The role of a probiotics mixture in the treatment of childhood constipation

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ABSTRACT

Background

Inconsistent data exist about the efficacy of probiotics in the treatment of constipation. Several studies in adults with constipation showed positive effects of probiotics on constipation. Only one study evaluated the effect of probiotics in constipated children and showed that lactobacillus GG was not an effective adjunct to lactulose. The aim of this pilot study was to determine the effect of a mixture of bifidobacteria and lactobacilli in the treatment of childhood constipation.

Methods

Children aged 4-16 years with constipation as defined by the Rome III criteria were eligible for the study. During a 4 week period, children received a daily mix of $4x10^9$ colony forming units of a probiotic mixture (*Ecologic® Relief*) containing Bifidobacteria (B.) bifidum, B. infantis, B. longum, Lactobacilli (L.) casei, L. plantarum and L. rhamnosus**.** Primary outcome measures were frequency of bowel movements (BMs) per week and stool consistency. Secondary outcome measures were number of faecal incontinence episodes per week, abdominal pain and side effects.

Results

Twenty children, 50% male, median age 8 (range 4-16) were included.
The frequency of BMs per week increased from 2.0 (1.0-5.0) to 4.2 (0.0-16.0) in week 2 (p=0.10) and 3.8 (2.1-7.0) in week 4 (p=0.13). In 12 children presenting with <3 BMs/ week, BMs per week increased significantly from 1.0 (0.0-2.0) to 3.0 (0.0-7.0) in week 2 (p=0.01) and 3.0 (0.0-10.0) in week 4 (p=0.01). The stool consistency was reported as hard in 7 children at baseline, in 4 children at week 2 (p=0.23) and in 6 children after 4 weeks of treatment (p=1.00). A significant decrease in number of faecal incontinence episodes per week was found in the entire group: 4.0 (0.0-35.0) to 1.5 (0.0-14.0) in week 2 (p=0.01) and 0.3 (0.0-7.0) in week 4 (p=0.001). The presence of abdominal pain decreased significantly from 45% to 25% in week 2 (p=0.04) and 20% at week 4 (p=0.006). No side effects were reported.

Conclusion

This pilot study shows that a mixture of probiotics, has positive effects on symptoms of constipation. To confirm these findings, a large randomised placebo controlled trial is required.

Introduction

Functional constipation is a common and frustrating phenomenon in children. The prevalence of childhood constipation in the western world is 1-30%. (1) No organic cause is found in 90% to 95% of those constipated children. (2) This functional defecation disorder is characterized by infrequent defecation less than three times per week, more than two episodes of faecal incontinence per week, the passage of large and painful stools which clog the toilet and retentive posturing. Upon physical examination a palpable faecal mass is often found in the abdomen and the rectum. (3, 4)

Childhood constipation is usually treated with a combination of toilet training, a bowel diary and oral laxatives such as lactulose or polyethylene glycol (PEG). Laxatives aim to soften the stools, thereby contributing to a break-through of the vicious circle of defecation avoidance caused by pain during defecation. Only 60% of constipated children accomplish successful treatment with laxatives.(5) It is clear that development of other treatment options is still required.

There is growing interest in the use of probiotics in organic and functional gastrointestinal disorders. Probiotics are live microbial food ingredients which are reported to be effective in the treatment of IBD, travellers diarrhoea and constipation. (6-8) Colonic microflora influence the peristalsis of the colon. (9) Therefore, imbalance in the colonic microflora has been suggested to play a role in gastro-intestinal diseases such as constipation. Probiotics, such as Bifidobacteria (B.) and lactobacilli (L.), both produce lactic, acetic and other acids resulting in a lowering of pH in the colon. A lower pH enhances peristalsis of the colon and subsequently decreases colonic transit time which is beneficial in the treatment of constipation. (9, 10)

To date, several studies have been performed, mainly in adults, in order to determine the effects on constipation symptoms when probiotics are supplemented in feeding. (9-14) It has been shown that several probiotic strains, such as *L. shirota* and the *B. animalis*, increase defecation frequency and soften stools in constipated adults. (11) When B. *animalis* was supplemented a decrease in colonic transit time has been shown even in healthy adults. (12) Furthermore, *L. rhamnosus* has been described to decrease abdominal pain, flatulence, distension and borborygmi symptoms in IBS patients. (15)

In healthy children, bifidobacteria *(B.)* b*ifidus*, *B*. i*nfantis* and *B.* l*ongum,* are commonly found in the faeces. (16). Although reduced quantities of bifidobacteria have never been found in constipated children, due to their

consequence on peristalsis we would expect a positive effect on constipation when they are supplemented to feeding. In constipated children however, only one study on probiotics has been performed. This study showed that the probiotic strain *Lactobacillus GG* did not have an additional positive effect on constipation symptoms, when used as an adjunctive therapy with lactulose. (13) One study described more increase in defecation frequency in constipated elderly when two different lactobacilli (*L. Casei* and L. *Plantarum)* strains rather than one strain were supplemented. (17) The use of a combination of different probiotic strains as therapy for childhood constipation, nevertheless, has not been studied yet. We hypothesized that a combination of several strains of bifidobacteria and lactobacilli would be effective in the treatment of childhood constipation. In a pilot study, we aimed to determine the therapeutical effect of a combination of probiotics strains, containing the bifidobacteria *B. bifidus*, *B*. *infantis* and *B. longum and the lactobacilli L. casei, L. plantarum* and *L. rhamnosus,* on childhood constipation.

Methods

Subjects:

Children between 4 to 16 years of age referred to the outpatient clinic of the Emma Children's Hospital in Amsterdam, the Netherlands, with constipation were eligible for study entry. Childhood constipation was defined by the Rome III criteria as having at least 2 out of 6 of the following symptoms: bowel movements <3 times/ week; faecal incontinence >2 times/ week; large amounts of stools obstructing the toilet once in 10 days; painful defecation; withholding behaviour; palpable abdominal or rectal mass on physical examination. (4) Exclusion criteria were the use of any oral laxative < 4 weeks before intake, mental retardation, metabolic disease, functional non-retentive incontinence, and a history of gastro-intestinal surgery. All children older than 12 years and/or parents gave informed consent. This pilot was approved by the medical ethical committee of the Academic Medical Centre of Amsterdam.

Study design:

Seven days prior to baseline assessment and during the treatment period all children recorded frequency of bowel movements, the number of faecal incontinence episodes, stool consistency, abdominal pain, flatulence and pain

during defecation as well as adverse effects such as vomiting and diarrhoea in a standardized bowel diary.
At baseline assessment, a medical history and information on the current defection pattern was collected. Additionally, a physical examination including a rectal digital exam was performed to assess whether an abdominal or rectal faecal mass was present.
Before start of the probiotics treatment, all children received once daily for 3 days a rectal enema (Klyx: sodium-dioctylsulfosuccinate and sorbitol) in order to accomplish rectal disimpaction. After rectal disimpaction, children were administrated a daily probiotics mixture of 4 x 10^9 colony forming units (CFU), containing *Bifidobacteria (B.) bifidum, B. infantis, B. longum, Lactobacilli (L.) casei, L. plantarum* and *L. rhamnosus* (*Ecologic® Relief, Winclove Bio Industries BV, The Netherlands*) for 4 weeks. During the treatment period children were instructed to start toilet training. Toilet training consists of sitting on the toilet 3 times per day for 5 minutes after each meal with the intention of trying to defecate.
Evaluation was conducted during visits to the outpatient clinic at 2 and 4 weeks after start of treatment. During each visit the physician assessed the patient's daily bowel diary and examined the child.

Outcome measures:
Primary outcome measures were frequency of bowel movements per week and stool consistency. Secondary outcome measures were number of faecal incontinence episodes per week, presence of abdominal pain and incidence of adverse effects such as vomiting and diarrhoea.

Analysis

Descriptive statistical measures were calculated for baseline characteristics using SPSS version 12.0.1 statistical software (SPSS Inc, Chicago, Ill). Change of frequency of bowel movements and faecal incontinence was assessed using the non-parametric paired Wilcoxon test. For the analysis of change of hard stools, the Mc Nemar test was used. For the comparison of abdominal pain between baseline and the evaluation time points, the Wilcoxon rank test was used. All continuous values were expressed as median (range). A p- value < 0.05 was considered significant.

Results

Between February 2006 and July 2006, 20 children were enrolled into this pilot study and all patients completed the study. Baseline characteristics are summarized in table 1. Onset of constipation symptoms appeared in 31% of the children before the age of 12 months. In 85% of the children, onset of constipation symptoms was between 0 to 4 years of age.

The frequency of bowel movements (BMs) per week increased from 2.0 (1.0-5.0) to 4.2 (0.0-16.0) in week 2 (p=0.10) and 3.8 (2.1-7.0) in week 4 (p=0.13) (figure 1). In 12 children presenting with <3 BMs per week, BMs per week increased significantly from 1.0 (0.0-2.0) to 3.0 (0.0-7.0) in week 2 (p=0.01) and 3.0 (0.0-10.0) in week 4 (p=0.009) (figure 2).

The stool consistency was reported as hard in 7 children at baseline, in 4 children at week 2 (p=0.23) and in 6 children at week 4 (p=1.00). At week 4, hard stools appeared in 5 children who also had hard stools at baseline. One child with normal stools at baseline, reported hard stools only at the end of the study. Two of the 7 children who presented with hard stools, reported normal stools at the end of the study.

The number of faecal incontinence episodes per week decreased significantly from 4.0 (0.0-35.0) to 1.5 (0.0-14.0) in week 2 (p=0.007) and 0.3 (0.0-7.0) in week 4 (p=0.001) (figure 3).

The presence of abdominal pain decreased significantly from 45% (n=9) to 25% (n=5) in week 2 (p=0.04) and 20% (n=4) at week 4 (p=0.006). There were no side effects such as vomiting, bloating and increased flatulence during the study period.

Figure 1. Bowel movements per week in the overall group at baseline, week 2 and week 4. Increase in bowel movements frequency was not significant (*p=0.10;**p=0.13) compared to baseline.

Figure 2. Bowel movements per week in children presenting with <3 BMs/ week at baseline, week 2 and week 4. The frequency of bowel movements increased significantly in both periods compared to baseline (*p= 0.01;**p=0.009).

Figure 3. Number of faecal incontinence episodes per week in the overall group at baseline, week 2 and week 4. The decrease in number of faecal incontinence episodes decreased significantly in both periods (*p=0.007;**p=0.001) compared to baseline.

Discussion

This pilot study showed that a probiotics mixture containing different strains of bifidobacteria and lactobacilli, increases the frequency of bowel movements in constipated children presenting with a defecation frequency of less than 3 times per week. This probiotic mixture was also effective in decreasing the number of faecal incontinence episodes and in reducing the presence of abdominal pain. No significant changes in stool consistency were found.

Given their safety profile, probiotics could be an attractive compound to manipulate gastrointestinal motility in constipated children. However, mechanisms underlying enhancement of gastrointestinal transit are not yet unravelled. The current hypothesis is that bifidobacteria and lactobacilli produce lactic, acetic and other acids resulting in a lowering of pH in the colon. The effect of a lower pH is the enhancement of peristalsis of the colon, subsequently leading to a decrease in colonic transit time. (9, 10)

In this study, we found that administration of a mixture of probiotics had a positive effect on frequency of bowel movements and consequently leading to a decrease in faecal incontinence episodes. In contrast to our findings, Banaszkiewicz showed no additional effect of *lactobacillus GG* (*LGG*) to placebo in children with constipation who were all treated with lactulose. The lack of an additional effect of *LGG* can not be explained by the latter study, as lactulose itself reaches its therapeutic effect through fermentation by colonic bacteria leading to a lower pH and subsequently enhancing peristalsis identically to probiotics like *LGG*. (18)

Recent studies in healthy adults showed that the strain *B. animalis DN-173 010* shortens total colonic and sigmoid transit time. (12, 14) The decrease in transit time in these studies could not be explained by a change in faecal weight, bacterial mass or faecal excretion of secondary bile salts. In the majority of children with constipation a significant delay in sigmoid transit time is found. (19) Since the *B. animalis DN-173 010* decreases sigmoid transit time, this strain may be beneficial for this group of constipated children.

It has been assumed that probiotics soften the stools by stimulating water and electrolyte secretion. (20-22) However, we were not able to show a significant softening of stools after 4 weeks of treatment. As only a minority of children (35%) had hard stools at baseline, it is necessary to investigate whether probiotics have a positive effect on hard stools in a larger randomised controlled trial.

A significant decrease in abdominal pain was found after 4 weeks of treatment with the probiotics mixture. This is in accordance with several studies

performed in adult irritable bowel syndrome (IBS) patients with abdominal pain/discomfort, distension/ bloating and difficult defecation. (23, 24) A recent randomized placebo controlled trial conducted in 360 women with IBS showed that the strain *B. infantis* was associated with significant improvement of both abdominal pain and the subjects' global assessment of symptoms. (25) This positive effect on abdominal pain occurred irrespective of any effect on stool frequency which indicates that the observed effect was not attributable to either a laxative or anti-diarrhoeal effect. It has been suggested previously that abdominal pain and bloating may decrease as a consequence act of probiotics diminishing visceral hypersensitivity by its anti-inflammatory effect on the enteric mucosa. (26)

No side effects of the probiotics were found in our study. This is in accordance with literature about the safety of probiotics. (27, 27)The safe use of especially bifidobacteria is supported due to the long historical consumption of fermented milk and growing knowledge about bifidobacteria taxonomy and physiology. Furthermore, studies performed with lactobacilli and bifidobacteria showed to be well tolerated in adults and children.(6, 13, 27-29)

The interpretation of clinical trials of probiotic strains in functional gastrointestinal disorders is complicated by several factors. Results between studies are difficult to compare due to differences in endpoints, variations in probiotics dose and strains. Whereas one group uses mixtures of probiotics, others use single isolates, making it difficult to determine what were the active moieties. (15, 30) Nonetheless, a recent review suggested that overall, sufficient evidence is available to warrant further evaluation. (31)

In conclusion, this non randomized non placebo controlled pilot study evaluating the effect of a mixture of probiotics, showed beneficial effects on symptoms of constipation and a decrease of abdominal pain. Therefore a randomised placebo controlled trial is now required to confirm these data.

Table 1.

Baseline characteristics	
Number of subjects	20
Age in years	8 (4-16)
Sex (male)	10
Time of constipation before intake (years)	3.5 (0.3-6.5)
Treatment time before intake (months)	12 (0-48)
Bowel habits, n (%)	
• Bowel movements < 3 / week	12 (60%)
• Faecal incontinence ≤ 2/ week	1 (5%)
• Faecal incontinence > 2/ week	15 (80%)
• Large amounts of stools	12 (60%)
Stool consistency, n (%)	
• Hard stools	7 (35%)
• Normal stools	10 (50%)
• Soft stools	3 (15%)
Painful defecation, n (%)	
• No pain	7 (35%)
• Sometimes painful	7 (35%)
• Always painful	6 (30%)
Abdominal pain, n (%)	
• No abdominal pain	3 (15%)
• Sometimes abdominal pain	8 (40%)
• Often abdominal pain	9 (45%)
Physical examination, n (%)	
• Abdominal scybala	4 (20%)
• Rectal scybala	4 (20%)
• Anal Fissures	0

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Figure 1

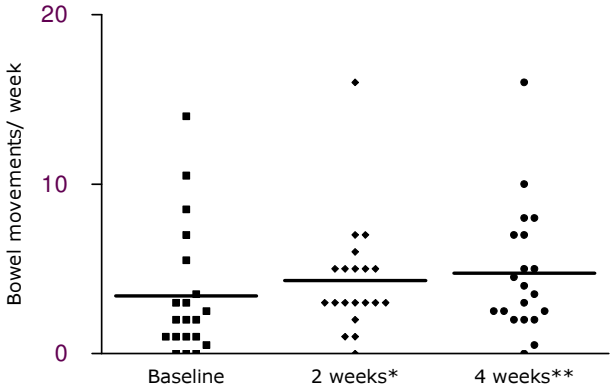


Figure 2

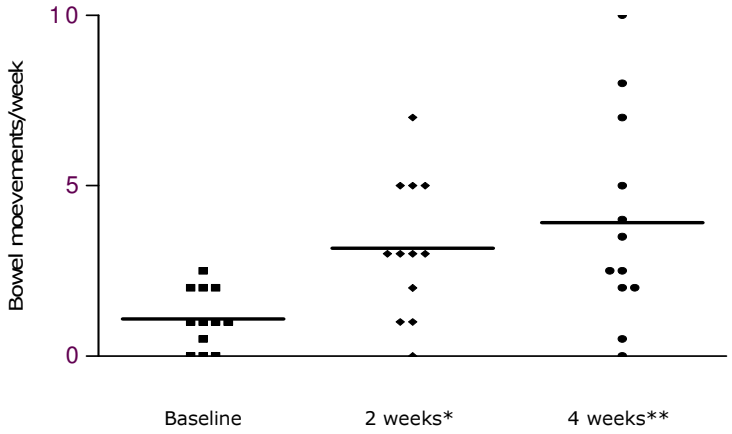
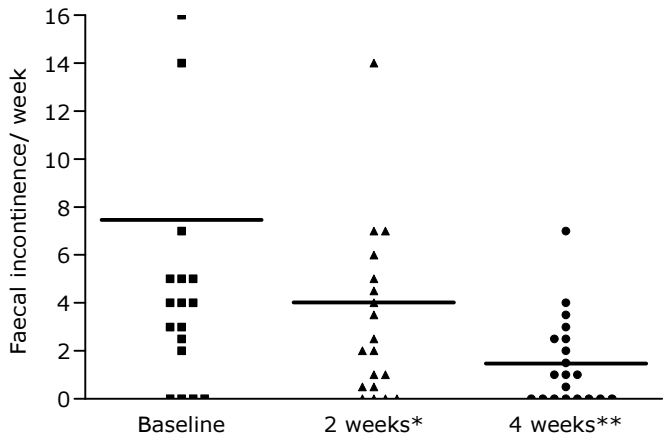


Figure 3


Faecal incontinence/ week
16
14
12
10
8
6
4
2
0
Baseline
2 weeks*
4 weeks**