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Bongers, M.E.J.

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Chapter 3

Application of rectal enemas in children with severe constipation: a randomized controlled trial

Marloes E.J. Bongers
Maartje M. van den Berg
Johannes B. Reitsma
Wieger P. Voskuijl
Marc A. Benninga
ABSTRACT

Background & Aims
Treatment of childhood constipation is often long-lasting. After 5 years of intensive oral laxative use, up to 30% of constipated children still have unsuccessful outcome. Children refractory to oral laxatives may benefit from regular rectal evacuation by enemas. This randomized controlled trial aimed to compare clinical effectiveness of additional treatment with rectal enemas (intervention) to conventional treatment alone (control) in severely constipated children.

Methods
In a tertiary hospital in the Netherlands 100 children, aged 8-18 years, with functional constipation for at least 2 years were randomized to either intervention or control. The control group received education, behavioral strategies and oral laxatives. In addition, intervention consisted of 3 rectal enemas/week reduced by 1 enema/week every 3 months. Outcome measures were defecation and fecal incontinence frequency and overall success at 12, 26, 39 and 52 weeks. Overall success was defined as ≥3 defecation/week and <1 fecal incontinence episode/week, irrespective of laxative use.

Results
Defecation frequency normalized in both groups, but was significantly higher in the intervention group compared to control at 26 and 52 weeks (5.6 vs 3.9/week, p=0.02, and 5.3 vs 3.9/week, p=0.02, respectively). There were no significant differences, however in reduction of fecal incontinence episodes (p=0.49) and overall success rates (p=0.67) between the treatment groups. After one year of treatment, overall success rate was 47.1% in the intervention group versus 36.1% in the control group.

Conclusions
There is no additional effect of rectal enemas compared to oral laxatives alone as maintenance therapy for severely constipated children.
INTRODUCTION

Treatment of pediatric functional constipation is challenging. Studies in constipated children show an insufficient response to conventional treatment (education, bowel diary, toilet training and oral laxatives) and relapses are common \(^1,^2\). After one year of intensive conventional treatment approximately 30-40% of children with functional constipation still have a low defecation frequency and suffer of fecal incontinence \(^3,^4\). Moreover, long-term follow-up studies showed similar percentages of persistence of functional constipation in children \(^1,^2,^5,^6\). Constipation and secondary fecal incontinence are a source of distress and concern for the child and its family. Physical complaints, such as painful defecation and abdominal pain associated with constipation, and long duration of symptoms may result in impaired quality of life, reported by both child and parents \(^7\).

Conventional treatment generally consists of education of the child and parents, demystification of constipation, dietary advice, behavioral modification and administration of laxatives \(^8-^10\). Laxative therapy comprises two phases: disimpaction with oral or rectal laxatives when fecal impaction is present and maintenance therapy with oral laxatives for several months \(^9,^10\). Failure of conventional treatment may be caused by poor adherence to treatment, but could also result from the fact that conventional treatment is not addressing the underlying pathophysiology.

Refractory constipation is characterized by recurrent fecal impaction \(^11\). Mechanisms leading to repetitive accumulation of feces in the rectum may be retentive posturing of the child, anal sphincter dyssynergia, abnormal rectal function or motility disorders of the colon \(^11-^13\). A recent study found that an increased rectal compliance (i.e. the capacity to stretch upon a pressure stimulus) was a predominant feature in the majority of constipated children \(^13\). Due to a higher rectal compliance these children require larger stool volumes to trigger sensation of urge to defecate, contributing to longer intervals between defecation. Longer intervals between defecation result in hard stools, subsequently leading to difficulties in stool evacuation and eventually in fecal impaction. Based on these findings we hypothesize that children refractory to oral laxatives may benefit from regular rectal evacuation by enemas. Therefore, the aim of this study was to demonstrate whether additional treatment with rectal enemas is clinically more effective than conventional treatment alone in severely constipated children.
METHODS

Study participants

Children were recruited from a specialized outpatient clinic for functional defecation disorders at the Department of Pediatric Gastroenterology of the Emma Children’s Hospital/AMC in Amsterdam, the Netherlands. All children between 8 and 18 years with functional constipation were eligible for enrollment. Functional constipation was defined as presence of at least 2 of 4 of the following symptoms: 1) spontaneous defecation frequency <3 per week, 2) fecal incontinence episodes ≥2 per week, 3) passage of large diameter stools that may obstruct the toilet and 4) palpable abdominal or rectal mass on physical examination. Only children who had symptoms of functional constipation for at least 2 years and were unresponsive to conventional treatment were included. Children who had been treated with enemas on a regular basis (more than 3 rectal enemas in previous treatment) were excluded from the study. Furthermore, children with organic causes of constipation, including Hirschsprung’s disease, muscle disorders, prior recto-anal surgery, spina bifida, mental retardation or hypothyroidism were excluded. All subjects and/or parents gave informed consent. The study protocol was approved by the medical ethical committee of the Academic Medical Centre of Amsterdam.

Study Design

The study had a randomized controlled design and consisted of two parallel treatment groups: conventional treatment (control group) or conventional treatment combined with regular application of rectal enemas (intervention group). After baseline measurement and if written informed consent was given, the physician performed a telephone call to a randomization centre and revealed the allocation to the child and parents immediately. A computer-based system was used to generate a sequence of random group assignment for consecutive patients. This computer program used minimization to achieve a balanced randomization on two factors: gender and age (<13 years versus ≥13 years).

Baseline assessment

To verify eligibility for enrolment and to obtain baseline data assessment, children and parents were asked to record defecation and fecal incontinence frequency, passage of large amount of stools, painful defecation and abdominal pain in a diary one week prior to entry. In all patients, laxative treatment was discontinued during this week. At entry, a standardized interview was
conducted to determine defecation pattern including defecation frequency, stool consistency, painful defecation, fecal incontinence episodes, abdominal pain and stool withholding behavior. Abdominal and rectal examination was performed to evaluate presence of fecal impaction.

Treatment strategies
At start of treatment, all children underwent rectal disimpaction by rectal enema (120 ml sodium-dioctylsulfosuccinate and sorbitol) on three consecutive days. If rectal disimpaction was unsuccessful, rectal enemas were continued for a maximum of seven days. Conventional treatment consisted of education, behavioral strategies and oral laxatives. Patients were instructed to start toilet training three times daily after each meal and not to withhold stool when they felt urge to defecate. Parents were advised to apply a non-accusatory approach. Motivation was enhanced by praise and small gifts. Oral laxative therapy consisted of polyethylene glycol with a starting dose of 0.5 g/kg. If treatment was considered insufficient the dose was increased until success was achieved. In the control group, a rectal enema or bisacodyl suppository of 5 mg was only prescribed in case of reoccurrence of fecal impaction. In the intervention group, children received 3 rectal enemas weekly during the first 3 months. Thereafter this frequency was reduced by 1 enema per week every 3 months.

Follow-up and outcome measures
In both treatment groups, patients kept a bowel diary to record daily defecation frequency and fecal incontinence episodes, painful defecation, abdominal pain and laxative use. Visits to the outpatient clinic for evaluation of defecation pattern and laxative use were scheduled for all children at 2, 4, 6, 12, 26, 39 and 52 weeks. In addition, at week 52, subjective feelings about application of rectal enemas were assessed. Children in the intervention group filled out the following four questions, derived from a previously developed health-related quality of life questionnaire: 15: Question 1: After application of rectal enema I have stomach ache; Question 2: After application of rectal enema I am feeling worse; Question 3: Application of rectal enema is important to solve my defecation disorder; and Question 4: I find the application of a rectal enema terrible. Answers were based on a five point Likert scale.
Main outcome measures were defecation frequency per week, fecal incontinence frequency per week, and overall treatment success after 12, 26, 39 and 52 weeks of treatment. Overall success was defined as ≥3 bowel movements per week and <1 fecal incontinence episode per week, irrespective
of laxative use. Secondary outcome measures were abdominal pain and painful defecation at 12, 26, 39 and 52 weeks, and scores on the short questionnaire about regular application of rectal enemas after one year of treatment.

Statistical Analysis

Clinical symptoms of functional constipation at baseline are presented in a descriptive manner. In general, our outcome data consisted of repeated measurements over time in the same patient, and therefore we applied models that explicitly take into account the correlation that is likely to exist between measurements within the same individual.

To study defecation frequency (continuous variable) over time, we used a linear mixed model that contained: treatment (control vs. intervention), time (categorical with 4 levels), baseline measurement (continuous) and the interaction between treatment and time. No mathematical pattern was imposed on the covariance structure for measurements within the same individual (unstructured). Mixed model analysis has the advantage that data from all available visits are used in analysis, and not only the complete cases.

To examine whether one treatment was more effective than the other, we first performed a single overall test which jointly tested whether the differences in outcomes between the two treatment groups at all 4 follow-up visits were zero (e.g. both treatment are equally effective). Only if the overall test was significant, we tested for differences in outcomes at specific time points to avoid the problem of multiple testing.

Generalized estimation equation (GEE) models were used to analyze trends over time in binary outcomes (defecation frequency <3 per week or ≥3 per week, fecal incontinence frequency <1 per week or ≥1 per week, clinical success yes/no, abdominal pain yes/no, painful defecation yes/no). GEE models are an extension of generalized linear models in order to deal with correlated outcomes. Within the GEE framework, a working correlation matrix is estimated to adjust the standard parameters for the correlation that is present. Again, the working correlation matrix was considered unstructured. GEE models were similar in nature as the mixed models and also contained: treatment given, time categorical, and the interaction between treatment and time.

Prior to the study a sample size calculation was made expecting a 30% difference in the proportion of success between control and intervention. It was estimated that conventional treatment reached success in 30% of the children after one year of treatment. Under the additional assumption of a significance level of 0.05 with a power of 0.80, and 2-sided hypothesis testing, a minimal sample size of 84 with 42 children in each group was required. Statistical analyses
were performed by using SPSS windows version 12.0.2 (SPSS Inc., Chicago, Illinois, USA) or SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was accepted at p < 0.05. This trial is registered as an International Standard Randomized Clinical Trial, number ISRCTN 99089299. There was no external funding source.

RESULTS

Patients

Between September 2001 and November 2005 a total of 102 children referred by general practitioners, school doctors, and pediatricians enrolled in the study (figure 1). Fifty-one patients were allocated to the intervention group and 51 to the control group. Two randomized patients never commenced their allocated therapy and were therefore excluded from the analysis. A total of 87 patients completed the trial, while 13 patients (control n=7 and intervention n=6) terminated the trial prematurely (figure 1). All those patients remained in the analysis. In November 2006, one year follow-up of the last included patients was completed.

Of the 100 patients who started with allocated treatment, 65 were boys, the median (25th–75th percentile) age at baseline was 10.7 (9.4-12.3) years and the median duration of symptoms was 6.9 (5.0-9.2) years. A defecation frequency of <3/week was found in 84% and fecal incontinence episodes ≥2/week in 82% of all patients. Baseline characteristics for the two treatment groups are presented in table 1.

Treatment adherence

Six patients randomized to the strategy control switched to the intervention strategy as their response to oral laxative therapy was insufficient. This switch to the other treatment arm occurred at week two in 2 patients, at week 6 in 1 patient, at week 18 in 2 patients and at week 26 in 1 patient. These patients were considered as treatment failures in the control group, and analyzed as such. Furthermore, 11 control patients needed short-term disimpaction treatment, i.e. rectal enemas or bisacodyl suppositories for 1 to 3 days, during the trial period. Fecal impaction reoccurred once in 5 patients, while 6 patients needed disimpaction twice for separate episodes. In 7/11 (64%) of these patients, fecal impaction reoccurred in the first 6 weeks after starting conventional treatment. None of the patients switched to rectal laxatives on a regular basis, and were therefore not considered as treatment failures. Two patients assigned to the
intervention group responded unsatisfactorily to regular rectal enemas and switched to daily rectal lavage with tap water. These patients were considered as treatment failures in the intervention group. In 7 children rectal enemas were stopped in advance of the predetermined scheme as they reached successful outcome, while 4 patients refused further application of rectal enemas although they still exhibited symptoms of constipation (two in the first 12 weeks and two between 27-39 weeks).

Main outcome measures
The results of the intention-to-treat analyses of the main outcome measures based on all 100 patients are shown in figures 2, 3 and 4. Compared to baseline an increase in defecation frequency is seen for both the intervention and control group (figure 2). The overall test showed a significant difference in defecation frequency between the two groups (p=0.01). Defecation frequency was significantly higher in the intervention group compared to the control
group at 26 and 52 weeks (modeled mean frequency per week 5.6 vs 3.9/week, p=0.02, and 5.3 vs 3.9/week, p=0.02, respectively). In addition, a defecation frequency of <3 per week was more often present in the control group than the intervention group during the trial period, but the overall test showed no significant difference between groups (p=0.27).

At baseline, fecal incontinence frequency <1 per week was reported in 14% and 10% of children in the control group and intervention group, respectively. Fecal incontinence frequency decreased during the trial period (figure 3). The

Table 1. Baseline characteristics per randomized group*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Male gender</td>
<td>33/50 (66)</td>
<td>32/50 (64)</td>
</tr>
<tr>
<td>Age at baseline, yrs</td>
<td>11.0 (9.5-12.5)</td>
<td>10.5 (9.2-11.8)</td>
</tr>
<tr>
<td>Age at onset of constipation, yrs</td>
<td>4.0 (3.0-5.0)</td>
<td>4.0 (3.0-5.0)</td>
</tr>
<tr>
<td>Duration of symptoms, yrs</td>
<td>7.0 (5.1-9.3)</td>
<td>6.5 (4.7-9.3)</td>
</tr>
<tr>
<td>Defecation frequency / week</td>
<td>1.0 (0.0-2.5)</td>
<td>1.5 (0.4-2.5)</td>
</tr>
<tr>
<td>Defecation &lt;3 /week</td>
<td>44/50 (88)</td>
<td>40/50 (80)</td>
</tr>
<tr>
<td>Fecal incontinence frequency / week</td>
<td>7.0 (2.4-14.0)</td>
<td>7.5 (3.0-10.3)</td>
</tr>
<tr>
<td>Fecal incontinence ≥2 /week</td>
<td>39/50 (78)</td>
<td>43/50 (86)</td>
</tr>
<tr>
<td>Large amount of stools</td>
<td>35/50 (70)</td>
<td>37/50 (74)</td>
</tr>
<tr>
<td>Stool withholding behavior</td>
<td>29/49 (59)</td>
<td>33/48 (69)</td>
</tr>
<tr>
<td>Abdominal / Rectal fecal impaction</td>
<td>27/49 (54)</td>
<td>25/50 (50)</td>
</tr>
</tbody>
</table>

* depicted as proportion (%) or median (25th - 75th percentile)

Figure 2. Defecation frequency per week for both treatment groups

*Overall test for differences between intervention and control at all four- time points; results depicted are modeled means using a linear mixed model. Additional tests for differences between intervention and control at specific time points: #p=0.63; §p=0.02; ¥p=0.46; $p=0.02. (Dotted line indicates the lower limit of a normal defecation frequency per week)
percentages of children with <1 fecal incontinence episodes per week were not significantly different between the two treatment groups (p=0.49). Overall treatment success was not significantly different between intervention and control during the trial period (p=0.67). After one year treatment, 47.1% of patients in the intervention group was successful compared to 36.1% in the control group (figure 4).

Relationship between defecation frequency and fecal incontinence episodes
At baseline, all children presenting with a defecation frequency <3 per week showed a wide range of fecal incontinence episodes from 0 to 42 times per week. After one year of intensive monitoring and treatment, 83% (72/87) of all children had a normalized defecation frequency. Fifty percent of these children (36/72) still experienced weekly fecal incontinence, ranging from 1 to 14 episodes per week.

Secondary outcome measures
At baseline, abdominal pain and painful defecation were present in respectively 69.4% and 60.4% in the intervention group versus 78.0% and 52.0% of children in the control group. Pain decreased during treatment in both groups and no statistical significant difference was found between the two groups (table 2). Children in the intervention group, who filled out a short questionnaire after one year, indicated that abdominal pain after a rectal enema was present: never/
seldom in 39%, sometimes in 31% and often/always in 30%. Children felt worse after application of a rectal enema: never/seldom in 76%, sometimes in 11% and often/always in 13%. Thirty-eight percent of children thought that rectal enemas were not at all or only a little important to solve their defecation disorders, 20% found it quite important, and 42% rated it as very to extremely important. A rectal enema was perceived as very to extremely terrible in 15% of children, while 11% reported it as quite terrible and 74% found it no problem at all.

Table 2. Percentages (%) of children with abdominal pain and painful defecation in both treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>78,0</td>
<td>69,4</td>
</tr>
<tr>
<td>Week 12</td>
<td>29,7</td>
<td>25,6</td>
</tr>
<tr>
<td>Week 26</td>
<td>38,9</td>
<td>19,6</td>
</tr>
<tr>
<td>Week 39</td>
<td>26,6</td>
<td>15,7</td>
</tr>
<tr>
<td>Week 52</td>
<td>30,6</td>
<td>20,3</td>
</tr>
<tr>
<td>Painful defecation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>52,0</td>
<td>60,4</td>
</tr>
<tr>
<td>Week 12</td>
<td>16,2</td>
<td>13,8</td>
</tr>
<tr>
<td>Week 26</td>
<td>18,0</td>
<td>11,4</td>
</tr>
<tr>
<td>Week 39</td>
<td>19,3</td>
<td>17,0</td>
</tr>
<tr>
<td>Week 52</td>
<td>20,9</td>
<td>8,8</td>
</tr>
</tbody>
</table>

*p=0.36; #p=0.35 (Overall test for differences between control and intervention at all time points using GEE analysis).
DISCUSSION

This is the first randomized controlled trial investigating the role of rectal enemas as maintenance treatment of childhood constipation. Rectal enemas were well tolerated, but regular enema administration led to no clinical benefit compared to oral laxatives alone in children with severe constipation. Overall, children in the intervention group had a significantly higher defecation frequency compared to the control group after six months and one year of treatment. Nevertheless, the clinical relevance of this finding is questionable, as mean defecation frequency improved to a normal frequency in both groups at all evaluation moments. Yet, persistent low defecation frequency after one year treatment was still present in a subgroup of children (control group 30.2% versus intervention group 12.6%, p=0.05). Those children may suffer from a colonic dysmotility due to neuromuscular abnormalities, which was earlier recognized in adults and children with intractable constipation 19-23. Discussion remains whether pediatric refractory constipation reflects a true intrinsic gut anomaly causing slow-transit constipation or results from an acquired motility disorder after years of severe functional constipation 24, 25.

More fluctuation in defecation frequency within the normal range was seen in the control group. This could be the result of earlier reduction and/or discontinuation of oral laxatives. In this group, oral laxatives were reduced after three to four months if children exhibited regular bowel movements, probable resulting in a slight decrease in defecation frequency at six months. In response, adjustment of oral laxatives dosage led to an increase in mean defecation frequency at nine months, while again at one year a decrease was seen. At that moment 37.2% of children in the control group were off laxatives compared to 29.5% in the intervention group. A more constant defecation frequency in the intervention group most likely resulted from the fact that in the first nine months only rectal enemas, and not oral laxatives, were reduced in a step-by-step manner. Abdominal pain and painful defecation, possible side effects of rectal enemas, were not more frequently reported by children in the intervention group. Self-report of the children underlined that the vast majority of children did not perceive rectal enemas as terrible. These findings contradict the general belief that application of rectal enemas is traumatic for children and need to be avoided as much as possible.

Limited improvement in fecal incontinence frequency was seen during one year of treatment. Even the regular application of rectal enemas had no additional positive effect. Approximately half of all children continued to experience one or more episodes of fecal incontinence per week, despite a normal defecation frequency in the majority of these children. Fecal incontinence associated...
with constipation is thought to be secondary to fecal impaction, either as involuntary overflow incontinence or as stool leakage from the rectum as feces approaches the anus \(^{11, 26}\). Therefore, persistence of fecal incontinence in children with successful disimpaction and a normal defecation frequency is more difficult to understand. Fecal continence is maintained by involuntary and voluntary muscle contractions, the latter depending on the perception of rectal distention \(^{27}\). Diminished perception of rectal distention, i.e. rectal hyposensitivity, has been reported in both children and adults with constipation and fecal incontinence \(^{26, 28-31}\). Rectal hyposensitivity can be caused by either abnormal rectal wall properties (e.g. compliance, tone or contractility) or impaired afferent pathway function (e.g. impaired mechanoreceptors, afferent nerve sensitivity or defect central processing) \(^{32}\). Recent studies showed that abnormal thresholds for sensation were only present in 5-10% of constipated children, while rectal compliance was increased in approximately two third of these children \(^{13, 33}\). As a result of elevated rectal compliance, greater rectal volumes are required to elicit sensory thresholds without change in afferent nerve sensitivity \(^{13, 33, 34}\).

Nevertheless, constipated children with fecal incontinence often report “loss of sensation of stool in the rectum” or “late recognition of stool in the rectum and a sense of extreme urgency”. It could be hypothesized that an interaction between sensory and behavioral/psychosocial factors plays a role in persistence of fecal incontinence. In general, stool withholding behavior upon urge to defecate is thought to play a role in the development and/or persistence of constipation in most children \(^{26, 35}\). In our study, postponement of defecation was indeed reported in 64% of all children at intake. Regarding the onset of constipation around the age of four years, we speculate that these children displayed stool withholding behavior for many years. This habitual behavior to ignore the defecatory urge may still be present in a subgroup of children, despite regular defecation without pain and hard stools, and result in persistence of fecal incontinence. Furthermore, although sensory testing with rectal barostat revealed no abnormalities in the majority of children, in daily life, children suffering from fecal incontinence may be less aware of rectal sensations when distracted by playing games or watching TV.

Disappointing low success rates were found in our study population compared to one-year success rates of 60-70% in previous studies. \(^{1, 35, 36}\). This underlines that our study population represents children with severe functional constipation. To develop better treatment strategies for these children better understanding of the multifactorial etiology is needed. To date, novel therapies, such as new classes of drugs, electrical sacral nerve/transcutaneous stimulation or botulinum toxin injection, are potential helpful
when conventional treatment fails. Moreover, there is increasing interest in alternative therapies, like acupuncture or hypnosis, which may benefit children with functional gastrointestinal disorders refractory to standard treatment. Evidence for efficacy of these novel treatments is mainly based on small clinical trials, mostly in adults, and needs to be confirmed by well-designed randomized studies in constipated children.

A limitation of this study is that 13% of children dropped out during one year treatment and 8% switched treatment. The drop-out rate was not different between the two treatment groups, hence most likely of limited effect on the results. However, overall success rate could be biased by the fact that drop-outs may have been more severely constipated compared to the children that completed the study. We tried to minimize this bias by using the described linear mixed model and generalized estimation equation in which not only the children that completed the trial, but all cases were included. In the analysis we further corrected for deviation from randomized allocation, as all switchers were analyzed in their original randomized group but considered as treatment failures. Ideally switching needs to be avoided in randomized clinical trials, but this type of deviation would also occur in routine practice.

In conclusion, this randomized controlled trial showed that application of rectal enemas on a regular basis was well tolerated, but had no additional effect on conventional treatment with oral laxatives for severely constipated children. Therefore, there is no place for rectal enemas in the maintenance therapy in these severely constipated children. Rectal enemas should only be used for initial disimpaction.
REFERENCES


