Original Article

Weaning strategies for osmotic laxatives in children with functional constipation: a pilot multicenter randomized controlled trial

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Background: Long-term maintenance of laxatives is crucial for treating functional constipation (FC) in children. This study aimed to compare the success rates of discontinuation based on different drug reduction methods, in order to identify the optimal strategy for discontinuing laxative use.

Methods: This open-label randomized controlled trial was conducted from September 2020 to September 2021. Children with FC who had been successfully treated with lactulose for more than three months were included. Patients were randomly assigned to one of two groups: dose reduction or frequency reduction over a three-month period. The primary outcome was the weaning success rate at week 12. Participants were divided into two subgroups based on the pre-weaning lactulose dosage: the low-dose group (≤1.5 g/kg/day) and the high-dose group (>1.5 g/kg/day).

Results: A total of 16 patients were enrolled, with a median age of 43 months and 11 boys. There were no significant differences in baseline characteristics between the two groups. The primary outcome showed no significant difference: 66.7% for dose reduction *vs.* 57.1%. for frequency reduction. Weaning success rates decreased at week 16 (33.3% *vs.* 57.1%) and week 24 (33.3% *vs.* 42.9%) without significant differences. In the subgroup analysis, the high-dose group showed a significantly higher weaning success rate at 12 weeks compared to the low-dose group (81.8% *vs.* 20%, P=0.04). Other measures, including median defecation frequency, incontinence episodes, stool consistency, painful defecations, and compliance, were also similar between the groups. Patient satisfaction was 77.8% for dose reduction and 57.1% for frequency reduction, with no significant difference.

Conclusions: The method of reducing the dose or frequency of lactulose did not affect the weaning success rate in children with FC. However, a pre-weaning lactulose dose exceeding 1.5 g/kg/day may lead to better outcomes at week 12. Despite gradual reduction over more than 3 months, the weaning success rate remained low, highlighting the importance of careful drug discontinuation and follow-up.

Trial Registration: The Clinical Research Information Service of the Korea Center for Disease Control and Prevention (https://cris.nih.go.kr/cris, registration No. KCT0006286).

Keywords: Functional constipation (FC); lactulose; drug discontinuation; weaning

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Introduction

Functional constipation (FC) is a common issue in childhood, with prevalence varying by geographic region (1). In South Korea, the prevalence of FC among children attending kindergarten or elementary school ranges from 6.7% to 11.8% (2). The incidence of constipation peaks between ages 2 and 4 years, which coincides with the typical start of toilet training (3). Approximately 95% of constipation cases in children are classified as FC, with no underlying organic causes (4). The pathophysiology of pediatric FC is multifactorial, but stool withholding, often beginning after a painful bowel movement, is a common factor (5). This vicious cycle of stool retention can lead to fecal impaction, overflow fecal incontinence, loss of rectal sensation, and diminished urge to defecate (6). To address this issue, maintenance therapy following fecal disimpaction, coupled with education and long-term follow-up, is essential (4,5).

Randomized controlled trials (RCTs) have investigated pharmaceutical treatments for children with FC (7-10). Evidence supports the use of osmotic laxatives, such as polyethylene glycol (PEG) or lactulose, as effective treatments for FC in children (4). However, no RCTs have addressed the optimal duration of osmotic laxative therapy or the best approach for discontinuing maintenance therapy for children with FC.

To date, only expert opinions with very low levels of evidence are available (5). These recommendations suggest that maintenance therapy should continue for at least 2 months and that all constipation-related symptoms should be resolved for at least 1 month before discontinuing therapy. Additionally, it is advised that treatment be reduced gradually, though there is no established method for gradual reduction.

For adults, long-term use of PEG for over 6 months has been shown to be effective and safe (11), leading to recommendations for the long-term use of non-absorbable carbohydrates in adults with FC (12). However, there is no evidence on the optimal way to discontinue medication in adults with FC.

Therefore, we aimed to compare weaning success rates based on different drug weaning methods and to identify the optimal strategies for drug discontinuation in children with FC. We present this article in accordance with the CONSORT reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-436/rc).

Highlight box

Key findings

- This is the first randomized controlled trial investigating weaning protocols (dose *vs.* frequency reduction) for osmotic laxatives in children with functional constipation (FC).
- At week 12, weaning success rates were 66.7% in the dose reduction group and 57.1% in the frequency reduction group. Stool consistency and patient satisfaction were similar between the groups.

What is known and what is new?

- Maintenance with osmotic laxatives is essential for managing FC, with gradual tapering generally recommended, although no trials have specifically assessed different weaning methods.
- The lactulose weaning methods—whether through dose reduction or frequency reduction—did not significantly impact the weaning success rate during the 3-month weaning period or the subsequent 3-month off-therapy period.
- Pre-weaning lactulose doses greater than 1.5 g/kg/day may enhance the success rate of weaning at 12 weeks.

What is the implication, and what should change now?

- After successful maintenance therapy with lactulose in children with FC, the method of drug discontinuation does not significantly affect the weaning success rate.
- Despite the gradual weaning of lactulose over 3 months in patients who had been successfully treated for at least 3 months, the weaning success rate remained low.

Methods

Study design

This open-label, randomized controlled pilot trial was conducted at pediatric gastroenterology outpatient clinics in three tertiary university hospitals in South Korea: Hallym University Sacred Heart Hospital, Soonchunhyang University Bucheon Hospital, and Daejeon Eulji Medical Center, from September 2020 to September 2021. The study was registered with the Clinical Research Information Service of the Korea Center for Disease Control and Prevention (https://cris.nih.go.kr/cris, registration No. KCT0006286, date of registration: 19 July 2019, date of first enrollment of patients: 19 July 2019). All participating hospitals were informed and agreed with the study. The institutional review boards of all three participating hospitals approved the study (Hallym University Sacred Heart Hospital 2020-05-022-001, Soonchunhyang University Bucheon Hospital 2020-06-019-002, Daejeon Eulji Medical Center 2013-10-013-002). All participants or their parents provided written informed consent. The

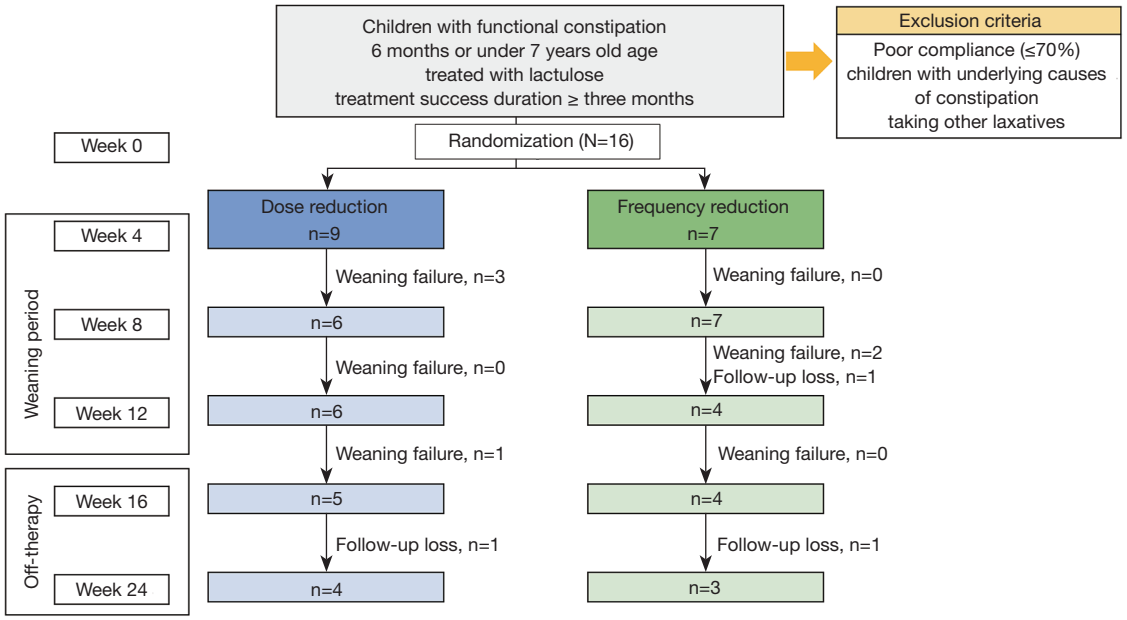

Figure 1 Study flow throughout the study period.

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Participants

FC diagnosis was based on the following Rome IV criteria: children must exhibit two or more of the following symptoms at least once per week for a minimum of one month; two or fewer defecations per week; history of stool retention or retentive posturing; painful or hard bowel movements; presence of a large fecal mass in the rectum; large-diameter stools that obstruct the toilet in toilet-trained children; and at least one episode of incontinence per week (13,14). Treatment success was defined as three or more bowel movements per week and no episodes of incontinence in toilet-trained patients, and three or more bowel movements per week in non-toilet-trained patients. Inclusion criteria were as follows: children aged 6 months to 6 years diagnosed with FC based on the Rome IV criteria; treated with lactulose (Duphalac Easy syrup®, 1.34 g/mL of lactulose, by JW Pharmaceutical, Seoul, Republic of Korea); and with treatment success lasting more than three months (*Figure 1*). Initial disimpaction was performed when a hard mass in the lower abdomen was detected on physical examination, a large stool mass was identified on rectal examination, or excessive stool was observed in the distal colon on abdominal radiography. Lactulose was used as maintenance treatment. Exclusion criteria included other underlying causes of constipation, such as hypothyroidism, metabolic disorders, Hirschsprung's disease, spina bifida, and use of medications that could interfere with bowel movements. Patients with poor compliance, defined as taking less than 70% of the prescribed medication dosage at enrollment, were excluded. Additionally, patients in the developmental stage of toilet training were excluded.

Intervention

This study was conducted over 24 weeks and consisted of two periods: a 12-week weaning period with four outpatient visits (weeks 0, 4, 8, and 12) and a 12-week off-therapy period with two telephone visits (weeks 16 and 24) following drug discontinuation (Figure S1).

At week 0, patients were randomly assigned to one of two groups: dose reduction or frequency reduction. In the dose reduction group, the daily dose of lactulose was gradually reduced over the 12-week weaning period. In the frequency reduction group, the frequency of lactulose administration per week was gradually reduced while the daily dose remained the same. Specifically, in the dose reduction group, the daily dose was reduced by about 1/8 every 2 weeks and administered daily. In the frequency

reduction group, the daily dosage remained constant while the frequency of administration was reduced to 5, 3, and 2 times per week at 4-week interval. If treatment success was maintained throughout the weaning period, the drug was completely discontinued at week 12.

During the weaning period, the use of other drugs, including stimulant laxatives, was prohibited. Arbitrary adjustments to the lactulose dose or administration interval were also not allowed. If symptoms worsened during this period, lactulose administration was adjusted by the physician at each hospital visit. However, during the off-therapy period, re-administration of lactulose was permitted if the patient's symptoms worsened.

Data collection

At the screening visit (week 0), baseline clinical characteristics were collected, including age, sex, weight, lactulose dose, treatment duration, treatment success duration, defecation frequency per week, stool consistency, number of incontinence episodes, and frequency of painful defecation. Parents were provided with a defecation diary to record body weight, medication dosage, adherence, defecation frequency, fecal incontinence, stool consistency, frequency of painful bowel movements, and any adverse events. We evaluated treatment outcomes, drug usage, dosage, and side effects based on the defecation diary. Stool consistency was evaluated using the Bristol Stool Form Scale (15). During follow-up visits (weeks 4, 8, and 12), information from the defecation diaries was collected. Compliance was assessed using the defecation diary and the amount of remaining medication. After drug discontinuation, telephone inquiries were made at week 16 (1 month off therapy) and week 24 (3 months off therapy) to assess weaning success and satisfaction with the drug discontinuation methods.

Outcome measures

During the weaning period, weaning success was defined as three or more bowel movements per week with no episodes of incontinence in toilet-trained patients, and three or more bowel movements per week in non-toilet-trained patients. The primary outcome was the weaning success rate at week 12. During the off-therapy period, the definition of weaning success remained the same. However, if lactulose was re-administered due to worsening symptoms, it was classified as weaning failure. An additional subgroup analysis of weaning success rates was performed based on the pre-weaning lactulose dosage. Participants were categorized into two subgroups: the low-dose group (≤1.5 g/kg/day) and the high-dose group (>1.5 g/kg/day).

Secondary outcomes included defecation frequency, number of fecal incontinence episodes, stool consistency, number of painful defecations, and compliance. To evaluate overall clinical symptoms during the weaning period, an additional subgroup analysis was conducted using the following criteria: the number of patients with three or more bowel movements per week, a Bristol Stool Form Scale score of 3 or higher, and the absence of defecation pain. Patient satisfaction with the drug reduction methods was evaluated at weeks 12 and 24.

Statistical analysis

Categorical variables, such as weaning success and side effects, were compared using Fisher's exact test. The Mann-Whitney *U* test was employed to compare continuous variables, including stool frequency, stool consistency, number of incontinence episodes, number of painful defecations, and compliance. Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed. Data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). A difference between the two groups was considered significant when the P value was <0.05. Data were presented as medians with ranges or as numbers with percentages. As there was no prior research on the subject, the sample size could not be calculated, and the study was designed as a pilot. Random allocation was conducted using Random Allocation Software 2.0 (Informer Technologies, Inc.).

Results

Baseline characteristics

A total of 16 children with FC were enrolled in this study, with nine in the dose reduction group and seven in the frequency reduction group. There were no significant differences between the two groups regarding sex, median age at enrollment, treatment duration, or treatment success duration (*Table 1*). The median treatment duration was 10 (range, 3–24) months, and the median treatment success duration was 5 (range, 3–15) months. The median defecation frequency was 4.5 (range, 3–17) times per week, and the median stool consistency was 4 (range,

Table 1 Baseline characteristics

Variable	Dose reduction (n=9)	Frequency reduction (n=7)	P
Male	6 (66.7)	5 (71.4)	0.64
Age (months)	42 [11–62]	44 [36–80]	0.41
Body weight (kg)	14.8 [10–16]	15.7 [13–22]	0.21
Treatment duration (months)	10 [3–24]	12 [3–24]	0.76
Treatment success duration (months)	4 [3–12]	6 [3–15]	0.61
Frequency of defecation (/week)	4 [3–17]	5 [4–5]	0.84
Number of incontinence (/week)	0	0	>0.99
Stool consistency	4 [4–5]	4 [3–5]	0.75
Number of painful defecation (/week)	0 [0–1]	0 [0–1]	0.61
Compliance	95 [80–100]	95 [90–100]	0.92
Dose of lactulose (mL/day)	20 [10–30]	30 [10–50]	0.30
Dose of lactulose (mL/kg/day)	1.4 (0.6–2.1)	1.5 (0.7–3.2)	0.47
Frequency of medication (/week)	7	7	0.17

Data are presented as medians with ranges or as numbers with percentages.

3–5), with no significant differences between the groups. At enrollment, all patients were receiving daily lactulose with a median dose of 1.44 (range, 0.6–3.2) mL/kg/day, and compliance was good at 90% (range, 80–100%). The dosage and frequency of lactulose administration differed significantly between the two groups during the weaning period, indicating that the drug reduction methods were significantly different (Table S1).

Primary outcome: weaning success rate

There was no significant difference in the weaning success rate at week 12 between the two groups (*Figure 2*). The weaning success rate at week 12 was 66.7% (6/9) in the dose reduction group and 57.1% (4/7) in the frequency reduction group (P>0.99). This result remained unchanged in the PP analysis: 83.3% (5/6) in the dose reduction group and 100% (4/4) in the frequency reduction group (P>0.99).

During the weaning period, success rates were also similar between the two groups (*Figure 2A*,*2B*). After therapy discontinuation, the weaning success rate remained at 33.3% at both weeks 16 and 24 in the dose reduction group, and while it decreased from 57.1% at week 16 to 42.9% at week 24 in the frequency reduction group. There were no significant differences in weaning success rates between the groups during the off-therapy period (P=0.62 and P>0.99).

In the ITT analysis, the weaning success rate at 12 weeks was significantly higher in the high-dose group compared to the low-dose group (*Figures 2C*, P=0.04). However, this difference was not significant during the off-therapy period. Additionally, in the PP analysis, there were no significant differences in weaning success rates between the high-dose and low-dose groups throughout the study period (*Figure 2D*).

Secondary outcomes and adverse events

In the ITT analysis, there were no significant differences between the two groups in defecation frequency, number of fecal incontinence episodes, stool consistency, number of painful bowel movements, or compliance during the weaning period (*Table 2*). Both groups maintained defecation frequencies of approximately 4 to 5 times per week, with good stool consistency and compliance, and no instances of painful defecation. There were no reported fecal incontinence events during the weaning period for either group. In the PP analysis, defecation frequencies were 4.5 (range, 3–10), 5.5 (range, 3–8), and 5 (range, 3–9) times per week at weeks 4, 8, and 12 in the dose reduction group, compared to 5.4 (range, 4–7), 5 (range, 4–7), and 4.75 (range, 4–6) times per week in the frequency reduction

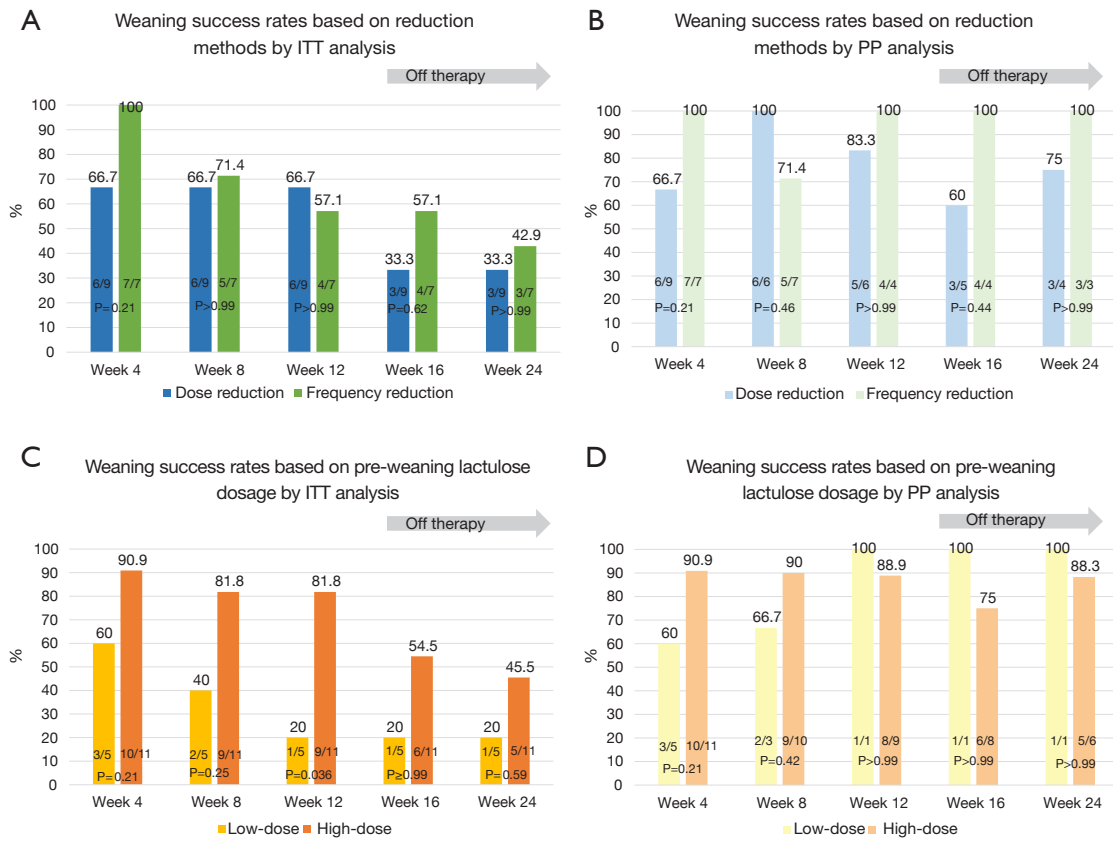

Figure 2 Weaning success rates by drug discontinuation strategy. (A) Weaning success rates based on reduction methods by ITT analysis; (B) weaning success rates based on reduction methods by PP analysis; (C) weaning success rates based on pre-weaning lactulose dosage by ITT analysis; (D) weaning success rates based on pre-weaning lactulose dosage by PP analysis. There were no significant differences in weaning success rates between the dose reduction group and the frequency reduction group at 4 weeks, 8 weeks, 12 weeks, or during the off-therapy period, according to both ITT and PP analyses. ITT, intention-to-treat; PP, per-protocol.

group, with no significant differences between groups. Stool consistencies, number of incontinence episodes, painful defecation, and compliance were also comparable between groups in the PP analysis.

Overall clinical symptoms during the weaning period were favorable and are detailed in Table S2. The number of patients with ≥3 bowel movements per week was 14 (87.5%) at week 4, 16 (100%) at week 8, and 13 (81.3%) at week 12. The number of patients with a Bristol Stool Form Scale score ≥3 was 16 (100%) at week 4, 15 (93.8%) at week 8, and 13 (81.3%) at week 12. The percentage of patients without painful defecation was 68.7% (n=11) at week 4, increasing to 81.2% (n=13) at week 8, and 100% (n=16) at week 12. No significant differences were observed in the number of patients between the dose reduction group and the frequency reduction group.

Adverse events reported included abdominal pain, distension, and diarrhea; however, no serious events occurred during the study period (Table S3). Specifically, two patients in the dose reduction group reported abdominal pain and distension at week 4, while two patients in the frequency reduction group reported abdominal pain at weeks 4 and 8. There were no significant differences in adverse events between the groups.

Patient satisfaction rates were similar between the two groups. In the ITT analysis, satisfaction rates were 77.8% *vs.* 57.1% at week 12 (P=0.60) and 77.8% *vs.* 42.9% at week 24 (P=0.30), in the dose reduction group and the frequency reduction group, respectively. In the PP analysis, satisfaction rates were 83.3% *vs.* 100% at week 12 (P>0.99) and 100% *vs.* 100% at week 24, in the dose reduction group and the frequency reduction group, respectively.

Table 2 Secondary outcomes during the weaning period

Variable	Weeks	Dose reduction (n=9)	Frequency reduction (n=7)	P
Frequency of defecation (per week)	Week 4	4 [2–5]	5.5 [4–7]	0.12
	Week 8	5 [3–8]	5 [3–9]	0.91
	Week 12	5 [3–6]	4.5 [4–6]	0.68
No. of incontinence (per week)	Week 4	0 [0–3]	0 [0–0]	0.20
	Week 8	0 [0–0]	0 [0–0]	>0.99
	Week 12	0 [0–0]	0 [0–0]	>0.99
Stool consistency	Week 4	4 [3–4]	3.5 [3–4]	0.34
	Week 8	4 [3–4]	4 [2–5]	0.91
	Week 12	4 [3–4]	4 [4–4]	0.78
Number of painful defecation (per week)	Week 4	0 [0–1]	0.5 [0–3]	0.33
	Week 8	0 [0–1]	0.5 [0–1]	0.82
	Week 12	0 [0–1]	0 [0–0]	0.46
Compliance	Week 4	90 [80–100]	95 [90–100]	0.39
	Week 8	95 [90–100]	100 [60–100]	0.39
	Week 12	100 [83–100]	100 [60–100]	0.58
Patients' satisfaction	Week 12	7/9 (77.8)	4/7 (57.1)	0.60
	Week 24	7/9 (77.8)	3/7 (42.9)	0.30

Only intention-to-treat analysis results are presented; results from the per-protocol analysis are consistent. Data are presented as medians with ranges or as numbers with percentages.

Discussion

It is well established that maintenance therapy for pediatric FC is crucial, yet there is no RCT examining the optimal duration of maintenance therapy or weaning methods. According to expert opinions, maintenance therapy should continue for at least two months, with weaning beginning when symptoms are sufficiently reduced or absent for at least one month (4). This implies that weaning of laxatives may be considered when patients show a defecation frequency of at least three times per week and no longer meet the Rome IV criteria for FC. Dosage and frequency of medication should be reduced gradually to prevent relapse (16). While these principles are outlined, specific protocols for drug reduction are not provided. To address this gap, we conducted this pilot RCT to investigate optimal methods for weaning osmotic laxatives in children with FC.

We enrolled children with FC and randomly assigned them to two different weaning protocols: gradual reduction of lactulose dosage or reduction in the frequency of medication intake. We did not find significant differences in weaning success rates between the two groups during the three-month weaning period or the subsequent three-month off-therapy period. Approximately 62% of patients successfully weaned off lactulose at week 12, though success rates at weeks 4, 8, and 12 gradually decreased. After therapy cessation, success rates declined to 45.2% at week 16 and 38.1% at week 24. Although we included only patients who had been on lactulose for at least three months and had maintained treatment success for at least three months, the weaning success rates post-therapy were low in the ITT analysis. The success rates were higher in the PP analysis, indicating that patients who successfully weaned off lactulose were better followed up.

In the subgroup analysis, the pre-weaning high-dose lactulose group (>1.5 g/kg/day) demonstrated a significantly higher weaning success rate at 12 weeks compared to the low-dose lactulose group (≤1.5 g/kg/day). The recommended dose of lactulose for maintenance treatment is 1–4 g/kg/day (4). Although our study has a small sample size and should be interpreted with caution, the findings

suggest that adequate doses of lactulose for maintenance treatment may facilitate successful weaning.

Not only were weaning success rates, but also other outcomes such as defecation frequency, number of incontinence episodes, stool consistency, painful defecation, compliance, and patient satisfaction with the weaning methods not significantly different between the two groups. Additionally, there was no difference in the number of adverse events reported. Overall clinical symptoms during the weaning period were favorable for most patients, except for defecation pain reported by approximately 31% of patients in the early stages of weaning. More than 80% of patients had ≥3 bowel movements per week and a Bristol Stool Form Scale score ≥3. These outcomes did not differ significantly between the two groups. Therefore, we suggest that the choice of weaning method may be guided by the preferences of both physicians and patients, provided that basic principles are followed.

A recent pediatric pilot study on laxative weaning in children with FC involved reducing the dose of senna by 10–25% with re-evaluations every two weeks over a period of 3 to 6 months. If symptoms worsened, a lower dose was maintained until re-evaluation. Nine patients (56.3%) successfully weaned off laxatives in a median of 3.7 months [interquartile range (IQR), 1.3–11.6 months], which is similar to our findings (17). However, this study was not a RCT, and senna, a stimulant laxative, is not typically used for long-term maintenance therapy in children with FC (4). There are no other studies on the weaning protocols for osmotic laxatives, either in children or adults.

We found limited research on the prognosis of pediatric FC. A systematic review of 14 prospective follow-up studies involving 1,752 children with FC examined outcomes. Among patients followed for 6 to 12 months, approximately 49% had recovered and stopped laxatives by the follow-up. About 60% of children with FC had no symptoms of constipation, regardless of laxative use, after 6 to 12 months. After a follow-up period of 5 to 10 years, approximately 56% of patients with FC had recovered without requiring laxatives (18).

Our study has several limitations. First, as a pilot study, it includes a small number of patients, so the results should be interpreted with caution. Further research with a larger population is needed to validate these findings. Second, PEG was not used as maintenance therapy in this study because it was not approved for pediatric FC in South Korea during the study period. In countries where PEG is unavailable, lactulose is recommended as the first-line treatment. Third, the study focused solely on weaning methods for lactulose and did not account for other factors that could influence outcomes, such as dietary habits, weight-related issues, and eating patterns. However, according to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN/NASPGHAN) recommendations, additional fiber intake, fluid intake, and physical activity have minimal effect on the treatment of FC (4).

Despite these limitations, this study represents the first RCT study investigating weaning protocols for osmotic laxatives in FC. Conducting a prospective study with good compliance is challenging due to the ease of symptom control with medication. Although the sample size was small, all participants were followed up for a significant duration with good compliance, and random assignment to the two groups was performed without significant differences. Additionally, the methods for weaning, including the dose of lactulose and the frequency of administration, were significantly different between the groups, indicating adherence to the study protocol.

Given the multifactorial pathophysiology of FC in children, treatment should not rely solely on pharmacological approaches, and lifestyle modifications, dietary changes, and toilet training are also crucial for effective management (19). The ability to discontinue maintenance therapy typically depends on the duration and effectiveness of initial treatment, as well as the quality of follow-up care. Therefore, pediatricians should emphasize the importance of follow-up care and educate patients with FC about comprehensive treatment strategies.

Conclusions

After successful maintenance therapy with lactulose in children with FC, the method of drug discontinuation did not significantly influence the weaning success rate. However, pre-weaning lactulose doses exceeding 1.5 g/kg/day may enhance the success rate of weaning at 12 weeks. Despite gradual tapering of the medication over a period of 3 months in patients who had experienced successful treatment for at least 3 months, the overall weaning success rate remained low. Therefore, careful management of drug discontinuation and thorough follow-up is essential.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-436/rc

Trial Protocol: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-436/tp

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-436/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-436/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The institutional review boards of all participating hospitals approved the study (Hallym University Sacred Heart Hospital 2020-05-022-001, Soonchunhyang University Bucheon Hospital 2020-06-019-002, Daejeon Eulji Medical Center 2013-10-013-002). All participants and their parents provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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