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Functional constipation in children: A follow-up of two randomized controlled trials

Zaparcie czynnościowe u dzieci – prospektywna ocena z dwóch badań klinicznych z randomizacją

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A B S T R A C T

Background: The goal of treatment of functional constipation (FC) is to restore a regular defecation pattern and to prevent relapses. Aim: To assess long-term outcomes in children with FC. Methods: This was a follow-up study of children previously enrolled in 2 independent randomized controlled trials. In the first trial, children randomly received glucomannan (GNM) or placebo for 4 weeks. In the second study, children received a fermented dairy product with Bifidobacterium lactis I-2494 (B. lactis) or placebo for 3 weeks. Follow-up data were collected using a standardized questionnaire. The primary outcome measure was treatment success (>3 spontaneous bowel movements with no episodes of soiling during the last week, abdominal pain, or need for laxatives). The secondary outcomes were FC according to the Rome III criteria and the need for laxative therapy. Results: In the GNM study, follow-up data at 24 months were obtained from 63 of 72 (87.5%) of children. Treatment success was reported in 36/63 (57%), FC in 17/63 (27%), and the need for laxatives in 13/63 (21%). There were no differences in outcomes between groups. In the B. lactis study, follow-up data at 36 months were obtained from 57 of 82 (70%) of children. Treatment success was reported in 26/57 (46%), FC in 21/57 (37%), and the need for laxatives in 15/57 (26%). There were no differences in outcomes between groups. Conclusion: A substantial portion of children remained symptomatic after 2–3 years of follow-up indicating a need for regular evaluation of children with FC.

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Introduction

Functional constipation is a common gastrointestinal problem in children. The estimated worldwide prevalence varies from 1% to 30% [1, 2]. Currently, the diagnosis of functional constipation is based on the Rome III criteria and includes two or more of the following: <2 defecations in the toilet per week; at least one episode of fecal incontinence per week; history of retentive posturing or excessive volitional stool retention; history of painful or hard bowel movements; presence of a large fecal mass in the rectum; and a history

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of large-diameter stools which may obstruct the toilet [3]. The criteria are fulfilled when their defining symptoms appear at least once per week for at least 2 months prior to diagnosis [3]. Evidence-based guidelines from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [4], as well as the National Institute for Health and Clinical Excellence (NICE) guidelines [5], consistently recommend disimpaction, if present, followed by a maintenance therapy. Available therapeutic measures include toilet training and the use of oral osmotic laxatives (e.g., lactulose, polyethylene glycol), stimulant laxatives (e.g., bisacodyl), or mineral oil [4–6]. However, none of these measures offers long-lasting effects, hence, interest in alternative therapies.

Previously, we evaluated the effect of gut microbiota modification with prebiotics or probiotics in children with functional constipation in 2 randomized controlled trials [7, 8]. The rationale for the use of prebiotics/probiotics in the treatment of functional constipation was based on data demonstrating differences in the intestinal microbiota between healthy individuals and patients with chronic constipation [9, 10]. In these studies, the rate of treatment success ranged from 57% [8] to 67% [9], but there was no difference between the groups in any of the studies.

Constipation unfavorably influences the quality of life of affected children [11, 12]. While the goal of treatment of functional constipation is to restore a regular defecation pattern and to prevent relapses, the persistence of symptoms of constipation was reported in 30–52% of children followed up for at least 5 years [13, 14]. This indicates that functional constipation is not a transient, mild disorder. Data from Poland are limited. The aim of the current study was to assess long-term outcomes in children with functional constipation who had participated in those 2 previous trials [8, 9].

Methods

The current trial was a follow-up study of children who had participated in 2 previously published, randomized controlled trials carried out at our center. The designs of these studies have been described elsewhere [8, 9]. Briefly, in the first trial (n = 80) [8], children aged 3–16 years with functional constipation according to the Rome III criteria were randomly assigned to receive glucomannan (GNN), 2.52 g/d, or a comparable placebo for 4 weeks. GNN was as effective as placebo in achieving therapeutic success in constipated children [8]. In the second, multicenter, 2-nation (The Netherlands and Poland) trial (n = 159) [9], children aged 3–16 years with functional constipation according to the Rome III criteria were randomly allocated to receive a fermented dairy product with Bifidobacterium lactis 1-2494 (B. lactis) twice daily for 3 weeks or a comparable placebo. The effectiveness of the experimental treatment was comparable to that of the placebo [9].

Follow-up data were collected using a standardized questionnaire at 24 months after completion of the GNN study and at 36 months after completion of the B. lactis study. Participants were contacted by phone or regular mail. The questions asked related to the frequency, size, and consistency of stools defecated into the toilet, the presence of abdominal pain, and the need for laxative therapy. The primary outcome measure was treatment success, defined as ≥3 spontaneous bowel movements with no episodes of soiling during the last week, no abdominal pain, and no need for laxative treatment. The secondary outcomes were functional constipation according to the Rome III criteria and the need for laxative treatment.

Statistical analysis

The computer software Stats Direct [version 2.7.9,(2012-07-09)] was used to calculate the relative risk (RR) and mean difference (MD), both with a 95% CI. The difference between study groups was considered significant when the p value was <0.05, when the 95% CI for RR did not include 1.0, or when the 95% CI for MD did not include 0. All statistical tests were two tailed and performed at the 5% level of significance.

Results

The baseline characteristics of the 2 included populations [8, 9] are summarized in Table I. The primary and secondary outcomes are summarized in Table II.

In the GNN study, follow-up data at 24 months were obtained from 63 of 72 (87.5%) of the children. Overall, treatment success was reported in 36 of 63 (57%) of the children, and there was no difference in treatment success rates between the GNN and placebo groups (RR 1.08, 95% CI 0.70 to 1.66). Functional constipation was reported in 17 of

<table>
<thead>
<tr>
<th>Table I – Baseline characteristics</th>
<th>Study #1</th>
<th>Study #2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GNN</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Male/female</td>
<td>18/22</td>
<td>16/24</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>6.1 ± 3.3</td>
<td>5.9 ± 2.5</td>
</tr>
<tr>
<td>Duration of constipation in years (mean ± SD)</td>
<td>2.7 ± 3.1</td>
<td>2.6 ± 2.9</td>
</tr>
<tr>
<td>Stool frequency per week (mean ± SD)</td>
<td>1.73 ± 0.55</td>
<td>1.7 ± 0.5</td>
</tr>
</tbody>
</table>

B. lactis – Bifidobacterium lactis 1-2494; GNN – glucomannan.
63 (27%) of the children; the rate did not differ between groups (RR 0.86, 95% CI 0.38 to 1.94). The need for laxatives was reported in 13 of 63 (21%) of the children; the rate was similar in both groups (RR 0.83, 95% CI 0.31 to 2.20). The mean age of children with constipation was higher than that of children with treatment success, although the difference was of borderline statistical significance (9.7 ± 3.19 vs. 7.83 ± 3.4 years; MD 1.87, 95% CI –0.01 to 3.75).

In the B. lactis study, only a subset of 76 children enrolled in Poland was invited to participate in the present follow-up. Follow-up data at 36 months were obtained from 57 of 82 (70%) of the children (Table II). Treatment success was achieved in 26 of 57 (46%) of the children, and the rate did not differ between the B. lactis and placebo groups (RR 0.97, 95% CI 0.55 to 1.70). Functional constipation was diagnosed in 21 of 57 (37%) of the children. The rate of functional constipation was similar in the B. lactis and the placebo groups (RR 1.06, 95% CI 0.54 to 2.10). The need for laxatives was reported in 15 of 57 (26%) of the children, and the rate was similar in both groups (RR 0.84, 95% CI 0.35 to 2.02). The mean age of children with constipation was significantly higher than that of children with treatment success (11.38 ± 3.44 vs. 8.8 ± 2.71 years; MD 2.58, 95% CI 0.78 to 4.38).

### Discussion

#### Principal findings

This follow-up study of children previously enrolled in 2 independent, randomized controlled trials [8, 9] showed that a substantial portion of the children remained symptomatic after 2–3 years of follow-up. Approximately one quarter of the children fulfilled the strict Rome III criteria for functional constipation or needed laxatives. Children with constipation were older than children with treatment success.

#### Strengths and limitations

The study population is one of the major strengths of our study. We followed up a homogeneous population in which the initial diagnosis of functional constipation was made based on standardized Rome III criteria [3]. While different interventions were used in the original studies, both were similar in nature, i.e., focused on modification of gut microbiota. Hence, our decision to present the results of both cohorts in a single report. As initially no differences were found between the experimental and the control groups, our main focus was on long-term outcomes and not on the differences between groups. The response rate to the invitation to this follow-up study was high. This was particularly true for the GNN study that was carried out exclusively at our center. In regard to the B. lactis study, the response rate to this follow-up study was also high; however, we only invited children living in Poland to participate. Thus, the results from the B. lactis study should be interpreted with caution. Still, the findings compare well with those of the GNN study, which reduces the risk of attrition bias.

#### Comparison with previous findings

In general, our results are consistent with previously published observations. One of the first, long-term, follow-up observations was reported in 1993 by Loening-Baucke [15] who evaluated long-term outcomes in 90 of 174 (52%) children (mean age: 6.9 ± 2.7 years) after an initial diagnosis of constipation. Treatment success, defined as no soiling with ≥3 bowel movements per week while not receiving treatment, was observed in 57 of 90 (63%) of the children. The recovery rate was significantly higher in children <2 years of age than in children between 2 and 4 years of age. Symptoms of chronic constipation persisted in one third of patients, 3–12 years after initial evaluation and treatment.

Staiano et al. [16] followed up 62 children (mean age: 5.2 ± 2.8 years) with chronic idiopathic constipation for a period of 5 years. Each child received the same initial treatment over a 12-week period and was then followed up every 3 months. After 5 years from diagnosis, functional constipation persisted in 52% of the children [16].

Van Ginkel et al. [17] reported data on 418 constipated children (median age: 8 years) who were followed up 5 years (range: 1–8 years) after intensive initial medical and behavioral treatment. The cumulative percentage of children who were treated successfully during follow-up was 60% at 1 year, increasing to 80% at 8 years. Successful treatment was more frequent in children without encopresis and in children with the onset of bowel problems when older than 4 years of age.

In a non-blinded, randomized study by Loening-Baucke and Pashankar [15], 79 children (mean age: 8.1 ± 3.0 years) with chronic constipation and fecal incontinence were assigned randomly to receive polyethylene glycol (n = 39) or milk of magnesia (n = 40). After 12 months, the percentages of children who experienced improvement were similar in both groups (62% vs. 43%, respectively, p < 0.086). Furthermore,
33% of the polyethylene glycol-treated children and 23% of the milk of magnesia-treated children had recovered ($p = 0.283$).

Finally, van den Berg et al. [16] attempted to describe the clinical course of severe functional constipation in early childhood. Forty-seven children (median age: 3.5 months) who had constipation during their first year of life were observed. Treatment success was defined as a period of at least 4 weeks with $\geq 3$ painless bowel movements per week. Six months after the initial evaluation, 69% of the children had recovered. After initial success, a relapse occurred in 15% of the children within 3 years. A shorter duration of symptoms (<3 mo) before referral correlated significantly with a better outcome.

In Poland, one long-term, follow-up study [17] revealed that 60% of all children (2–16 years) initially recruited for treatment with Lactobacillus GG as an adjunct to lactulose or lactulose alone were treated successfully at 24 months. However, 25% (20/79) of the children continued to use laxatives during the last 6 months of the study.

Collectively, the available data are consistent with regard to the rate of recovery and exacerbations of constipation. However, evidence is insufficient to identify risk factors associated with poor, long-term, clinical outcomes.

**Conclusion**

A follow-up of children with functional constipation diagnosed according to the Rome III criteria showed that a substantial number of children continue to have bowel problems. Identification of the predictive factors of an unsatisfactory course of constipation seems to be the basis for the development of accurate preventive strategies. These data confirm that functional constipation is not a mild, self-limiting entity.

**Authors' contributions/Wkład autorów**

AH and AC contributed to the study design and conducted the study. AH analyzed the data. AH wrote the first draft of the manuscript. All authors approved of the final version. AH is the guarantor.

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**Conflict of interest/Konflikt interesu**

None declared.

**Ethics/Etyka**

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

The own research were conducted according to the Good Clinical Practice guidelines and accepted by local Bioethics Committee, all patients agreed in writing to participation and these researches.

**References/Piśmiennictwo**


[15] Loening-Baucke V, Fashankar DS. A randomized, prospective, comparison study of polyethylene glycol 3350...
