PEG 3350 (Transipeg®) versus lactulose in the treatment of childhood functional constipation:

A double blind, randomised controlled multi-centre trial

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Abstract
Background
Recently, polyethylene glycol (PEG 3350) has been suggested as a good alternative laxative for lactulose as a treatment option in paediatric constipation (PC). However, no large randomised controlled trials exist evaluating the efficacy of either laxative.

Aim
To compare PEG 3350 (Transipeg®: i.e. Polyethylene glycol with electrolytes) with lactulose in PC and evaluate clinical efficacy / side effects.

Methods
100 patients (aged 6 months-15 yrs) with PC were included in an 8 week double blinded, randomised controlled trial. After faecal disimpaction, patients < 6 years received PEG 3350 (2.95 gram/sachet) or lactulose (6 gram/sachet), while children ≥ 6 years started with 2 sachets/day. Primary outcome measures were defecation and encopresis frequency / week and successful treatment after 8 weeks. Success was defined as a defecation frequency ≥ 3 / week and encopresis ≤ 1 every 2 weeks. Secondary outcome measures were side effects after 8 weeks of treatment.

Results
A total of 91 patients (49 male) completed the study. A significant increase in defecation frequency (PEG 3350: 3 pre vs. 7 post treatment / week; lactulose: 3 pre vs. 6 post / week) and a significant decrease in encopresis frequency (PEG 3350: 10 pre vs. 3 post / week; lactulose: 8 pre vs. 3 post / week) was found in both groups (NS). However, success was significantly higher in the PEG group (56%) compared to lactulose (29%). PEG 3350 patients reported less abdominal pain, straining and pain at defecation than children using lactulose. However, bad taste was reported significantly more often in PEG group.

Conclusion
PEG 3350 (0.26 ± 0.11 g/kg), compared with lactulose (0.66 ± 0.32 g/kg), provided a higher success rate with fewer side effects. PEG 3350 should be the laxative of first choice in childhood constipation.
Introduction
Despite the fact that childhood constipation is the most common complaint in childhood gastrointestinal disease, no large placebo controlled, randomised trials are available (1). There is no information concerning the maximum dose, duration or long-term side effects of any compound used in the treatment of childhood constipation. Therefore, the treatment of these children is symptomatic and based mainly on clinical experience. It consists of behavioural intervention and oral and sometimes rectal laxatives. The behavioural component includes structured toilet training and keeping a bowel diary.

In the Netherlands the first line compound is an osmotic laxative such as lactulose. This synthetic disaccharide is fermented by colonic bacteria and results in a decrease of colonic pH, resulting in expansion of faecal volume and acceleration of colonic transit. The action of lactulose is dependent on the colonic microflora, and a large amount of gas is produced as a result of this fermentation, causing bloating and abdominal pain (2,3). Lactulose is also associated with changes in bacterial colonic flora and a subsequent decrease in efficacy with long-term use (2).

Recently, low dose polyethylene-glycols (PEG) have been suggested as alternative treatments for constipation. This non-absorbable compound with a high molecular mass is not metabolised by colonic bacteria and acts by osmosis and volume expansion in the large intestine (4). PEG 3350 appears to be safe as the PEG load recovery in urine is minimal and similar for normal (0.06%) and inflammatory bowel subjects (0.09%) (5). PEG electrolyte solutions were successfully and safely used to rapidly clean the colon of adults and children with refractory constipation (6-9). In the long term treatment of constipated adults, PEG was recently shown to be superior to placebo or lactulose with less side-effects (10-12). There have been indications that low doses of PEG are also a good alternative in the treatment of constipated children (13,14). However, there are no randomised controlled trials comparing the efficacy of PEG 3350 and lactulose in paediatric constipation. The aim of this study was to compare the clinical efficacy and safety of PEG 3350 (Transipeg®: Polyethylene glycol with electrolytes) and lactulose in the treatment of functional childhood constipation.
Patients & Methods

Patients
Children with constipation were referred by general practitioners, school doctors, and paediatricians. Childhood constipation was defined as having at least 2 out of 4 of the following symptoms for the last 3 months: less than 3 bowel movements per week; encopresis more than once a week; large amounts of stool every 7-30 days (large enough to clog the toilet); palpable abdominal or rectal mass on physical examination (15). Children aged 6 month to 15 years were included in this study. Children with organic causes for defecation disorders, including Hirschsprung's disease, spina bifida occulta or hypothyroidism were excluded from the study.

Study design
The study had a two parallel group, double blind, randomised, prospective, multicentre comparative design and was performed in the Academic Medical Centre at Emma Children's Hospital, Amsterdam, and two non-teaching hospitals also in the Netherlands. The design was approved by the ethics committees of each centre and conducted in compliance with the Helsinki Declaration. Patients were randomly assigned to receive either lactulose (6 g [sachet]) or PEG 3350 (2.95 g [sachet]). Unlabeled, numbered boxes with unlabeled sachets were prepared by the AMC pharmacy and handed out to the patients after randomisation. The box contained 180 sachets containing either lactulose 6 grams per sachet or PEG 3350 2.95 gram per sachet.

Run-in phase
For one week before the study medication was prescribed, defecation and encopresis frequency, stool consistency, and abdominal pain were recorded. The use of oral laxatives was not allowed during this week. At the end of the week patients received one enema daily for three days to clear any rectal faecal remains. Subjects ≤ 6 years of age received 60 ml Klyx (sodium-dioctylsulfosuccinate and sorbitol) while those > 6 years of age received 120 ml Klyx. Other recorded baseline characteristics were: feeling of bloating, nausea, vomiting, flatulence, painful defecation, and diarrhoea.
Chapter 9

Treatment phase
Based on earlier studies and clinical experience (15,16) patients aged between 6 months and 6 years of age (inclusive) began treatment with one sachet of either PEG 3350 or lactulose per day (2.95 g or 6 g respectively), while those older than 6 years of age were given two sachets per day (5.9 g PEG 3350 or 12 g lactulose). Clinical efficacy and tolerability were recorded in a diary using scores for defecation and encopresis frequency, abdominal pain, feelings of bloating, nausea, vomiting, flatulence, painful defecation, and diarrhoea. Patient assessment of the taste of the treatment was also recorded. Toilet training after each meal (5 minutes) was advised and small gifts and praise were used to enhance compliance.

After one week of treatment, efficacy and tolerability as recorded in the diary were assessed. If the treatment was considered to be having insufficient effect (persisting symptoms) the dose was increased by one sachet (an additional 2.95 g PEG 3350 or 6 g lactulose). However, if diarrhoea was reported (overdosing) the original dose was reduced by 50% (i.e. to one sachet or half a sachet). A stimulant laxative was prescribed if the clinical condition had not improved compared with baseline (not successful) with the maximum amount of laxative sachets per day. Clinical evaluation and assessment of diaries was carried out at enrolment and at 1, 2, 4, and 8 weeks, where treatment dose was also appropriately adjusted (Figure 1).

Figure 1 Defecation frequency (left) and encopresis frequency (right) in the PEG group (white bars) and Lactulose group (black bars).
Follow-up
After the initial double blind phase patients were asked to continue in an open label assessment for an additional 18 weeks, in which all patients were treated with PEG 3350. Symptoms continued to be recorded in a diary, with outpatient clinical follow-up at 4, 8, and 26 weeks after entering the follow-up period, providing a total study time of 34 weeks. If patients were unable to visit the outpatient clinic for follow-up, history was obtained by telephone.

Efficacy
The primary efficacy endpoints were frequency of stools, frequency of encopresis and overall treatment success at 8 weeks. An increase in defecation frequency was considered to have improved if it rose to three or more times a week, while encopresis had to decrease to an incidence of one episode or less every two weeks.

Overall treatment success was defined as three or more bowel movements a week and one encopresis episode or less every two weeks. Stool consistency was also recorded but due to the nature of the parameter and the difficulty in applying semi-quantitative values to the categories, statistical analysis of this endpoint is limited.

Safety
The incidence of adverse events during the eight weeks of treatment was also documented. Both the incidence and severity of gastrointestinal (GI) adverse events were recorded in the diary and assessed at week 1, 2, 4, and 8 of the double blind period of the trial, with a three point scale: 0 = no GI symptoms present, 1 = GI symptoms present to some extent, 2 = GI symptoms present.

Statistics
It was estimated that a total sample of 90 patients would be adequate to show a difference of at least 30% more success at 8 weeks using PEG 3350 compared to lactulose with a two-tailed alpha level of 0.05 with a power of 80%. The analysis was performed as a per protocol analysis including those subjects that completed the double blind treatment period. Values are expressed as mean ± standard deviation (SD). Comparisons between the two treatment groups were performed using Student’s t tests or non-parametric Mann-Whitney U tests according to the distribution of values and \( \chi^2 \) tests. A P value < 0.05 was considered significant.
Logistic regression was applied in order to detect variables prognostic for success. The following variables were included in the logistic regression: age at enrolment, number of months treatment before enrolment, composite variable of encopresis and soiling, family history, and gender.
Results
Between 01-05-2001 and 01-05-2002, 100 patients (aged 6 months-15 years) with childhood functional constipation were included in this study. The majority of patients (76) were treated in the outpatient clinic of our tertiary hospital; 24 patients were included and treated in the 2 non-teaching hospitals. As shown in Table 1, no significant differences were found with respect to demographic data and recorded baseline characteristics between the two treatment groups. There were 9-drop outs due to various reasons (see Table 1). Therefore, the final data set consisted of a total of 91 patients (46 in the PEG group and 45 in the lactulose group). As no withdrawals occurred due to efficacy reasons, data analysis is based on these 91 patients (per-protocol analysis).

Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>PEG 3350</th>
<th>lactulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients at randomisation</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>6.5 ± 3.2</td>
<td>6.5 ± 3.4 (P = 0.9)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>27/23</td>
<td>28/22 (P = 0.7)</td>
</tr>
<tr>
<td>Number of patients not withdrawn</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>6.5 ± 3.2</td>
<td>6.6 ± 3.4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>24/22</td>
<td>25/20</td>
</tr>
<tr>
<td>Inclusion criteria (in no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defecation frequency &lt;3/week</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Encopresis &gt; 1/week</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Large amounts of stool</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Faecal impaction</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Premature withdrawal</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Helicobacter positive</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Reason unknown</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bad palatability of study medication</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

PEG: Polyethylene glycol

Clinical efficacy at 8 weeks
Compared to intake, a significant increase in mean defecation frequency / week and a significant decrease in mean encopresis frequency / week were found at 8 weeks in both groups (Table 2). There was no significant difference between the two patient groups with respect to these two parameters at 1, 2, 4, and at 8 weeks of the study (see Figure 1 and Table 2). Dividing patients in accordance
with age (< 6 years and ≥ than 6), the same results were found with respect to defecation and encopresis frequency at 8 weeks (see Table 2).

**Table 2** PEG 3350 vs. lactulose, clinical parameters, success percentages (95% CI) and dosage of laxative (Student T test).

<table>
<thead>
<tr>
<th></th>
<th>PEG 3350</th>
<th>P-value</th>
<th>lactulose</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Defecation frequency/ week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All age groups</td>
<td>2.59 ± 3.34</td>
<td>&lt;0.01</td>
<td>2.75 ± 3.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; 6 years</td>
<td>1.39 ± 1.09</td>
<td>&lt;0.01</td>
<td>1.76 ± 1.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥ 6 years</td>
<td>3.69 ± 4.25</td>
<td>&lt;0.01</td>
<td>3.83 ± 4.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Encopresis frequency/ week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All age groups</td>
<td>9.70 ± 14.98</td>
<td>&lt;0.01</td>
<td>7.73 ± 11.17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; 6 years</td>
<td>14.25 ± 19.69</td>
<td>&lt;0.01</td>
<td>7.54 ± 14.02</td>
<td>0.172</td>
</tr>
<tr>
<td>≥ 6 years</td>
<td>5.52 ± 6.83</td>
<td>0.07</td>
<td>7.93 ± 7.18</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Success percentages</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 8 weeks (95% C.I.)</td>
<td>56% (39-70)</td>
<td>0.02</td>
<td>29% (16-44)</td>
<td>0.02</td>
</tr>
<tr>
<td>FU 4 weeks</td>
<td>53% (36-68)</td>
<td>0.18</td>
<td>36% (21-53)</td>
<td>0.18</td>
</tr>
<tr>
<td>FU 8 weeks</td>
<td>54% (37-71)</td>
<td>0.36</td>
<td>41% (26-58)</td>
<td>0.36</td>
</tr>
<tr>
<td>FU 26 weeks</td>
<td>63% (46-76)</td>
<td>0.13</td>
<td>47% (32-62)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Medication (sachet/day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 8 weeks</td>
<td>1.99 ± 0.3</td>
<td>0.03</td>
<td>2.4 ± 0.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

PEG: Polyethylene glycol, FU: Follow-up. The lactulose group experienced a significant increase in success after changing to PEG at the end of the intervention period (29%) compared to FU at 26 weeks (47%) (P=0.05)

**Success percentages**

A significantly higher number of patients in the PEG group were successfully treated after 8 weeks of treatment compared with the lactulose group (PEG: 56% vs. lactulose: 29%; P=0.02). This difference was irrespective of age (< 6 years and ≥ 6 years). Success rates did not change in the PEG 3350 treatment group during the follow-up period (see Table 2). In the group of children on lactulose, who openly switched to PEG 3350 at the end of the 8-week study period, a significant increase in success rate was found (29% to 47%; P=0.05) after 26 weeks follow up.

A total of 26 patients were treated with laxatives for at least one year prior to the start of the study. Of these patients, 14% and 33%, respectively, were treated successfully with lactulose or PEG 3350 (NS). In contrast, in those children treated for less than 1 year, a significant difference in success was found between patients treated with PEG 3350 (63%) or lactulose (31%) (P=0.02).
Prognostic variables for success
In multivariate analysis to identify predictors of success, using a logistic regression model, the factors age at enrolment and family history did not significantly contribute to success of the treatment. However, the overall success rate after the 8 week treatment period was higher in female patients (P=0.025), lower in children who were treated for more than one year before enrolment in the present study (P=0.008) and lower in those children with higher frequencies of encopresis at enrolment (P=0.017).

Side effects
During the 8 week study period there were no serious or significant adverse events recorded. Figure 2 shows that significantly more adverse events were reported by patients using lactulose compared with patients on PEG. However, significantly more children complaint of bad palatability of PEG compared with those receiving lactulose. This resulted in the premature withdrawal of 1 patient in the PEG group. Serious side effects were not reported in either group.

Figure 2 Side effects after 8 weeks of study of PEG group (white bars) and lactulose group (black bars).

Treatment dosage
The mean PEG dosage at 4 weeks and 8 weeks for children who clinically improved was $5.07 \pm 1.36 \, \text{gram} / \text{day}$ and $5.40 \pm 2.30 \, \text{gram} / \text{day}$, respectively. In the lactulose group, doses associated with improvement were $11.52 \pm 4.56 \, \text{g/day}$ (1.9 sachets).
and 13.86 ± 6.66 g/day (2.3 sachets) at 4 and 8 weeks respectively. Dividing clinically successful patients (after 8 weeks) into those < 6 years and those ≥ 6 years, the optimal dose of PEG was 0.26 ± 0.13 g/kg/day and 0.26 ± 0.07 g/kg/day, respectively. The optimal dose of lactulose in clinically successful patients < 6 years and ≥ 6 years was 0.96 ± 0.45 g/kg/day and 0.45 ± 0.27 g/kg/day, respectively.

In the PEG group the mean stool frequency increased by 1.89 / week (P =0.03) after an increase in the dose with one sachet during the clinical visit. No increase in stool frequency was found in the lactulose group after increasing the dose. Nine children in the PEG 3350 group and ten children in the lactulose group needed an additional stimulant laxative (bisacodyl) (NS).
Discussion

In this randomised controlled, double blind study in children with constipation, we found that compared with baseline, both PEG 3350 (PEG 3350) and lactulose resulted in a significant increase in defecation frequency and a significant decrease in encopresis frequency after 8 weeks of treatment. Clinical improvement was irrespective of age at intake (i.e. < 6 years and ≥ 6). Follow up at 6 months showed a comparable increase in defecation frequency and decrease in encopresis frequency in both groups. During the intervention- and open-label follow-up period, these clinical parameters were not significantly different between the two treatment groups.

PEG 3350 (PEG 3350) was associated with a significantly higher success rate, (56%) than lactulose (29%). Similar success percentages for PEG 3350 were found by Loening-Baucke, both after the intervention period and at 6 months follow up (13). Comparison with other paediatric studies using PEG 3350 in the treatment of constipation is difficult as no criteria for success were mentioned in these studies (14,17). A similar success rate of lactulose was reported in an earlier study evaluating the additional effect of biofeedback training (33%) in children with chronic constipation (15). In this latter study, a significant increase in success was found (52%) at six months follow up compared with the success percentage at the end of the intervention period (15). It is unclear if the similar significant increase in success of the group of children who openly switched to PEG 3350 at the end of the 8-week study period is the result of PEG 3350 or of our intensive follow up programme.

In accordance with previous studies, a low encopresis frequency and a short period of treatment before enrolment were associated with successful treatment outcome (18). A longer period of treatment suggests an early age of onset of constipation, indicating a primarily organic underlying mechanism, in contrast with children who have shown normal defecation for many years before experiencing constipation. Our study shows that children with encopresis are more difficult to treat, underscoring the necessity of long-lasting laxative (oral and/or rectal) treatment. Conflicting data exist concerning the relation between success and relevant cofactors such as sex, positive family history, clinical parameters, anorectal parameters (abnormal contraction of the external sphincter), histological parameters (a decreased number of interstitial cells of Cajal, reduced ganglionic density and size), and symptoms before intake (18-25).
In accordance with others evaluating PEG 3350 in the treatment of children with constipation, only mild side effects were reported (6,13,14,26). In contrast with an adult study comparing PEG 3350 with lactulose, abdominal pain, straining on defecation, and pain during defecation occurred significantly less often in those children receiving PEG 3350 compared with children receiving lactulose (11). Surprisingly, flatulence did not differ between the two treatment groups, as has been reported by others (10,11). Therefore, mechanisms other than colonic fermentation must also play a role in abdominal pain and the production of flatus in these children, like an osmotic effect or an increase of colonic motility (10,27,28).

We have no good explanation as to why children receiving lactulose experienced significantly more straining and pain during defecation than children receiving PEG 3350. One can speculate that the dose of lactulose was too low. However, no difference was found in stool consistency or the prevalence of diarrhoea, suggesting an adequate dosage of lactulose.

In the Netherlands, PEG 3350 without electrolytes (Miralax; Braintree Laboratories, Braintree, Massachusetts, USA) is not available. Although a significant number of children did not like the salty taste of PEG 3350, compliance was high. Only one child prematurely finished the study because of bad palatability.

The mean effective dose of PEG 3350 for the treatment of constipation in children ≤ 6 years and older than 6 years was 0.26 ± 0.13 g/kg/day, and 0.26 ± 0.07 g/kg/day, respectively. Although the dose administered was lower than that used in other studies in children with constipation, comparable effects on clinical parameters were found (13;14;17). In contrast to these studies, we used PEG-ELS with additional electrolytes (iso-osmotic), which might exhibit a more potential osmotic effect than PEG without electrolytes (hypo-osmotic) (29).

In both treatment groups, approximately 20% of patients needed additional stimulant laxatives during the intervention period. This is in contrast with results of Attar and colleagues (11) who showed that significantly less (adult) patients with PEG 3350 needed stimulant laxatives (suppositories or micro-enemas) compared with lactulose. For practical purposes, we were not able to prescribe a higher dose, as suggest by others (28), as the maximal amount of PEG 3350 in this study was 8.85 grams per day.

In conclusion, the results of this study show that PEG 3350 was more effective with fewer side effects than lactulose in the treatment of childhood constipation.
Therefore, PEG 3350 should replace lactulose as the first treatment option in children with mild and severe constipation. The optimal dose of PEG 3350 for children younger than six years is $0.26 \pm 0.13$ gram/kg/day and $0.26 \pm 0.07$ gram/kg/day for those older than six years.
References


