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Gastroenterology

Efficacy of lubiprostone for functional constipation treatment in adolescents and children: Randomized controlled trial

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Abstract

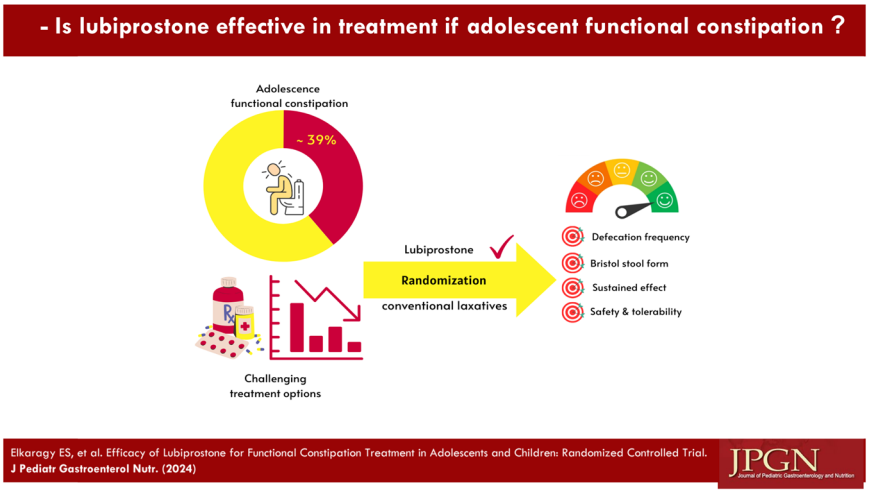
Objectives: Adolescent and pediatric functional constipation (FC) is a common clinical problem. Currently, data on lubiprostone for the treatment of pediatric FC are scarce. This study investigated the efficacy and safety of lubiprostone in the treatment of pediatric FC.

Methods: In a single-blinded, randomized controlled study, we included 280 patients aged 8–18 years with FC. Patients were randomized either to a weight-based lubiprostone dose ($n = 140$) or conventional laxatives ($n = 140$), including lactulose, bisacodyl, or sodium picosulfate, for 12 weeks, followed by 4 weeks posttreatment follow-up.

Results: Improvement in constipation was achieved in 128 (91.4%) patients in the lubiprostone group, and in 48 (34.3%) patients of the conventional therapy group ($p < 0.001$) and was sustained after treatment discontinuation. One quarter of the lubiprostone group experienced the first spontaneous bowel motion within 48 h after dose initiation. A total of 75.7% of the lubiprostone group could achieve and sustain Bristol stool form of 3 or 4 during the last 4 weeks of therapy and through the 4 weeks of follow-up versus 50 (35.7%) patients in the conventional therapy group ($p < 0.001$). No life-threatening adverse drug reactions were encountered, and no treatment-related discontinuation. Mild self-limited colicky abdominal pain and headache were the most prevalent side effects in the lubiprostone group.

Conclusions: Lubiprostone is an effective and well-tolerated pharmacotherapy for youthful age and pediatric age groups, which may alter the paradigm of pediatric FC treatment.

Abbreviations: BSF, Bristol stool form; FC, functional constipation; ITT, intention-to-treat; PEG, polyethylene glycol; SBM, spontaneous bowel motion; TRAE, treatment-related adverse effect.



KEYWORDS

bowel movement, defecation, lactulose, laxatives, young adults

1 | INTRODUCTION AND AIM

Constipation is a common clinical problem worldwide affecting up to 39% of children and adolescents[1–3] with a negative health impact. It is essential to diagnose and start therapy early to reduce the physiological and psychological consequences.[4] Currently, the clinical diagnosis of functional constipation (FC) in paediatrics and adolescents is dependent on ROME IV.[5]

To date, the treatment of FC has been challenging. In addition to diet, exercise, and fluid intake, pharmacological agents have been evaluated with variable success rates, tolerances, and acceptability. Although oral polyethylene glycol (PEG) is superior to lactulose, it is not accepted by many patients and is not palatable (especially formulas with electrolytes), so its utility is still a challenge in clinical practice.[2,6] Lactulose, although safe and commonly used, is associated with bloating, diarrhoea, and an extra-sugary taste. Lactulose is not superior to stimulants or osmotic laxatives in terms of success rates.[2] Furthermore, parents refrain from long-term medication use for fear of the rebound "which is present with some medications," and habituation.[2]

Lubiprostone, an approved safe and effective pharmacotherapy for adult FC, is a specific activator of chloride channel-2 which is abundant on the apical membrane of intestinal epithelial cells.[7] Lubiprostone enhances the influx of chloride into the intestinal lumen, followed by sodium and water to maintain isotonic equilibrium. This excess fluid softens stool and improves intestinal transit via the activation of local stretch receptors.[8,9]

To the best of our knowledge, studies addressing the therapeutic use of lubiprostone for childhood FC are scarce.[10–12] Although safety results of lubiprostone have been comparable to conventional laxatives[10,12]; lubiprostone was an effective therapy in a noncontrolled trial by Hyman et al.[10] and was not superior to a placebo in a controlled trial by Benninga et al.[11] European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) could not provide clear statements about the efficacy of lubiprostone for the treatment of childhood FC, representing a gap in clinical practice.[6] The current study aimed to assess the efficacy and safety of lubiprostone in the treatment of childhood FC.

What is Known

- Current treatment of childhood functional constipation (FC) is challenging.
- Lubiprostone efficacy for childhood and adolescents' FC is not fully evaluated.

What is New

- Lubiprostone is an effective and safe therapy for childhood and adolescent functional constipation.
- Lubiprostone effect is found to be sustained after treatment discontinuation.

2 | SUBJECTS, STUDY DESIGN, AND SAMPLE SIZE

This was a prospective, parallel, single-blinded, randomized controlled trial. The sample size was calculated for a power of 85%, an α-error of 0.05, and effect sizes of 30% and 15% for lubiprostone and lactulose,

respectively.[13] The calculated sample size was adjusted for dropouts.[14] Based on these parameters, we intended to enrol a minimum of 129 patients in each group. Patients were recruited from the Department of Internal Medicine, Department of Pediatrics, and Department of Physical and Rehabilitation Medicine at the Faculty of Medicine, University of Alexandria, Egypt. Study recruitment started on February 15, 2022, and the last follow-up was on December 19, 2022.

2.1 | Eligibility criteria

- Patients aged 8 to <18 years of age who have a confirmed diagnosis of pediatric FC according to the Rome IV criteria,[5] who give written informed consent personally or from their legal guardians.
- Discontinuation of any medication affecting gastrointestinal motility at least 2 weeks before starting the treatment allocation.
- The patient's daily diary indicates an average of <3 times/week of spontaneous bowel movements (SBMs), with ≥25% of SBMs involving at least some straining and/or a 5-point modified Bristol stool form (BSF) scale of 1 or 2.

Participants were excluded if they had constipation attributed to physical, social, mental, or cognitive illness; inflammatory bowel disease; Hirschsprung's disease; medications known to cause constipation (Anticholinergic, calcium channel blockers, iron supplements…); or anatomical, neurological, endocrine, or metabolic etiologies. Patients who were candidates for or underwent abdominal surgery or had any condition other than constipation that could affect gastrointestinal motility or defecation were excluded. Patients with alarming signs of constipation, such as unexplained significant weight loss and patients with untreated fecal impaction at the time of enrollment were also excluded.

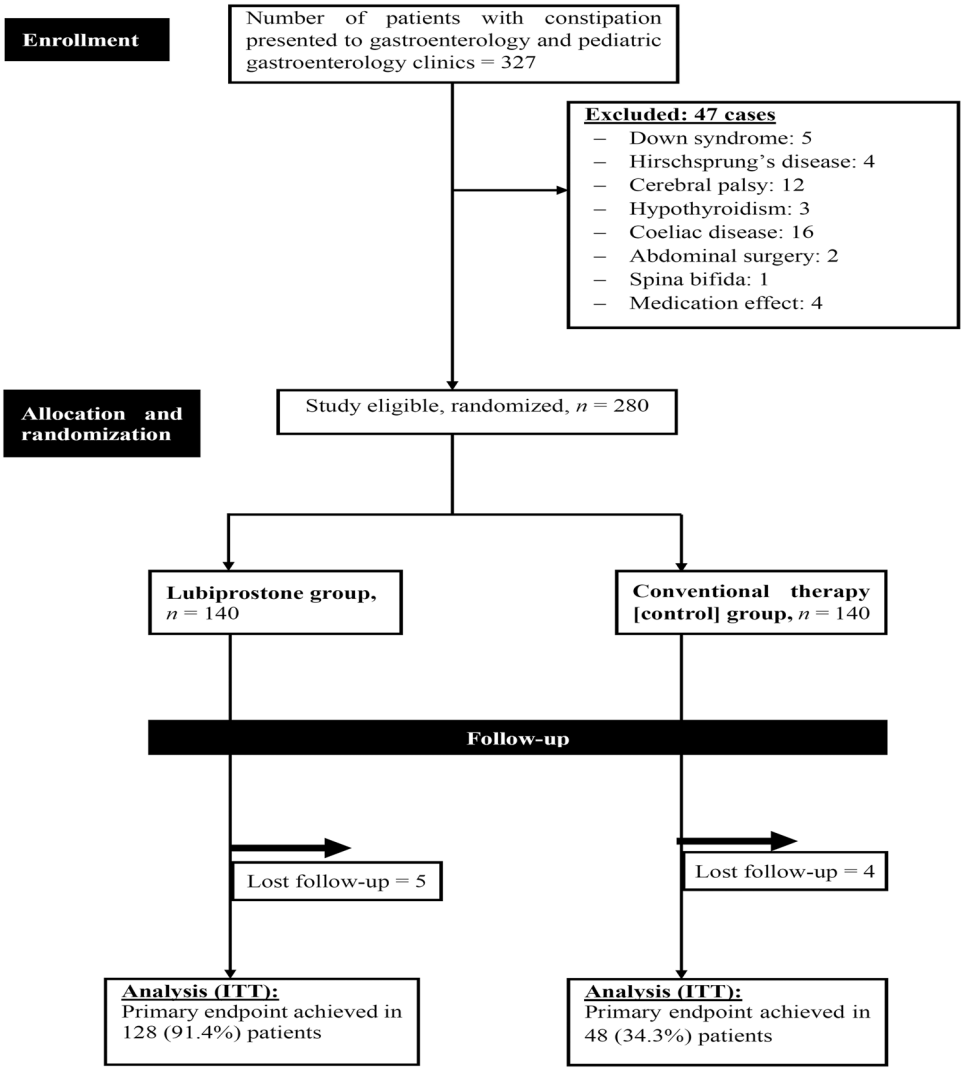


FIGURE 1 The CONSORT flow chart of the study.

2.2 | Ethical approval and informed consent

Informed consent was obtained from the parents or guardians of all enrolled participants. We discussed with all participants/legal guardians that we test a new medication that has been approved for adults CIC, and we compare it with conventional treatments in adolescents, but participants were not informed about the pharmaceutical form of medications (to facilitate concealment). In addition, when participants were randomized, we did not mention to them whether the prescribed treatment belonged to the medication of interest or to conventional therapy to avoid the placebo effect. The study was conducted following the provisions of the Declaration of Helsinki, as revised in 2013, and the Good Clinical Practice Guidelines. Institutional ethical committee approval was obtained (IRB: 0305299). The study was registered on clinicaltrial.gov registry: NCT05144295. Figure 1 shows the CONSORT flow diagram of the study.

3 | METHODS

Eligible patients were clinically evaluated for demographic data, weight, duration of constipation, number of SBM per week, BSF assessment, and focused history to exclude thyroid illness, food allergy, and alarming symptoms (weight loss, gastrointestinal bleeding, ……), and baseline laboratory investigations including a hemogram.

3.1 | Randomization and intervention

Using a computer-assisted, simple parallel randomization method, the participants were assigned to either lubiprostone capsules or conventional therapy (at a 1:1 ratio). The lubiprostone-assigned group received a weight-based dose calculated for their weight at the time of enrollment. Patients weighing <50 and ≥50 kg were administered lubiprostone 8 mcg TID or 24 mcg BID, respectively. The participants in the conventional therapy arm were randomly allocated to one of three conventional laxative therapies in our country (lactulose 1–3 mL/kg/day divided into two to four times [maximum 60 mL/day], bisacodyl tablet [5 mg/tablet] at a dose of 2 tab/day for <12 years or 3 tab/day for ≥12 years, or sodium picosulfate 0.75% drops in a daily dose of 2.5–20 mg/day). PEG was not available in our country at the time of study recruitment and allocation.

To prevent potential sources of selection bias, concealment of allocation was implemented by providing the treatment to the participants in opaque, sealed, serially numbered, nonlabelled jars/bottles of equal appearance and weight (after calculation of the corresponding appropriate dose) according to the allocation sequence. This was done by one of the investigators who had no further involvement in the research conduct, in collaboration with the clinical pharmacy department. Concealment in our study was intended for the participants, while the involved investigator was not blinded.

Apart from education (toilet training and withholding behaviour), participants were requested not to change their diet or daily physical activity throughout the study time to avoid confounding effects.

Patients and their parents/legal guardians were instructed to administer the doses at least 5 h apart with meals and a large volume of water. Both arms received treatment for 12 weeks, followed by 4 weeks of follow-up after the end of the treatment (Week 16). They were also instructed to document the number of SBM per week and define their BSF category for every bowel motion. They were given a pre-printed BSF chart and an empty timetable form pre-designed by the study team (in Arabic language). They were instructed to fill in the required data daily to ensure completeness of data and to avoid recall bias. These forms were collected regularly at every visit. The participants were encouraged to contact the study team by telephone if there were any adverse events, nonresponse, or impaction during treatment. In case of failure (48 h after the first dose), dose escalation was permitted through the investigator who was involved in concealment to avoid unmasking. For impaction, PEG ± enema was planned. Regular visits at 0, 2, 8, and 12 weeks for the assessment of efficacy and safety, and at Week 16 for efficacy follow-up was planned.

3.2 | Primary outcome

1. Improvement of constipation manifested as improved SBM defined as having ≥1 SBM/week increase in frequency compared with the baseline and maintaining ≥3 SBMs/week for at least 8 weeks, including the last four study weeks and 4 weeks of follow-up.

3.3 | Secondary outcomes

1. The number of participants who experienced their first SBM within 48 h after dose initiation.
2. Achieving and maintaining a Bristol score of 3 or 4 for the last 8 weeks of the study (the last 4 weeks of treatment plus 4 weeks of follow-up).
3. Number of SBMs per week at Weeks 8 and 12.

3.4 | Safety assessment

The safety assessment included all the patients who received at least one dose of their assigned treatment.

The safety endpoints included treatment-related adverse effects (TRAEs) grouped by the Medical Dictionary for Regulatory Activities version 19.1, system organ class and preferred term, and changes from baseline in an abbreviated physical examination including vital signs, body mass index (at every follow-up visit), and mean change in laboratory measures (at the baseline and Week 16).

3.5 | Statistical analysis

The sample size was calculated using G-Power software (v.3.1.9.4, Universität), and statistical analysis was performed using the IBM SPSS software package (Version 26.0; Armonk, NY: IBM Corp). Qualitative data were described using a number (percentage), while range (minimum–maximum), median, or mean ± standard deviation was used for quantitative data as appropriate. The chi-squared test or Fisher's exact test was used for categorical variables. The Kruskal–Wallis test and Mann–Whitney *U* test were used to compare means as appropriate. The Student's *t* test was used as appropriate. Statistical significance was set at a two-tailed $p < 0.05$.

4 | RESULTS

An initial screening phase for 6 weeks was followed to ensure the eligibility of the included participants. Forty-seven cases were excluded (Figure 1).

4.1 | Demographic data

The current study included 280 patients who were divided into two equal groups. Five (3.5%) patients in the lubiprostone group and four (2.8%) patients in the conventional therapy group lost follow-up visits. The analysis in the current study is an intention-to-treat (ITT) analysis. The two groups were age- and sex-matched. In the lubiprostone group, 112 (80%) patients received an 8 µg TDS dose, and 28 (20%) patients received a 24 µg BID dose. The mean ± SD duration of constipation before study enrollment was comparable in lubiprostone and conventional laxative groups (10.11 ± 5.00 vs. 9.94 ± 4.76 months, respectively, $p = 0.76$). Failure of previous laxative therapy [inadequate response to at least one laxative medication for a minimum of 4 weeks before enrollment] was encountered in 173 (61.8%) patients ($n = 280$), with the majority of failed medications including glycerin suppository, lactulose, senna, mineral oils, and bisacodyl. We did not encounter any case of stool impaction during the study course (Table 1 shows the baseline characteristics).

4.2 | Primary and secondary outcomes

Improvement in constipation (primary outcome) was achieved in 128 (91.4%) patients in the lubiprostone group and 48 (34.3%) patients in the conventional therapy group ($p < 0.001$, $\chi^2 = 105.42$). In the lubiprostone group, 34 (24.3%) patients experienced the first SBM within 48 h after dose initiation (secondary outcome) compared to 31 (22.14%) patients in the conventional therapy group ($p = 0.64$, $\chi^2 = 0.21$).

In addition, 106 (75.7%) patients in the lubiprostone group achieved a sustained BSF of 3 or 4 during the last 4 weeks of therapy and through the 4 weeks of follow-up (secondary outcome) compared to 50 (35.7%) patients in the conventional therapy group ($p < 0.001$, $\chi^2 = 48.9$). The numbers of SBM at Weeks 8 and 12 (secondary endpoints) are shown in Table 2.

4.3 | SBMs and BSF for lubiprostone and conventional therapy groups across the study period

At baseline, the mean ± SD of SBM for lubiprostone and conventional therapy groups was comparable (1.23 ± 0.37 vs. 1.19 ± 0.28, $p = 0.27$, respectively). With treatment, the SBM/week was significantly higher in lubiprostone than in the conventional therapy group over successive treatment Weeks 2, 8, 12, and 4 weeks after treatment discontinuation. The mean change in SBM (Δ SMB) at 12 weeks of treatment compared to baseline was higher for the lubiprostone versus conventional therapy group (3.52 ± 1.12 vs. 1.50 ± 0.96 motions/week, $p < 0.001$), this difference was also sustained at 16 weeks of study (Table 2).

At baseline, the minimum-maximum (median) for BSF was 1–2 (1) for both lubiprostone and conventional therapy groups ($p = 0.26$). With treatment, a statistically similar initial improvement in both groups was observed in the second and eighth weeks ($p < 0.05$). However, this effect was lost thereafter, and the median value was higher for lubiprostone versus the conventional therapy group at 12 and 16 weeks ($p < 0.001$). The Δ change in BSF was higher in the lubiprostone group than in the conventional therapy group (Table 2).

4.4 | Post hoc analysis to compare lubiprostone and different medications in the conventional therapy group

We compared lubiprostone with different treatment medications in the conventional therapy group (lactulose [$n = 60$], bisacodyl [$n = 38$], and sodium picosulfate [$n = 42$]) as regards SBM. At baseline, all subgroups were matched with the lubiprostone group ($p = 0.25$). At

TABLE 1 Baseline characteristics of the study groups (ITT analysis).

Baseline parameters	Lubiprostone ($n = 140$)	Conventional therapy ($n = 140$)	p*
Male gender: *n* (%)	69 (49.3)	77 (55)	0.40**
Age (years)	10.44 ± 2.39	10.57 ± 2.37	0.63
Duration of constipation (month)	10.11 ± 5.00	9.94 ± 4.76	0.76
Failed previous laxative therapy (yes)	85 (60.7)	88 (62.9)	0.81**
Weight (kg)	38.48 ± 9.95	37.70 ± 10.69	0.52
Hb (g/dL)	12.14 ± 0.83	12.29 ± 0.88	0.13
Platelets ($\times 10^3$)	259.65 ± 62.35	262.03 ± 64.44	0.75
WBCs ($\times 10^3$)	7.51 ± 1.67	7.58 ± 1.57	0.08
Medication received: *n* (%)			
Lubiprostone 8 μg TDS	112 (80)	-	
Lubiprostone 24 μg BID	28 (20)	-	
Lactulose syrup	-	60 (42.9)	
Bisacodyl tablet	-	38 (27.1)	
Sodium picosulfate drops	-	42 (30)	
Medication dose in the study			
Lactulose syrup (mL)		30.33 ± 6.96	
Bisacodyl tablet (mg)	-	12.36 ± 2.53	
Sodium picosulfate drops (mg)	-	10.78 ± 3.84	

Abbreviations: BID, two times a day; HB, hemoglobin; ITT, intention-to-treat; TDS, three times a day; WBC, white blood cell.
*p Value for independent sample Student's t test. **p Value for the chi-square test.

2 weeks, lubiprostone increased the mean SBM more than lactulose and sodium picosulfate but was similar to that of bisacodyl. Thereafter, the mean ± SD of SBM for lubiprostone was higher than that of all other laxatives used in the conventional therapy arm until the end of follow-up ($p < 0.001$). Similarly, the Δ change in SBM at 12 weeks and 16 weeks was significantly higher for the lubiprostone group in comparison to other subgroups (Supporting Information: Table 1).

4.5 | Following the medication effect over time regarding SBM over time

With treatment, patients who received lubiprostone showed an incremental improvement in the mean value of SBM (1.23 motion/week at baseline vs. 4.78 motion/week at 12 weeks), and this effect was maintained thereafter up to Week 4 after treatment discontinuation (4.73 motions/week). This effect was comparable for both the 8 and 24 μg doses of lubiprostone.

In comparison, the improvement in constipation in the conventional therapy group was incremental during the first 8 weeks, then the effect gradually decreased during Weeks 8–12 of the study, and was lost during 4 weeks after treatment discontinuation (Figure 2).

4.6 | Treatment-related adverse-effects

Overall, side effects were reported in 46% and 48% of lubiprostone and conventional therapy groups, respectively ($p = 0.99$). Mild self-limited colicky abdominal pain (26%) and headache (14%) were the most prevalent side effects in the lubiprostone group, whereas colicky abdominal pain (22%), diarrhoea (12%), and bloating were more common in the conventional therapy group (Supporting Information: Figure 3). All side effects were self-resolving, no severe TRAEs and no treatment-related discontinuation was encountered.

5 | DISCUSSION

FC in adolescents below 18 years is a growing problem worldwide. This may be because of dietary, cultural, and socioeconomic factors. In addition to lifestyle and behavioral interventions, pharmacotherapy is considered the mainstay of therapy.[1,2]

TABLE 2 Spontaneous bowel motion (SBM) and Bristol stool form (BSF) at baseline, and at different study weeks for both study groups (ITT).

Study week	Lubiprostone group ($n = 140$)	Conventional therapy group ($n = 140$)	p[a]	95% CI
SBM[b]				
SBM baseline	1.23 ± 0.37	1.19 ± 0.28	0.27	−0.03 to 0.12
SBM 2 weeks	3.05 ± 0.94	2.64 ± 1.58	0.01	0.10–0.71
SBM 8 weeks	4.21 ± 0.97	2.97 ± 1.32	<0.001	0.96–1.51
SBM 12 weeks	4.74 ± 1.11	2.70 ± 1.04	<0.001	1.78–2.31
SBM 16 weeks	4.69 ± 1.25	2.25 ± 1.01	<0.001	2.17–2.71
Δ SBM 0–12 weeks	3.52 ± 1.12	1.50 ± 0.96	<0.001	1.76–2.26
Δ SBM 0–16 weeks	3.52 ± 1.28	1.06 ± 0.87	<0.001	2.19–2.73
BSF[c]			p[d]	
BSF at baseline	1–2 (1)	1–2 (1)	0.26	-
BSF at 2 weeks	1–4 (2)	1–4 (2)	0.28	-
BSF at 8 weeks	1–4 (3)	1–5 (3)	0.12	-
BSF at 12 weeks	2–4 (4)	1–4 (2)	<0.001	-
BSF at 16 weeks	1–4 (4)	1–4 (2)	<0.001	-
Δ BSF 0–12 weeks	0–3 (2)	0–3 (1)	<0.001	-
Δ BSF 0–16 weeks	0–3 (2)	0–3 (1)	<0.001	-

Note: Δ delta (change from baseline).

Abbreviations: CI, confidence interval; ITT, intention-to-treat.

[a]Student's *t* test.

[b]Values are expressed as (mean ± SD).

[c]Values are expressed as minimum–maximum (median).

[d]Mann–Whitney *U* test.

Unfortunately, the currently available pharmacological interventions have many limitations, including efficacy and tolerance issues.[2,6] Lubiprostone has been approved for adult FC. However, data regarding its role in childhood and pediatric patients are limited.[10–12]

The current study showed that lubiprostone was superior to conventional laxatives in terms of improving SBM and BSF. In the current study, the clinical response was significantly higher in the lubiprostone group (91.4%) than in the conventional laxatives group (34.3%). Even in the subgroup analysis, lubiprostone was superior to different laxatives that were used in our study. In addition, the improvement in SBM was sustained even after treatment discontinuation, in contrast to conventional laxatives, which lost their effect in most cases that showed an initial improvement.

To the best of our knowledge, trials of lubiprostone in FC in patients aged <18 years are limited. Hyman et al. investigated the safety and effectiveness of lubiprostone in 124 patients with FC aged 12–17 years. They reported an overall response rate of 50.8%, with a significant increase in the mean SBM compared to the baseline (3.1 vs. 1.5 SBM/week, $p < 0.0001$). However, this was an open-label noncontrolled study.[10]

In a clinical trial by Benninga et al., which was designed to evaluate the efficacy and safety of lubiprostone in patients with FC aged 6–17 years in a placebo-controlled design, they concluded that lubiprostone was not superior to placebo in terms of efficacy (18.5% vs. 14.4% response rates), in contrast to our study results.[11]

The high response rate in our study in comparison to results reported by Benninga et al., may be explained by certain factors. First, the difference in race and ethnicity may have a potential influence on disease and treatment response[15]; Second, our study was conducted in a tertiary care hospital with a large population of children with CIC, which may have increased the likelihood of identifying eligible participants. Third, unlike Benninga et al., we did not include participants with faecal impaction, which may indicate a milder form of constipation among our cohort. Fourth, we included a relatively lower percentage of patients who failed laxative therapy before enrollment (61.7% vs. 72%). Fifth, we reported a

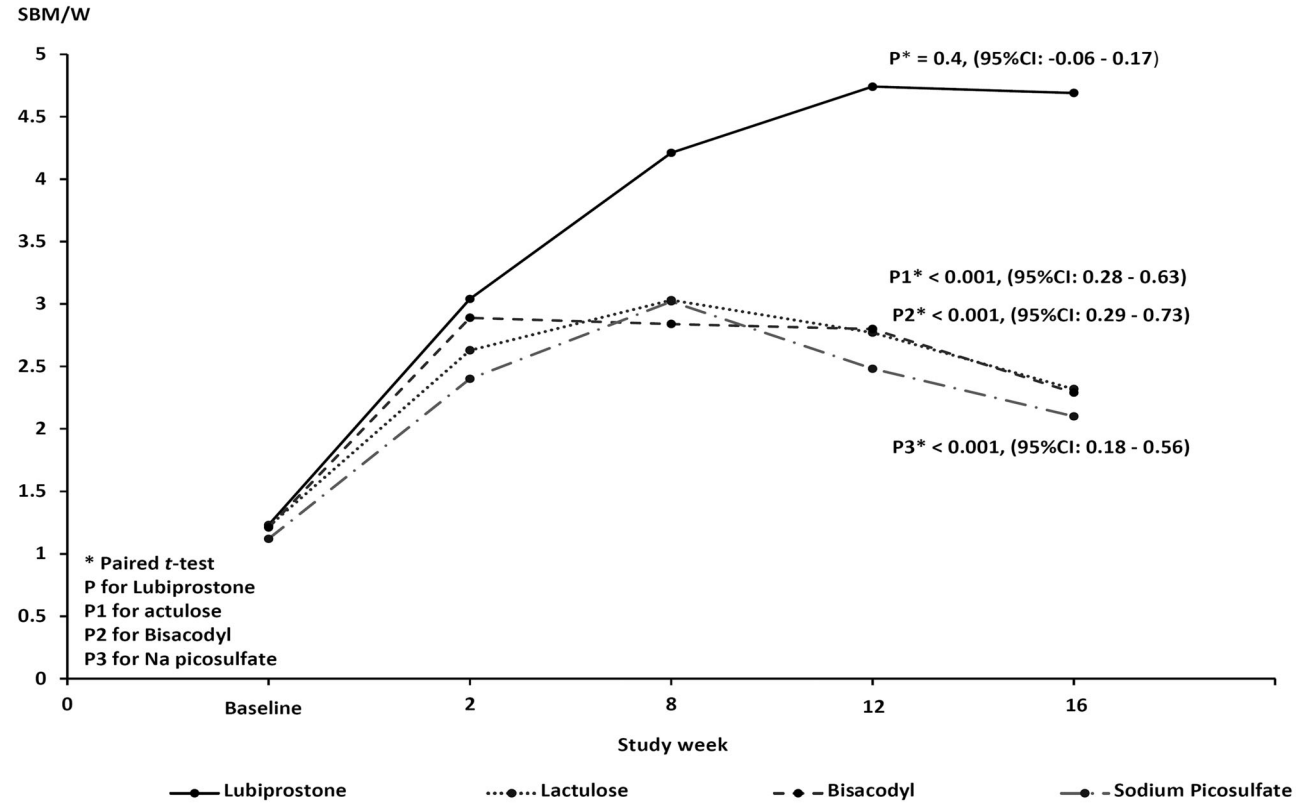


FIGURE 2 Medications effects over study weeks.

relatively lower withdrawal rate (3.2%) compared to 16% in the study reported by Benninga et al. Moreover, in the current study, we have a relatively short duration of constipation among our cohort (10.02 ± 4.87 months) in our study, although this was comparable between the lubiprostone group and conventional laxatives group ($p = 0.76$). We acknowledge that further research is needed to fully understand the reasons for the high response rate in our study.

Worth mentioning that, our study has the advantage of the active comparator, unlike the previous trial[11] which compared lubiprostone to placebo, not to active treatment; and the nonsignificant difference between the two arms may be due to the high response rate in placebo rather than the low response in lubiprostone arm "i.e. Placebo effect" which may range between 4% to 44% in previous clinical trials.[16]

The effect of lubiprostone in the current study was rapid, where one quarter of the cases achieved the first SBM within 48 h of the first dose. This can be explained by the rapid onset of action and time to peak plasma concentration of lubiprostone, which is approximately 1.5 h.[8] Also, this is considered a reflection of the mechanism by which lubiprostone facilitates defecation through fluid release into the GUT lumen. The mechanism of action of lubiprostone was reflected in BSF, which was improved by 2 points (range 0–3) at the end of the treatment duration. Moreover, the improved SBM frequency and BSF were sustained for 4 weeks after treatment cessation. The secretion of fluids into the gut lumen adds fluid to the stool, causing an increase in volume with bowel distension. This has been suggested to stimulate local stretch receptors and increase colon transit.[9,17] Resetting of the defecation reflex and coordination of colonic motility may be suggested as an additional mechanism responsible for the sustained effect of lubiprostone. This hypothesis requires further testing in future studies. Moreover, lubiprostone has been found to mitigate intestinal dysbiosis through increasing *Lactobacillus* and *Prevotella* spp. which are known to be deficient in patients with CIC.[18] Also, intestinal mucin secretion is facilitated by lubiprostone. All these properties may explain the high efficacy and sustainability of the laxative effect of lubiprostone.

In agreement with our study, Johanson et al. previously addressed the sustainability of the effect of lubiprostone on constipation in adults. They found that the effect of lubiprostone on SBM was sustained for 4 weeks after treatment discontinuation compared with placebo (5.59 vs. 3.04; $p = 0.046$).[19]

Data about short-term prognosis after weaning of conventional individual laxatives is limited. In a systematic review by Pijpers et al.,[20] 35%–65% of children were followed for 6–12 months. They reported a recurrence of constipation after cessation of therapy. In a retrospective study by Chanpong et al.,[21] 46% of

patients relapsed at a 1-year follow-up after PEG discontinuation. In another trial including enemas and oral lactulose, within 1 year after the 6- to 8-week treatment period, relapse occurred in 27% of patients ($n = 418$).[22] A recently published open-label comparative study compared PEG and lactulose in 43 children for 12 weeks of treatment followed by 4 weeks of weaning-off. They reported a higher relapse rate in the lactulose group versus the PEG group (13.6% vs. 5%, $p = 0.04$).[23]

In the current study, lubiprostone was well-tolerated. The overall side effects were comparable between the groups (46% vs. 48%, $p = 0.99$). Colicky abdominal pain and headaches were the most prevalent side effects in the current study, followed by nausea. No life-threatening adverse events or treatment-related withdrawals were observed.

The long-term safety of lubiprostone in adolescents has also been extensively tested by Hussain et al. They investigated the safety of lubiprostone exposure for 24 weeks in a phase III trial. Of their cohort, 57.1% and 48.4% reported ≥1 TRAEs for 12 and 24 mcg lubiprostone, respectively. Two serious TRAEs (6.5%) were reported in the lubiprostone 24-mcg BID group, and neither one was drug-related. The proportions of patients discontinuing because of adverse events were 12.5% and 16.1%, respectively. Upper abdominal pain was the only TRAE leading to discontinuation (of 12 patients in total) that occurred in >1 patient.[12] Diarrhea and vomiting were the most frequent (≥3% of patients). They reported no difference between different doses of lubiprostone as regards TARE. They did not report any safety issues regarding vital signs, abbreviated physical examinations, and laboratory parameters.[12] Similar results were also reported by Johanson et al.[24–26] In addition, Hyman et al. reported an overall incidence of side effects of 65%. Nausea, vomiting, diarrhea, abdominal pain, and headache (5.6%) were commonly reported side effects. In all these studies, the side effects were mild and not dose-dependent.[10]

In the current study, the large number of cases, the randomized design, active control rather than placebo, and the presence of follow-up after treatment discontinuation to assess relapse are potential strengths. We consider non-blinding for one of the study investigators a limitation in our study; however, the patients and the other study investigators were blinded, and we had to breach the blinding for one of the investigators " who is not further involved in the study" because of the difference in drug formats (lubiprostone is in capsule form, lactulose is a syrup, bisacodyl is in tablet form and sodium picosulfate is in oral drop form). Also, our cohort may have included milder forms of constipation; however, this applies to both study arms.

In conclusion, the current study highlights that lubiprostone is an effective and well-tolerated pharmacotherapy for young adults <18 years and pediatric age groups, which may alter the paradigm of pediatric FC treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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