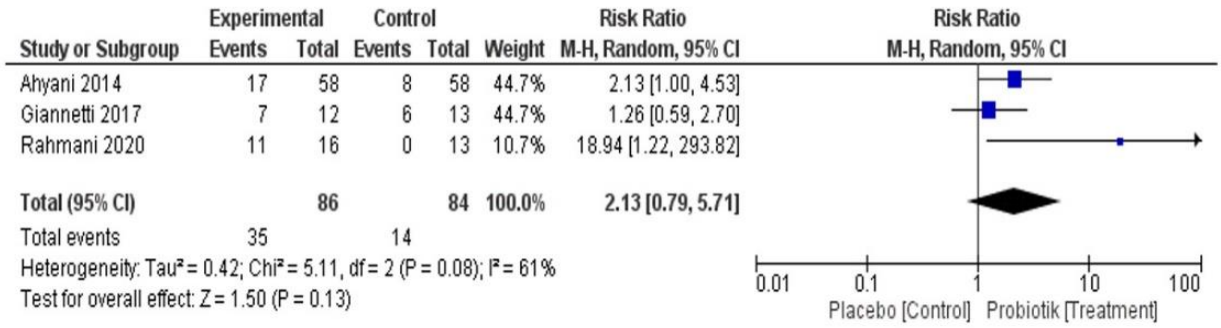

Figure 4. Overall symptoms in patients with functional dyspepsia treated with probitocs

***Lactobacillus rhamnosus* 1.9 x 10^9 colony forming units (CFUs) & *Lactobacillus achidopilus* 0.1 x 10^9 CFU versus placebo**

Ahyani et al. showed that the improvement after probiotic administration in children with functional dyspepsia was not statistically significant compared with that after placebo (29.3% vs. 13.8%, p=0.432). However, there was a decrease in the frequency of pain in the group with probiotics (p<0.0001) are shown in Figure 5.

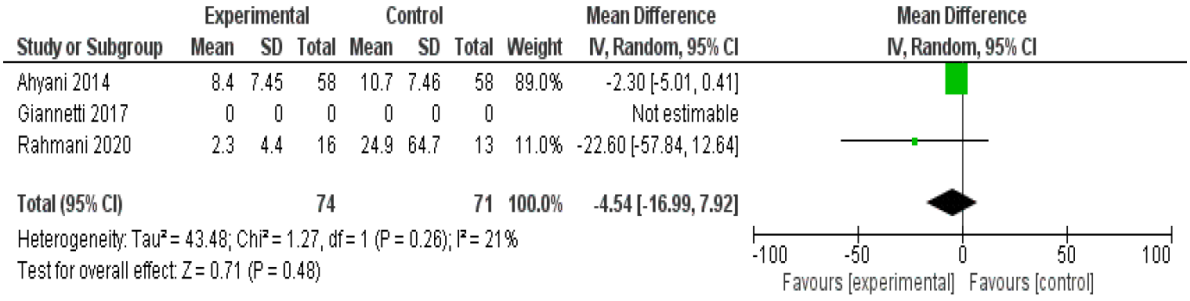

Figure 5. Pain duration on differences of probiotics choices.

Lactobacillus reuteri versus placebo

Rahmani et al. showed a positive effect of probiotics administered to children with functional dyspepsia compared with that of placebo (p<0.001), showed by the reductions in pain frequency, pain severity and pain duration (p<0.001).

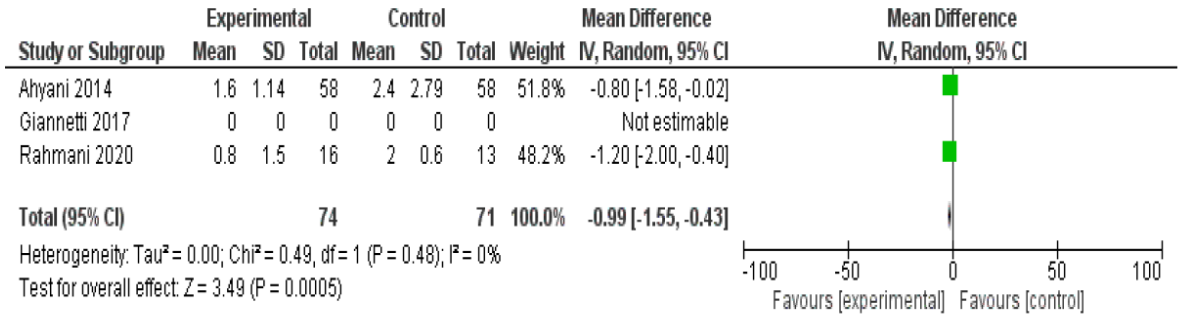

Figure 6. Pain severity and duration in patients treated with probiotics

Probiotic combination of *Bifidobacterium infantis* M-63, *breve* M-16V, and *longum* BB536 versus placebo

Research by Giannetti et al. did not show any reduction in symptoms in the probiotic group with functional dyspepsia compared with placebo (20% vs. 36%, p=0.3). The sample in this study was very small because participants with functional dyspepsia were a fraction of the total number of participants that included patients with IBS.

DISCUSSION

Within the last decades probiotics have a known role in treating the gastrointestinal disease in children. Ahyani et al. reported a significant reduction in the frequency of pain in functional dyspepsia patient administered with probiotic (10). Rahmani et al. also showed an improvement of symptoms with probiotics administration in children with functional dyspepsia (p<0.001). The authors of the study also reported significant reductions in pain frequency (p=0.001), pain severity (p<0.001), and pain duration (p<0.001) after probiotic administration (11). In contrast, Giannetti et al. did not find any improvement in symptoms in the probiotic group with functional dyspepsia compared with placebo (20% vs. 36%, p=0.3) (12).

It is well known that disturbances of gut microbiota homeostasis are associated with the pathogenesis of various gastrointestinal diseases with visceral pain as their main manifestation, including functional dyspepsia (13). Previous studies have also reported the involvement of the gut microbiota in the pathogenesis of visceral pain with inducing the expression of analgesic receptors, in colonic epithelial cell lines (14). The administration of Bifidobacteria in experimental mice can also improve symptoms of visceral hypersensitivity due to colorectal distension (15). Supplementation with probiotic LGG can also improve the suppression of neonatal inflammation-induced visceral hypersensitivity in mice (16). Luczynski et al. reported that it is easy to elicit visceral hypersensitivity due to the increased expression of toll-like receptors and cytokines in the spinal cords of germ-free mice, when their intestines are not colonized by microbiota (17).

Nowadays, the gastrointestinal health was determined by the number of microbiotas withing the gut itself. Changes in composition of the microbiota can cause various abnormalities inside and outside the gastrointestinal

tract (18). Igarashi et al. reported changes in the ratio of the microbiota species composition of the gut microbiota after the administration of probiotics; but until now, it is still not clear if these changes in the gut microbiota are directly related to improvement in clinical symptoms or whether this is a secondary phenomenon (19).

Another possible mechanism underlying the reduction of symptoms in patients with functional dyspepsia is related to the bile acid metabolism. Several previous studies shown that the microbiota plays a role in the deconjugation of bile acids, thus increasing bile acid excretion through feces, while inhibiting the synthesis of bile acid in the liver. The improvement in upper gastrointestinal symptoms by probiotics may be partly due to their ability to reduce bile acid secretion in the proximal gastrointestinal tract (20).

Giannetti et al. reported an improvement in abdominal pain symptoms after placebo administration in 36% of pediatric patients with functional dyspepsia, but only 14.5% of pediatric patients with IBS. The study applied a crossover clinical design to minimize variability between groups of participants (12). Several previous studies have also reported the relevance of the placebo effect, although the data are still very limited for functional dyspepsia; for patients with IBS alone, the placebo response was reported between 16% and 71%, with a mean of 40%. The strength of the placebo effect in an RCT is strongly influenced by the strictness of the diagnostic criteria applied during the recruitment of participants, the presence or absence of run-in periods between the recruitment and randomization process, and whether or not follow-up was routine during the study period (21).

There are several probiotics that have been used in these studies, where two studies used probiotics from *Lactobacillus Spp.* (10,11), and one studies using a mixed probiotic strain of *Bifidiobacterium Spp.* (12). In their article, Ahyani et al. chose *Lactobacillus* because this species can stimulate immunity, affect motor migration and intestinal transit time, increase pain threshold, and reduce stress-induced intestinal hypersensitivity (11).

A systematic review by Agah et al., who investigated the effectiveness of probiotic administration for the management of functional dyspepsia in adults, reported that the effectiveness of probiotics may depend on the type of strain administered, and not all probiotic strains have been shown to relieve the pain. In adults, *Lactobacillus gasseri* and *Lactobacillus reuteri* are said to have a greater effect on gastrointestinal symptoms than other species (22).

In clinical trials examining the administration of probiotics for other functional gastrointestinal diseases such as IBS, some probiotics from certain species and strains still are effective than others, such as *Bifidobacterium* species (23), as well as *Lactobacillus* species. The probiotics from these species and strains are effective in reducing symptoms of abdominal pain and discomfort in both adults and children (24,25). Several studies have also shown that the combination of several probiotic strains, which consists of a mixture of *Bifidobacterium Spp.* and *Lactobacillus Spp.*, can reduce symptoms of pain and discomfort in patients with functional abdominal pain (26).

In the current systematic review, it is difficult to choose the best probiotics, given the limited number of RCTs studied. Different species and strains of probiotics show different immunological and physiological effects on disease (27). To date, there are still no clinical trial data comparing the efficacies of different probiotics for children with functional dyspepsia.

CONCLUSION

We found the best duration of probiotic administration ranged from 14 days (2 weeks) to 42 days (6 weeks), and there was considerable variation. However, data on the optimal duration of probiotic administration for functional dyspepsia are still lacking. These systematic reviews and meta-analysis provide an update on the results of the systematic review conducted by Ding et al. (28), who conducted a subgroup analysis of two studies (29) which reported no significant changes after the administration of probiotics in children with functional dyspepsia. The two studies reviewed were limited by their sample size.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTIONS

All authors contributed equally for this study

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None

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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