INVITED COMMENTARY

Probiotics for Functional Constipation in Children: Does it Help?

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Functional constipation (FC) is a common problem in children, accounting for 3% of visits to general pediatric clinics, and up to 30% visits to pediatric gastroenterologists in developed countries [1]. The main factor involved in the pathogenesis in children is withholding behavior, usually occurring after experiencing painful defecation. Withholding of feces leads to prolonged fecal stasis in the rectum, with resultant absorption of fluids and hardening of stools. Successive retention of stools in the rectum makes them larger. As the cycle is repeated, successively greater amounts of larger and harder stools are built up in the rectum and passed with even greater pain accompanied by severe "stool withholding maneuvers."

Conventional treatment of children with FC involves non-pharmacological interventions such as parent education, toilet training, and high-fiber diet in combination with pharmacological interventions such as laxatives. According to the 2014 guidelines developed by the European and North American Societies for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN/NASPGHAN), polyethylene glycol (PEG) is the drug of choice [2]. When PEG is not sufficient, other laxatives (lactulose), may be considered as a second-choice treatment. In a proportion of patients; however, these treatment options do not provide sustained relief of symptoms. Data have shown that 10% of children with functional constipation take laxatives for longer than 12 months, and 40% are still symptomatic despite the use of laxatives [3]. Approximately 50% of children with functional constipation have had at least one relapse within the first 5 years after initial recovery [4]. Therefore, other therapeutic options such as probiotics are being sought. In adults, experimental studies have shown that constipation is often associated with dysbiosis of gut microbiota, consisting of the modified abundance of certain taxa of the colonic microbiome [5]. For example, some data have suggested the decreased abundance of *Bifidobacteria*, *Lactobacillus*, *Bacteroides*, and *Prevotella* [5]. One recent study in children showed that in those with FC, the most discriminative species were *Bacteroides fragilis*, *Bacteroides ovatus*, *Bifidobacterium longum*, *Parabacteroides* species (increased), and *Alistipes finegoldii* (decreased) [6]. However, it remains to be determined if these alterations are a cause or a consequence of altered gut motility. Probiotics are also believed to improve peristalsis and reduce intestinal stasis by modifying the gut microbiota, increasing the production of lactate and short-chain fatty acids, and reducing luminal pH. Considering the potential role of the microbiota, there is a question as to whether modulating the gastrointestinal microbiota plays a role in the management of FC.

The study by Lojanatorn, et al. [7] in this issue of *Indian Pediatrics*, examined the efficacy of *Bacillus clausii* in treating FC in 38 children aged between 1-5 years (20 in the probiotics arm and 18 in placebo arm). In this open-label, double-blinded, placebo-controlled study, children were assigned to receive either *B. clausii* or placebo, once daily for 28 days. At 4 weeks follow-up, the Bristol stool chart grade increased significantly in both groups, compared to baseline. Use of rectal enema decreased over time only in the *B. clausii* group (40% in first 2-week vs 15% between 2-4 weeks, P=0.003) while the placebo group did not show any reduction in rectal enema use (27% each, P>0.99). Neither group showed any reduction in abdominal pain. The primary outcome of the study, treatment success rates (defined as atleast three defecations/week and stool consistency atleast grade 3 on Bristol stool chart) were comparable at 2 weeks and 4 weeks follow-up. Hence, the authors concluded that a 4-week treatment with *B. clausii* was not more effective than a placebo in children with FC.

Different systematic reviews and meta-analyses that studied the role of probiotics in children with FC concluded that there is not enough evidence for the recommendation of probiotics for FC [4,8,9]. The meta-analysis by Wojtyniak, et al. [4] included 7 RCTs and 515 participants with significant heterogeneity with respect to study population, probiotic strains, dosages, study duration, and follow-up. The pooled results of two RCTs (n=108) that investigated the efficacy of *Lactobacillus rhamnosus casei* Lcr35 showed no significant difference between

probiotics and the placebo group [4]. Another meta-analysis by Jin, et al. [8] involving four RCTs and 382 children with FC reported that there were no significant differences in treatment success, spontaneous bowel movements per week, fecal incontinence episodes per week, straining at defecation and use of laxatives between probiotics and placebo. Interestingly, abdominal pain and use of rectal enema were significantly less in the probiotics arm, similar to findings of the present study [7]. One trial evaluated the effectiveness of *L. rhamnosus* GG, and one, *Bifidobacterium lactis* DN-173010; neither probiotic was significantly more efficacious than placebo. In another meta-analysis of six RCTs involving 498 children, Huang, et al. [9] showed that the use of probiotics significantly increased the stool frequency. Although, the authors of this meta-analysis have claimed a significant improvement in stool frequency with probiotics, the 95% confidence intervals clearly indicate that the difference was not significant. Also, there was significant heterogeneity among the studies (I^2 =84%), each RCT was from a different country and had a small sample size, and most studies used separate probiotic species (2 *L. rhamnosus* GG, 2 *L. rhamnosus Lcr35 casei*, 1 *L. sporogenes*, 1 *B. lactis* DN-173010), which might have influenced the validity and reliability of the conclusions.

Guerra, et al. [10] carried out a crossover double-blind trial in 59 Brazilian children with FC according to Rome III criteria. The patients were randomized into two groups to receive either a goat yogurt supplemented with 10^9 colony-forming units/mL of *B. longum* daily or only the yogurt for a period of 5 weeks. Afterward, the groups were inter-crossed for another 5 weeks. Both treatment groups demonstrated improvement in defecation frequency, compared to the baseline. However, the improvement obtained with probiotics was significantly higher [10]. In the second phase of treatment, the group initially treated with probiotics showed worsening stool consistency when using only yogurt. However, the difference was not significant. The study concluded that an improvement in defecation frequency was observed using both supplemented and non-supplemented yogurt, but an additional improvement with *B. longum* supplementation was obtained. Coccorullo, et al. [11] performed a double-blind randomized placebo-controlled study in 44 formula-fed infants with a diagnosis of FC. One group received supplementation with the probiotic *L. reuteri* (DSM 17938) and the other group received a placebo. *L. reuteri* was administered at a dose of 10^8 colony-forming units in 5 drops of oil suspension once per day for 8 weeks. Infants treated with *L. reuteri* had a significantly higher defecation frequency than placebo after 2, 4, and 8 weeks of treatment. The results were graphically presented without reporting absolute numbers, and there was no mean difference for outcome measures between the two groups [11].

To conclude, current limited evidence does not support the use of probiotics in the treatment of FC in children. ESPGHAN/NASPGHAN guidelines recommend against the use of probiotics in FC. Further research with well-established and homogeneous methodologies is needed to determine causal relationships between functional constipation and alteration of fecal microbiota, as well as the efficacy of using probiotics to treat children and adolescents.

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