DOI: https://doi.org/10.53555/nnmhs.v9i4.1647 Publication URL: https://nnpub.org/index.php/MHS/article/view/1647

FUNCTIONAL CONSTIPATION IN CHILDREN : A SYSTEMATIC REVIEW

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Abstract

It is essential to test and diagnose children as soon as possible for functional constipation (FC), which is considered a substantial burden of illness in children. When treated in a timely manner and with the proper medication, babies who have FC have a better chance of making a full recovery. It is estimated that inflammatory bowel disease is responsible for up to 25% of pediatric gastroenterologist visits and 3% of all pediatric outpatient visits globally. It is difficult to estimate the real prevalence of FC in children as a result of the variability of the studies in terms of target population sample, diagnostic criteria, participant ethnicity and environment, technique of data gathering, and lifestyle and psychological characteristics, amongst other considerations. It is possible that the key causes for the worldwide variation in prevalence among studies that have been published are the absence of consensus on diagnostic criteria and cultural variations. Probiotics have the capacity to improve the balance between species, impact intestinal motility by creating lactic acid and short-chain amino acids, and stimulate gut peristalsis by adjusting stool pH. Additionally, probiotics have the potential to increase the number of short-chain amino acids produced in the body. A wide variety of probiotic strains have been the subject of a significant number of investigations. On the other hand, there are not enough evidence available at this time to support the use of probiotics in children who suffer from chronic constipation.

Keyword: *Children; Constipation; Gastrointestinal; Probiotic*

INTRODUCTION

The toileting frequency of neonates and children varies with age. To reduce parental anxiety and prevent unnecessary testing and treatment, it is essential to understand the typical toileting habits of all age groups. The frequency of stool passage per day progressively decreases from more than four times per day during the first week of life to three times per day between 4-6 weeks of age and one to two times per day by age 4. Infants who are exclusively breastfed for the first 1-2 months of life will have infrequent stool passages with a mean duration of 6 days (2-28 d per stool passage) and no abnormalities.[1]

This condition will return to normal at a mean age of 3,9 months (range: 1-7 months). Therefore, if the stool is mild, infrequent bowel movements in this age group do not require intervention or treatment.[1] The majority of children evacuate defecation daily or every other day by the age of five without straining or withholding. In early neonates, the average intestinal transit time is approximately 8.5 hours, whereas after puberty the range is 30 to 48 hours. In 2006, Rome foundation added FC diagnostic criteria for youngsters to Rome III criteria. Rome IV succeeded Rome III in 2016.[2]

Functional constipation (FC) is considered a significant burden of disease in children and requires early screening and diagnosis. The prognosis for infants with FC improves with prompt and appropriate treatment.[3] Understanding the pathophysiology of FC can lead to effective treatment and a positive prognosis for these children, as general practitioners and pediatricians are typically the first caregivers. In this chapter, you will learn everything a physician needs to know about FC to provide improved patient care.[4,5]

Up to 25% of pediatric gastroenterologist visits and 3% of all pediatric outpatient visits worldwide are attributable to FC. Due to the heterogeneity of the studies in terms of target population sampling, diagnostic criteria, participant ethnicity and environment, method of data acquisition, and lifestyle and psychological factors, among others, it is difficult to determine the true prevalence of FC in children. Lack of agreement on diagnostic standards and cultural differences may be the primary reasons for the global diversity in prevalence among published studies.[3–7] The facts surrounding functional constipation in children will serve as the primary focus of the conversation.

METHODS

PRISMA 2020 complied with requirements for data acquisition, processing, and reporting. The decision to implement new restrictions was influenced by multiple factors. This review investigates the incidenct of functional constipation in children. All written materials regarding the effect of nocturia on mortality must be composed in English, according to the primary findings of the study. This systematic review analyzed scholarly articles published after 2015 that met the inclusion criteria of the study. The collection will exclude editorials, entries lacking a DOI, reviews of previously published books, and duplicate journal articles that are excessively extensive.

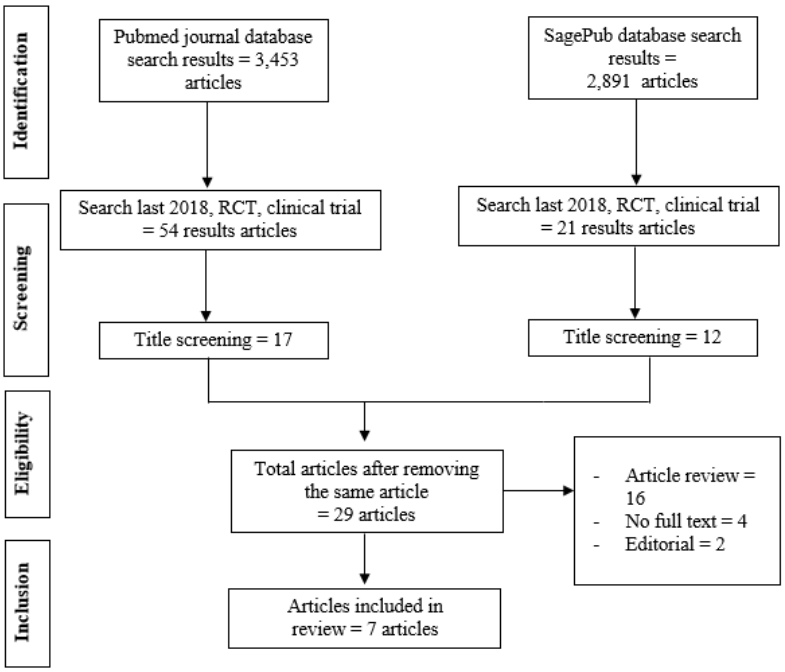

Figure 1. Article search flowchart

The search for studies to be included in the systematic review was carried out from April, 12th 2023 using the PubMed and SagePub databases by inputting the words: “functional constipation” and “children”. Where *("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields]*

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Equally influential on the acceptability of studies were their abstracts and titles. Consequently, they must rely on historical documents. Considering that research findings are typically consistent, unpublished English papers are required. For the systematic review, only studies meeting the inclusion criteria were considered. This restricts the search results to only those that meet the specified criteria. The evaluation procedure is divided into the following sections. The research took into account authors, publication dates, geographic locations, activities, and motivations.

After EndNote had recorded a search's results, the database scoured for duplicate articles and removed them. This article involved two people reviewing the titles and abstracts of all the papers. Each author carefully considers relevant abstracts and article titles before deciding which articles to cover. Each paper that meets the review criteria will be subject to a comprehensive and thorough analysis. After completing our investigation, we will review relevant scientific publications that we may have missed the first time. Relevant research was included, while we excluded research that was not relevant.

RESULT

Kubota, et al (2020)[8] study showed L. reuteri DSM 17938 + lactose hydrate as a placebo of MgO, L. reuteri DSM 17938 + MgO, and L. reuteri DSM 17938 + MgO exhibited significant improvement in defecation frequency in the fourth week compared with the baseline condition (group A: $p < 0.05$; group B: $p < 0.05$; group C: $p < 0.05$). The composition of stools changed significantly in the MgO group and the combination group, but not in the L. reuteri DSM 17938 group (group A: $p = 0.079$; group B: p 0.05; group C: p 0.05). The genus Dialister was much less common when MgO was present. The number of Clostridiales bacteria in the gut microbiome was lower the more often a person went to the bathroom.

Jarzebicka, et al (2019)[9] showed the PEG group had more defecations per week compared with the lactulose group (7.9 ± 0.6 vs 5.7 ± 0.5, $P = 0.008$) and both groups had similar frequency of defecation with pain (5% vs 5%, $P = 0.9$), stool retention (7% vs 10%, P = 057), large volume of stools (30% vs 31%, $P = 0.9$) and hard stools (7% vs 13%, $P = 0.58$). There were more patients with side effects in the lactulose group (15 vs 23, $P = 0.02$), mostly bloating and abdominal pain. In the treatment of constipation in babies and children, the usage of PEG 3350 is superior to that of lactulose since it is more effective and has fewer adverse effects.

Summeren, et al (2020)[10] conducted a study with 134 patients. The addition of physiotherapy to conventional treatment did not result in a statistically significant increase in treatment efficacy (adjusted relative risk [aRR] = 0.80, 95% confidence interval [CI] = 0.44-1.20). At 4 months, fewer children receiving physiotherapy (17%) had treatment success than those receiving conventional treatment alone (28%), but by 8 months, the proportions were equivalent (42% and 42%, respectively). The percentage of children without functional constipation was not statistically different between groups after 8 months, regardless of continued laxative use (aRR = 1.12, 95% CI = 0.82-2.1). Notably, parents reported a substantially greater relief in global symptoms after physiotherapy than after conventional treatment (aRR = 1.40; 95% CI = 1.00-1.70).

In study 1 by Benninga, et al (2022)[11], 606 patients were randomly assigned to treatment (placebo: n = 202; lubiprostone: n = 404). In terms of the aggregate SBM response rate, there was no statistically significant difference between the lubiprostone and placebo groups (P =.2245). In the double-blind and extension phases, both the 12-g BID and 24-g BID concentrations of lubiprostone were well tolerated, with a safety profile consistent with that observed in adult studies.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Therapetic Agent	Conclusion
Kubota, 2020[8]	Japan	Prospective, double-blind, placebo-controlled, randomized, and parallel-group trial	Sixty patients who were more than six months old and under six years of age with a diagnosis of functional constipation according to Rome IV	Group A (n = 20) received L. reuteri DSM 17938 and lactose hydrate as a placebo of magnesium oxide (MgO); group B (n = 19) received L. reuteri DSM 17938 and MgO; and group C (n = 21) received a placebo of L. reuteri DSM 17938 and MgO	Both L. rueteri DSM 17938 and MgO proved to be useful in the treatment of functional constipation in younger patients. MgO led to an imbalance in the microbiota of the gastrointestinal tract, which was not the case in the group that received probiotics.
Jarzebicka, 2019[9]	Poland	Randomized, multicenter study	102 patients	Polyethylene glycol 3350 (PEG) or lactulose	In the treatment of constipation in babies and children, the usage of PEG 3350 is superior to that of lactulose since it is more effective and has fewer adverse effects.
Summeren, 2020[10]	Netherland	Pragmatic randomized controlled trial	134 patients	Treatment plus physiotherapy or conventional treatment alone	They were unable to locate any evidence that would lead us to recommend PT for all children in

					primary care who have functional constipation.
Benninga, 2022[11]	Netherland	Phase 3, multicenter, randomized, double-blind, placebo-controlled	606 patients	Placebo and lubiprostone	In children and adolescents with PFC, lubiprostone did not provide statistically significant benefit over the placebo, but it did demonstrate a safety profile that was comparable to that in adults.
Xiao, 2021[12]	China	Multicenter, randomized, double-blind, placebo-controlled study	259 patients	Placebo and lubiprostone	In Chinese individuals diagnosed with functional constipation, the treatment with lubiprostone was more effective than the placebo while maintaining a favorable safety profile.
Sanctuary, 2019[13]	United States of America (USA)	Double-blind, crossover, randomized clinical trial (RCT)	11 patients	BCP only or the combination (BCP + Bifidobacterium infantis)	This group tolerates the combined therapy well. Gassiness was most prevalent. Both therapies decreased GI discomfort and abnormal behaviors in some patients. IL-13 and TNF-α decrease in certain subjects may explain improvement. This short pilot study suggests that these therapies need more exploration.
Wegner, 2018[14]	Poland	Double-blind, crossover, randomized clinical trial (RCT)	121 patients	Lactobacillus reuteri DSM 17938	In children aged 3-7 years old with functional constipation, the inclusion of L. reuteri DSM 17938 as an extra therapy to macrogol did not have any positive effect on the treatment of the condition.

Other study with lubiprostone showed the lubiprostone group had more SBMs (4.88 ± 4.09/wk) than the control group (3.22 ± 2.01/wk) (P <0.0001) at week 1. At weeks 2, 3, and 4, there were more SBMs in the lubiprostone group. At each week, the lubiprostone group had a significantly higher average amount of CSBMs and a higher regularity score than the placebo group. No major side effects (AEs) were caused by the drug. Most of the time, people felt sick.[12]

Sanctuary, et al (2019)[13] findings, this group appears to have a favorable response to the combined therapy. The most prevalent adverse effect was a sensation of having moderate gas. Certain patients who received either one of the therapies reported a decrease in the occurrence of specified aberrant behaviors, as well as a reduction in the frequency of particular gastrointestinal symptoms. One possible explanation for the improvement is that some of the participants' IL-13 and TNF-α production has decreased. Although only a few generalizations can be made based on the findings of this brief pilot study, they lend credence to the idea that more research into the effectiveness of these treatmentss is required.

Wegner, et al (2018) showed no statistically significant difference in the number of gastrointestinal movements per week in week 8 between the study group and the placebo group (7.53.3 vs. 6.92.5, respectively). In addition, there were no significant differences in the number of patients who complained of pain during defecation (13/47 vs 8/53), abdominal pain (19/41 vs 25/36), withholding stools (15/45 vs 13/48), passing hard stools (7/53 vs 3/58) or large stools (14/46 vs 12/49) or faecal incontinence (17/43 vs 11/50).[14]

DISCUSSION

Constipation has several causes. Diet, lifestyle, genetics, exercise, and other variables affect defecation frequency and composition and the human microbiota in complicated ways. Study showed probiotic-laxative treatment had no additive benefit. MgO increases serum magnesium, but probiotics modify the microbiota. Probiotics' effects on chronic constipation need to be examined in larger trials.[15] The contribution of Clostridia, Enterobacteriacea, and Bifidobacterium species is greater than that of bacteroides and Escherichia coli in the intestinal flora of children with constipation.[14]

Probiotics have the potential to enhance the equilibrium between species, influence intestinal motility by producing lactic acid and short-chain amino acids, and stimulate gut peristalsis by altering stool pH. Numerous studies have been conducted on a variety of probiotic strains. However, there are currently insufficient data to support the use of probiotics in children with chronic constipation. On the other hand, Lactobacillus reuteri DSM 17938 has been shown to alleviate constipation symptoms in neonates, children, and adults with functional gastrointestinal disorders, including constipation.[14]

There is no consensus on whether gut bacteria are healthy or ill, but there is agreement on which traits are good or bad. Low-diversity microbiota may lack "keystone" bacteria or microbial genes essential for ecosystem health. The gut microbiota's resilience is linked to the variety of beneficial bacteria.[16] In dysbiosis, one or more dangerous microorganisms prevail in the gastrointestinal system, whereas in the gut microbiota, helpful microbes predominate. Most intestinal commensals have unknown health effects, although some are useful and some are detrimental.[17]

Lactobacillus and Bifidobacterium are helpful microorganisms. Probiotics—"live microorganisms which, when administered in adequate amounts, confer a health benefit on the host"—are found in this genus. This genus is the only

one traditionally considered helpful bacteria in the prebiotic notion of selectively stimulating Lactobacillus and Bifidobacterium growth for health. This genus' strains boost immunity, improve digestion, inhibit pathogen colonization, and alter GI physiology. Eubacterium, Roseburia, and Faecalibacterium species are now considered beneficial microorganisms. These taxa generate SCFA butyrate, which reduces inflammation, oxidative stress, and gut barrier damage.[17]

Prebiotics are non-digestible short-chain carbohydrates that influence the growth and activity of the gut microbiota. Several studies have demonstrated the beneficial effects of oligosaccharide supplementation in infant formula. However, the available evidence is too low to recommend prebiotics for the treatment of bowel disorders in infants. So far there are no RCTs in children over one year old. Current treatment guidelines from the North American and European pediatric gastroenterology groups do not recommend the use of probiotics or prebiotics in children with functional constipation.[18]

Probiotic and osmotic laxative groups had more constipated children defecate than baseline. In the laxative group, stool consistency reduced dramatically, but not in the probiotic group. The combination of probiotics and osmotic laxative also improved stool consistency and frequency, although not synergistically. Probiotics are seldom used to treat constipation in children, although they modify the intestinal flora and increase intestinal motility, reducing transit time.[19,20] Kubota, et al (2020)[8] found that probiotics can enhance stool frequency but not consistency. This trial provided L. reuteri DSM 17938 twice a day for four weeks.

Osmotic laxative MgO is used to relieve constipation in all ages. MgO therapy daily increased blood magnesium concentration, but no clinical side effects have been documented in children. MgO would improve stool consistency and L. reuteri DSM17938 would promote defecation. MgO enhanced stool consistency and both affected defecation frequency. L. reuteri DSM 17938 treats breastfed infantile colic better than other therapies.[21] Fecal microbiota transplantation (FMT) may be a potential therapy for slow-transit constipation. Conventional therapy (education, behavioral methods, and oral laxatives) alone was compared to FMT in a randomized controlled experiment.[22]

Chronic constipation is common and resistant to lifestyle changes and over-the-counter medications. Prescription drugs are restricted, especially after tegaserod was removed off the market. Study Lubiprostone did not significantly improve PFC in children and adolescents, although it had a similar safety profile to adults. Lubiprostone specifically activates epithelial type 2 chloride channels to efflux chloride into the intestinal lumen. Fluid release into the gastrointestinal lumen softens stool, speeds intestinal transit, and relieves constipation. Lubiprostone is quickly digested and has poor systemic bioavailability.[11]

Fiber supplementation increases defecation in functional constipation patients, according to meta-analyses. However, treatment success was unaffected. However, children with functional constipation should follow age- and weight-appropriate fluid and fiber consumption. Several RCTs in pediatric functional constipation compare probiotics to placebo or osmotically active drugs as lactulose or PEG.[18] Fiber might also relieve constipation. Water retention and flora maintenance improve colonic microbiota. Dietary fiber affects feces type. High-soluble fiber foods ferment and enhance bacterial flora, whereas high-insoluble meals retain liquids and cause bulkier stools.[23]

CONCLUSION

It is essential to test and diagnose children as soon as possible for FC, which is considered a substantial burden of illness in children. According to research, treating children with probiotics is not only beneficial but also safe for the symptoms of functional constipation.

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