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Is Bifidobacterium breve effective in the treatment of childhood constipation? Results from a pilot study

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Abstract

Background
Probiotics are increasingly used in the treatment of functional gastrointestinal disorders. Studies in constipated adults with a Bifidus yoghurt (containing *Bifidobacterium breve*, *Bifidobacterium bifidum* and *Lactobacillus acidophilus*) showed a significant increase in defecation frequency. The aim of this pilot study was to determine if *Bifidobacterium breve* is effective in the treatment of childhood constipation.

Methods
Children, 3 to 16 years of age, with functional constipation according to the Rome III criteria were eligible for this study. During 4 weeks, children received one sachet of powder daily, containing $10^8$-$10^{10}$ CFU *Bifidobacterium breve*. The primary outcome measure was change in defecation frequency. Secondary outcome measures were stool consistency, frequency of episodes of faecal incontinence, pain during defecation, frequency of abdominal pain, frequency of adverse effects (nausea, diarrhea and bad taste), and frequency of intake of bisacodyl.

Results
Twenty children (75 % male, mean age 7.4) were included in this pilot study. The defecation frequency per week significantly increased from 0.9 (0-2) at baseline to 4.9 (0-21) in week 4 (p < 0.01). The mean stool consistency score increased from 2.6 (2-4) at baseline to 3.5 (1-6) in week 4 (p = 0.03). The episodes of faecal incontinence per week significantly decreased from 9.0 (0-35) at baseline to 1.5 (0-7) in week 4 (p <0.01). Pain during defecation decreased from 71% (12/17) at baseline to 33% (6/18) in week 4 (p = 0.08). Abdominal pain episodes per week significantly decreased from 4.2 (0-7) at baseline to 1.9 (0-7) in week 4 (p = 0.01). No side effects occurred.

Conclusion
*Bifidobacterium breve* is effective in increasing stool frequency in children with functional constipation. Furthermore it has a positive effect with respect to stool consistency, decreasing the frequency of episodes of faecal incontinence and in diminishing abdominal pain. A randomised placebo controlled trial is required to confirm these data.
Background

Functional constipation is a common and frustrating problem in childhood with an estimated prevalence of 3% in the western world.[1] This chronic condition 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.[2,3] It causes distress to child and family and results in severe emotional disturbance and family discord.[4] The pathophysiology underlying functional constipation is undoubtedly multi-factorial, and not well understood. Withholding behaviour is probably the major cause for the development of constipation and might be caused by the previous production of a large, hard painful stool, anal fissures, a primarily behavioural mechanism or the resistance to go to another toilet than their own.[4] To date, patients are treated with a combination of education, toilet training and oral laxatives. Disappointingly, only 50% of all children followed for 6 to 12 months are found to recover and were successfully taken off laxatives.[5] Another study showed that despite intensive medical and behavioural therapy, 25% of patients who developed constipation before the age of 5 years continued to have severe complaints of constipation, infrequent painful defecation and faecal incontinence, beyond puberty.[6] Furthermore, in 50% of the patients using these compounds, adverse side-effects were registered such as: abdominal pain, bloating, flatulence, diarrhea, nausea and bad taste.[7] No data exist concerning possible long-term adverse effects such as electrolyte disturbances, mucosal damage and habituation. Based on these data, developing new treatment strategies are of great importance for this specific disorder.

The use of probiotics has entered mainstream medicine. Probiotics are defined as live micro-organisms which when administered in adequate amounts confer a health benefit on the host.[8] The exact working mechanisms of probiotics are not well understood. However, there are some hypotheses why probiotics might have therapeutic potential for the treatment of constipation. Firstly, a dysbiosis in the gut flora in constipated patients has been suggested which might improve after the ingestion of probiotics. However, it remains important to understand if dysbiosis is a secondary manifestation of constipation, or if it is a factor contributing to constipation. Furthermore, probiotics can lower pH of the colon by producing lactic, acetic and other short chain fatty acids. A lower pH enhances colonic peristalsis and subsequently decreases colonic transit time.[9,10]

Probiotics are increasingly used for functional gastrointestinal disorders like constipation and functional abdominal pain.[11] However, there is a lack of trials investigating the efficacy and safety of probiotics in paediatric patients.[12] In our centre, a pilot study showed that mixture of probiotics (containing Bifidobacteria (B.) bifidum, B. infantis, B. longum, Lactobacillus (L.) casei, L. plantarum and L. rhamnosus), had positive effects on symptoms of constipation like number of bowel movements, consistency of stools and number of episodes of faecal incontinence.[13] Studies in constipated adults with Bifidus yoghurt (containing
Bifidobacterium breve, Bifidobacterium bifidum and Lactobacillus acidophilus) showed a significant increase in defecation frequency without any side effects.[14,15] Furthermore, a randomised controlled trial using Bifidobacterium breve in preterm infants showed no side effects and fewer abnormal abdominal signs like gas accumulation in the stomach, and less vomiting and improved weight gain.[16] So, further studies are needed to elucidate the role of different probiotic strains like Bifidobacteria in the treatment of constipated children. Therefore, we have performed a pilot study to determine if Bifidobacterium breve is effective in the treatment of childhood constipation.

**Methods**

**Subjects**
Children, 3 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 this study. Patients were included if they had been suffering from functional constipation according to the Rome III criteria for the last 2 months.[2,3] All children included had a defecation frequency of <3 times/week and one or more of the following criteria: faecal incontinence >1 episode/week, a large amount of stools that clog the toilet, painful defecation, withholding behaviour, or abdominal or rectal faecal impaction upon physical examination. Patients were not enrolled in this study if they had been treated for constipation less than 2 weeks before the start of the study. Other exclusion criteria were: a diagnosis of either IBS or functional non-retentive faecal incontinence according to the Rome III criteria; a diagnosis of mental retardation or metabolic disease (hypothyroidism), Hirschsprung’s disease, spinal anomalies, anorectal pathology, previous gastrointestinal 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, stool consistency according to the Bristol stool scale, the number of faecal incontinence episodes, pain during defecation, abdominal pain, as well as adverse effects such as vomiting and diarrhea in a standardized bowel diary. At baseline a medical history and information on the current defecation pattern was collected and also a physical examination including a rectal digital exam was performed. Before start of the probiotic treatment, all children received once daily for 3 days a rectal enema in order to accomplish rectal disimpaction. After rectal disimpaction, all children received daily one sachet of powder containing $10^8-10^{10}$ CFU Bifidobacterium breve Yakult, for 4 weeks. The patients were allowed to mix the powder with all liquids on condition that the liquid was
not hot. During the study, all children were instructed to try to defecate on the toilet for 5-10 minutes after each meal (3 times a day). Patients were not allowed to consume any other fermented dairy product during this study or any other laxatives, except for the rescue medication Biscaodyl. During the product consumption period, patients were instructed to take bisacodyl 5 mg if they did not defecate for 3 consecutive days. Clinical evaluation and assessment of diaries were carried out at enrolment and at 2, 4 and 6 weeks.

**Outcome measures**

The primary outcome measure was change in defecation frequency in week 4 compared to baseline. Secondary outcome measures were stool consistency, frequency of episodes of faecal incontinence, pain during defecation, frequency of abdominal pain, frequency of adverse effects (nausea, diarrhea and bad taste), and frequency of intake of bisacodyl.

**Analysis**

Descriptive statistics were performed for baseline characteristics, adverse effects and Bisacodyl use. Change of frequency of bowel movements and faecal incontinence was assessed using the non-parametric paired Wilcoxon test. For the analysis of change of stool consistency, the McNemar test was used. For the comparison of abdominal pain between baseline and the evaluation time points, the Wilcoxon rank test was used. A p-value < 0.05 was considered to be significant. All analyses were done with SPSS (version 16.0).

**Results**

Between July 2009 and January 2010, 22 children were included into this pilot study. Two children were lost to follow-up without having any outcome data during follow-up. Both patients were therefore excluded from the final analysis. The baseline characteristics are described in Table 1 (mean (range))

The defecation frequency per week significantly increased from 0.9 (0-2) at baseline to 5.3 (0-21) in week 2 (p < 0.01) and 4.9 (0-21) in week 4 (p< 0.01) (figure 1: Defecation frequency

| Table 1. Baseline patient characteristics: mean (range) |
|-------------------------------------------------------|
| Age in years                                          | 7.4 (4-13) |
| Boys, n (%)                                           | 15 (75%)   |
| Mean stool frequency per week                         | 0.9 (0-2)  |
| Stool consistency score                               | 2.6 (2-4)  |
| Faecal incontinence episodes per week                 | 9 (0-35)   |
| Pain during defecation                                | 71% (12/17) |
| Abdominal pain episodes per week                      | 4.2 (0-7)  |
Table 2. Main outcome measures (mean) with p-values

| Outcome                             | At baseline | Week 2 | Week 4 | P-value (week 4-week 0) |
|-------------------------------------|-------------|--------|--------|-------------------------|
| Defecation frequency p/week         | 0.9         | 5.3    | 4.9    | p<0.01                  |
| Stool consistency score             | 2.6         | 3.6    | 3.5    | p = 0.03                |
| Episodes of faecal incontinence p/week | 9.0       | 2.6    | 1.5    | p <0.01                 |
| Pain during defecation              | 71%         | 40%    | 33%    | p = 0.08                |
| Abdominal pain episodes p/week       | 4.2         | 2.2    | 1.9    | p = 0.01                |

over 4 weeks.). The mean stool consistency score significantly increased from 2.6 (2-4) at baseline to 3.6 (1-6) in week 2 (p=0.07) and 3.5 (1-6) in week 4 (p = 0.03). The episodes of faecal incontinence per week significantly decreased from 9.0 (0-35) at baseline to 2.6 (0-7) in week 2 (p=0.01) and 1.5 (0-7) in week 4 (p <0.01). Pain during defecation decreased from 71% (12/17) at baseline to 40% (8/20) in week 2 (p=0.10) and 33% (6/18) in week 4 (p = 0.08). Abdominal pain episodes per week significantly decreased from 4.2 (0-7) at baseline to 2.2 (0-7) in week 2 (p=0.02) and 1.9 (0-7) in week 4 (p = 0.01). Bisacodyl was used by 45% of patients during week 1, 25% of patients during week 2, 35% of patients during week 3 and by 20% of patients during week 4. No side effects were reported such as nausea, diarrhea and bad taste or increased flatulence during the study period. Table 2 gives an overview of the outcome measures with p-values.

**Discussion**

This pilot study showed that intake of *Bifidobacterium breve* for 4 weeks, significantly increased the defecation frequency. Furthermore, stool consistency, the frequency of
episodes of faecal incontinence and the frequency of abdominal pain significantly changed in favour of probiotics. A recent systematic review on the effects of laxative treatment and dietary measures in the management of childhood constipation found only 2 randomised controlled trials that evaluated the effects of probiotics.[17] In the first small study, 45 children younger than 10 years with chronic constipation were randomly assigned to receive magnesium oxide (50 mg/kg/day (n=18), or 8 x 108 cfu/day of the probiotic Lactobacillus casei rhamnosus (n = 18), or placebo (n = 9) twice daily for 4 weeks [18]. No statistically significant difference in the defecation frequency per day was found between the probiotic group and the magnesium oxide group. However, patients receiving either the probiotic strain or the oral laxative had a significantly higher defecation frequency compared to the placebo group (defecation frequency [times/day 0.57±0.17 and 0.55±0.13, respectively, compared to 0.37±0.10, P=0.03). The second trial was conducted to determine if Lactobacillus rhamnosus GG (LGG) is an effective adjunct to lactulose for treating constipation in children. A total of 48 children with constipation received 1 ml/kg/day of 70% lactulose plus 10^9 cfu of LGG or 1 ml/kg/day of 70% lactulose plus placebo, twice daily for 12 weeks [12]. There were no significant differences in rates of product success (defined as ≥ 3 spontaneous stools per week with no faecal incontinence) at 12 and 24 weeks between the LGG group (rates: 72% and 64%, respectively) and the placebo group (rates: 68% and 65%, respectively). In a recent trial, 44 children, at least 6 months old, with chronic constipation were randomly assigned to receive supplementation with the probiotic Lactobacillus reuteri (DSM 17938) (n=22) or placebo (n=22).[19] Infants receiving Lactobacillus reuteri had a significantly higher frequency of bowel movements than infants receiving a placebo at week 8 of supplementation (2.82 per week at week 0, compared with 4.77 at week 8 in the probiotic group, absolute numbers not given for placebo group, P = 0.027). There was no significant difference between Lactobacillus reuteri and placebo groups in the stool consistency at all weeks nor in the presence of inconsolable crying episodes. All three trials did not report any adverse events in the probiotic group.

In contrast to the few paediatric studies, data suggest that adults with constipation might benefit from ingestion of B. lactis DN-173 010, L. casei Shirota, and E. coli Nissle 1917. All studies showed an increased defecation frequency and improved stool consistency.[20] These findings, however are not directly applicable to the paediatric population due to the fact that constipation in children differs considerably from that in constipated adults with regard to its prevalence, onset, aetiology, symptoms, treatment, and prognosis.[21] But it is quite remarkable that all paediatric trials used Lactobacilli to investigate the probiotic effect. Besides the increase in defecation frequency and decrease in episodes of faecal incontinence, this study also showed a significant effect in softening of stools and in decreasing abdominal pain. Both effects could be a direct consequence of the improvement of the defecation but theoretically, it could also be caused by the working mechanism of the probiotics. It has been assumed that probiotics soften the stools by stimulating water and electrolyte secretion.
Furthermore, one paediatric study and several studies in adults with irritable bowel syndrome (IBS), have demonstrated that the abdominal pain decreased. Whorwell et al. conducted a randomised trial in 360 women with IBS who received *Bifidobacterium infantis*. It found a significant improvement of abdominal pain which occurred irrespective of any effect on stool frequency. The authors hypothesized that the probiotics were able to diminish visceral hypersensitivity by its anti-inflammatory effect on the enteric mucosa.

According to the available data, it is assumed that the risk of infection with the probiotic lactobacilli or bifidobacteria is similar to risks with commensal strains. However, there is concern that the use of probiotics may result in harmful events in at-risk populations like immunocompromized subjects or in patients with other life-threatening illnesses, who were admitted in the intensive care unit. Based on our results and their safety profile, adding probiotics to standard constipation treatment in otherwise healthy children could be very interesting.

The major limitation of our study is that this study is a non randomised non placebo controlled small pilot study. However, since this study show some promising results it is worthwhile to perform a large RCT to unravel the efficacy of *Bifidobacterium breve* in constipated children. In conclusion, this small pilot study suggests that *Bifidobacterium breve* is effective in the treatment of childhood constipation. A large randomised placebo controlled trial is now required to confirm these results.

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