

Treatment of Childhood Functional Constipation: Comparison of Senna, Trimebutine and Lactulose

Çocukluk Çağında Fonksiyonel Kabızlık Tedavisi: Senna, Trimebutin ve Laktülozun Karşılaştırılması

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ABSTRACT

Objective: Data for the drugs used in maintenance therapy of functional constipation is limited in childhood. We aimed to evaluate the efficacy of senna, trimebutine, and lactulose in children with functional constipation (FC) or functional fecal incontinence (FFI).

Material and Methods: Patients (2-18 years old) diagnosed as FC or FFI according to Rome III criteria who were treated with lactulose (n=36), senna (n=29), and trimebutine (n=33) were included. Patients completed a 0-5 Likert scale questionnaire about their symptoms. Stool consistency was evaluated by the Bristol Stool Chart. Compliance and tolerance to treatment and side effects were recorded. Clinical improvement and pharmacoeconomic evaluation were performed.

Results: Clinical improvement in the senna group was significantly higher (p=0.036). Senna showed the highest improvement in stool consistency (p<0.001) and decreased fecal incontinence (p=0.039). Abdominal distention, abdominal pain, nausea/vomiting, and anal fissure were improved by trimebutine (p<0.05). Both senna and trimebutine decreased painful defecation and stool withholding. Lactulose improved anorexia and anal fissure. Senna was the most cost-effective drug.

Conclusion: Treatment options for constipation should be tailored according to the predominant symptom. Lactulose may be recommended as the initial treatment for children with anorexia or anal fissure, trimebutine for abdominal distention, abdominal pain, nausea/vomiting, or anal fissure, respectively. Senna may be prescribed for the cost-effectiveness with high clinical improvement and less unpleasant taste.

Key Words: Constipation, Lactulose, Sennosides, Trimebutine

ÖZ

Amaç: Çocuklarda fonksiyonel kabızlık tedavisinde kullanılan ilaçlarla ilgili bilgiler sınırlıdır. Amacımız fonksiyonel kabızlık (FK) veya fonksiyonel fekal inkontinans (FFI) olan çocuklarda senna, trimebutin ve laktülozun etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Roma III kriterlerine göre fonksiyonel kabızlık (FK) veya fonksiyonel fekal inkontinans (FFI) tanısı koyulan, laktüloz (n=36), senna (n=29) ve trimebutin (n=33) tedavisi alan hastalar (2-18 yaş) alındı. Hastalar semptomlarıyla ilgili 0-5 Likert anket ölçeğini doldurdular. Dışkı kıvamı Bristol Dışkı Skalasına göre değerlendirildi. Tedaviye uyum, tolerans ve yan etkiler kaydedildi. Klinikteki düzelme değerlendirildi, farmakoekonomik inceleme yapıldı.

Bulgular: Senna grubunda klinik düzelme anlamlı ölçüde yüksekti (p=0.036). Senna dışkı kıvamında en fazla iyileşme sağladı (p<0.001) ve fekal inkontinansı azalttı (p=0.039). Karında distansiyon, karın ağrısı, bulantı/kusma ve anal fissür trimebutinle düzeldi (p<0.05). Senna ve trimebutin ağırlı defekasyonu ve dışkı tutmayı azalttı. Laktüloz iştahsızlık ve anal fissürü iyileştirdi. Senna en fazla maliyet etkinliği olan ilaçtı.

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Sonuç: Kabızlık için tedavi seçenekleri ağırlıklı görülen semptomla göre dizayn edilmelidir. Laktüloz iştahsızlık veya anal fissürü olan çocuklarda başlangıç tedavisinde önerilebileceği gibi, trimebutin karında distansiyon, karın ağrısı, bulantı/kusma veya anal fissür olanlarda seçilebilir. Senna maliyet etkinliği, yüksek klinik düzelme ve daha az tat problemi nedeniyle seçilebilir.

Anahtar Sözcükler: Kabızlık, Laktüloz, Senna, Trimebutin

INTRODUCTION

Functional constipation (FC) and functional fecal incontinence (FFI) are common problems in childhood, affecting 0.3-28% of children (1,2). Despite the paucity of randomized trials, laxatives, either single- or multi-agent therapy, are the first line of treatment in constipation (3-6). The treatment of FC and FFI in children consists of education, disimpaction, and prevention of re-accumulation of feces and behavioral therapy. After disimpaction has been accomplished, the goal of treatment is to produce regular, soft painless bowel movements and to prevent relapse of constipation by stool-softening therapy. Laxatives as maintenance treatment for constipation have been extensively investigated in adults, but, controlled studies about the use of laxatives are lacking in children. Available oral laxatives are classified as osmotic and stimulant laxatives. Senna is a stimulant laxative, increases colon peristalsis, and stimulates liquid and electrolyte excretion in both colon and small intestine. Data about the use of senna in functional constipation is restricted (7-10). Trimebutine is an efficacious drug in both hyper or hypomotility of the gastrointestinal system (GIS). The actions of trimebutine on GIS are mediated via an agonist effect on peripheral mu, kappa, and delta opiate receptors which shorten the gastric emptying time and regulate the colonic contractions (11). It is usually used in children with irritable bowel syndrome (IBS) to prevent abdominal pain (12,13). Trimebutine was found effective in chronic idiopathic constipation in an adult study (14). Lactulose has been used traditionally in FC for decades (15). This study aims to evaluate the efficacy and side effects of lactulose, senna, and trimebutine comparatively in childhood functional constipation and functional fecal incontinence.

MATERIALS and METHODS

This observational-retrospective study was performed in our pediatric gastroenterology department between January 2012 to April 2013 and was approved by the local ethics committee (Approval number: 07-273-13). We used our electronic database (Avicenna) to identify all children with FC and FFI. We routinely follow-up patients with constipation monthly for clinical evaluation. At admission and each polyclinic control visits, all patients filled out a 25-item questionnaire on their symptoms. The questionnaire form included; defecation frequency, stool consistency according to Bristol stool chart score, painful defecation, stool withholding, fecal incontinence, rectal bleeding, abdominal distention, abdominal pain, nausea/vomiting, enuresis, and anorexia (16). For the clinical symptoms

of functional constipation, the questionnaire had a visual 5-point Likert scale, where 1 represented never and 5 represented every day. The following answers were covered: (2) less than a week, (3) sometimes, (4) frequently. Additionally, dietary behaviors were assessed by the same questionnaire and the patients/parents asked how often the child consumed fruit, vegetables, and dry legumes. Answers were recorded using the 5-point Likert scale described above. Dairy cows' milk and water intake were determined as milliliters. Stool consistency was evaluated by the Bristol Stool Chart (BSC) score from 1 to 7. Patients' defecation diaries were used to evaluate defecation frequency. All patients were given BSC to record stool consistency every day, and after 4 weeks of treatment mean BSC score was calculated.

Since the efficacy of senna, trimebutine, and lactulose in FC were not known, they were used randomly without any selection criteria in our clinic. We included children between 2-18 years of age, diagnosed as FC according to Rome III criteria who were started on lactulose, senna, or trimebutine treatment at admission and who had a control visit after four weeks of therapy. We excluded children who had organic constipation, multisystemic illness, or using drugs that cause constipation. Children who had received two or more drugs for constipation were also excluded. We carefully reviewed the medical records of all subjects and systematically recorded the following data; patients demographics, medical history, physical examination, name of the commenced drug at the diagnosis. After four -weeks of constipation therapy, changes in bowel habits, physical examination, patients' compliance to treatment, drug taste, and drug side effects were also recorded by the same questionnaire. The compliance of treatment was defined as usage of the drug every day as prescribed dosage and intervals.

The primary outcome was the presence of clinical improvement. Clinical improvement was defined as ≥ 3 bowel movements per week, fecal incontinence ≤ 2 times/month, absence of abdominal pain, and painful defecation. The patients who met all 4 criteria were considered to have clinical improvement. Secondary outcomes were adverse events and pharmaco-economic assessment.

Senna, trimebutine, and lactulose were ordered in the standard manner as described for the treatment of constipation in children. Senna is available only in tablet form for the treatment of constipation in our country. Syrup form is used short-term for the preparation of colonoscopy, so we used senna only in tablet forms for the treatment of functional constipation. It was ordered in a single dose of 7.5 mg/day between 2-5

years (trituated and was given in powder form), 15 mg/day in two doses between 5-10 years, 22.5 mg/day in three doses >10 years. Trimebutine pediatric dosage was 72 mg/day in three doses between 2-5 years and 144 mg/day in three doses >5 years in syrup formulation. Lactulose was ordered in syrup formulation 1 ml/kg/day in two doses. Drug costs were evaluated according to 2013 prices.

Statistical analysis

Statistical analysis was done using SPSS version 20.0. Continuous variables were presented as mean \pm SD or median, and categorical variables were presented as frequency (percentage).

The chi-square and Fisher's exact tests were used to evaluate differences for categorical variables. The data which is not normally distributed (age, weight, body mass z-score, duration of constipation, how much cows' milk consumption, stool consistency by BSC) were analyzed by the Kruskal-Wallis test. Kruskal Wallis multiple comparison test was used to determine which group or groups cause to difference when significant differences existed between parameters in difference analysis.

Repeated measures which are not normally distributed before and after therapy of each drug (defecation frequency, painful defecation, stool withholding, fecal incontinence, rectal bleeding, abdominal distention, abdominal pain, nausea/vomiting, enuresis, anorexia, anal fissure, fecal impaction) were analyzed by Wilcoxon signed ranks test. All statistical significance was defined as $p < 0.05$ (2-tailed).

Pharmacoeconomic assessment

The mean cost of drugs given to patients were analyzed. The cost of four weeks of treatment, mean cost per one patient

were analyzed and pharmacoeconomic assessment was done according to efficacy by cost-effectiveness- analysis. In June 2013 price of drugs containing lactulose (Duphalac syrup 670 mg/ml 300 ml, Solvay Pharmaceuticals, €3.41, Osmolac syrup 667 mg/ml 250 ml, Biofarma Pharmaceuticals, €2.91), senna (Senokot tablet 7.5 mg/50 tablet, Aris Pharmaceuticals, €1.88) and trimebutine (Debridat syrup 24 mg/5 ml 250 ml, Abdi İbrahim Pharmaceuticals, Tribudat syrup 24 mg/5 ml 250 cc, €3.18) were recorded.

RESULTS

Baseline characteristics

One hundred and ninety-three potential patients were reviewed during our study period, of which 95 patients were excluded from the study because of lack of control visit ($n=80$) or using combined laxatives ($n=5$), or had organic constipation secondary to systemic illness ($n=10$). Thus, data from 98 patients were analyzed. Of 98 children, 59.2% had fecal impaction which resolved by sodium phosphate enema. There was no statistical difference between groups for treatment with sodium phosphate enema ($p=0.244$). Sixty percent of children with anal fissure were treated by warm bath 3 times a day and topical anesthetics.

Thirty-six (36.7%) children had received lactulose, 29 (29.6%) senna and 33 (33.7%) trimebutine. All of the questions in the questionnaire form were filled out by the patients at admission and after four weeks of therapy. Age, age distribution, gender, duration of constipation, dietary habits were not different between the 3 groups. Nine children in the lactulose group, 3 children in the senna group, 6 children in the trimebutine group had no cow's milk consumption. Table I presents the

Table I: Patients' Characteristics and Dietary Habits According to The Group; Lactulose, Senna and Trimebutine.

	Lactulose (n=36)	Senna (n=29)	Trimebutine (n=33)	p
Sex Male, *	15 (41.7)	16 (55.2)	10 (30.3)	0.141
Age (years), mean \pm SD	6.45(2.3-16.7)	8.3 (2.9-17.3)	6.1 (2.1-17)	0.070
Age distribution *				
<4 years	8 (22.2)	3 (10.3)	10 (30.3)	0.277
4-6 years	7 (19.4)	2 (6.9)	6 (18.2)	
6-12 years	14 (38.9)	15 (51.7)	11 (33.3)	
>12 years	7 (19.4)	9 (31)	6 (18.2)	
Sex (F/M)	23/13	13/16	23/10	0.116
Body mass index z-score, mean \pm SD	-1.15 (-3.20-3.57)	0.76 (-1.22-3.91)	0.03 (-1.46-4.50)	0.062
Duration of constipation (month) median *	24 (2-132)	24 (2-120)	12 (2-156)	0.071
Vegetable consumption/everydayn,*	27 (75)	24 (82.8)	23 (69.7)	0.489
Fruit consumption/everyday *	31 (86.1)	25 (86.2)	29 (87.9)	0.972
Dry legumes consumption/2 times per week *	33 (91.7)	23 (79.3)	28 (84.8)	0.362
Cow's milk consumption, *	27 (75)	26 (89.7)	27 (81.8.)	0.316
Cow's milk consumption ml/everyday, median (min-max)	383 \pm 336	276 \pm 197	250 \pm 176	0.128

*n,(%)

Table II: Comparatively analysis of clinical features of each groups before and after therapy.

	Lactulose (n=36)			Senna (n=29)			Trimebutine (n=33)		
	Before therapy	After therapy	p	Before therapy	After therapy	p	Before therapy	After therapy	p
Defecation frequency,*									
≤2 per week	8 (22.2)	2 (5.6)		11 (37.9)	0 (0)		10 (30.3)	5 (15.2)	
≥3 per week	28 (77.8)	34 (94.4)	0.034	18 (62.1)	29 (100)	0.001	23 (69.7)	28 (84.8)	0.025
Stool consistency (BSC) mean±SD	2.27±0.84	3.28±1.30	0.000	2.48±0.73	4.41±0.94	0.000	2.42±0.79	3.55±0.90	0.000
Painful defecation,*	21 (58.3)	14 (38.9)	0.092	19 (65.5)	7 (24.1)	0.004	25 (75.8)	9 (27.3)	0.000
Stool withholding,*	17 (47.2)	12 (33.3)	0.227	17 (58.6)	8 (27.6)	0.022	16 (48.5)	9 (27.3)	0.016
Fecal incontinence,*	5 (15.2)	2 (6.1)	0.375	11 (39.3)	4 (14.3)	0.039	4 (15.4)	4 (15.4)	1
Rectal bleeding,*	9 (25)	5 (13.9)	0.289	4 (13.8)	1 (3.4)	0.250	5 (15.2)	2 (6.1)	0.375
Abdominal distention,*	11 (30.6)	12 (33.3)	1	13 (44.8)	8 (27.6)	0.125	15 (45.5)	7 (21.2)	0.039
Abdominal pain,*	22 (61.1)	17 (47.2)	0.302	19 (65.5)	13 (44.8)	0.109	25 (75.8)	13 (39.4)	0.002
Nausea/vomiting,*	8 (22.2)	6 (16.7)	0.727	7 (24.1)	4 (13.8)	0.250	9 (27.3)	2 (6.1)	0.039
Enuresis,*	9 (27.3)	5 (15.2)	0.219	7 (25)	4 (14.3)	0.250	5 (19.2)	4 (15.4)	1
Anorexia,*	25 (69.4)	14 (38.9)	0.007	9 (31)	8 (27.6)	1	23 (69.7)	16 (48.5)	0.065
Anal fissure,*	17 (47.2)	6 (16.6)	0.001	21 (72.4)	8 (27.5)	1	21 (63.6)	4 (12.1)	0.021
Fecal impaction,*	19 (32.8)	-		17 (29.3)	-		22 (37.9)	-	
Sodium phosphate enema*,	19 (32.8)	-		17 (29.3)	-		22 (37.9)	-	

*(n(%,

Table III: Comparatively analysis of clinical features between three of the drugs before and after therapy.

	Before therapy				After Therapy			
	Lactulose (n=36)	Senna (n=29)	Trimebutine (n=33)	p	Lactulose (n=36)	Senna (n=29)	Trimebutine (n=33)	p
Defecation frequency,*								
≤2 per week	8 (22.2)	11 (37.9)	10 (30.3)	0.384	2 (5.6)	0 (0)	5 (15.2)	0.075
≥3 per week	28 (77.8)	18 (62.1)	23 (69.7)		34 (94.4)	29 (100)	28 (84.8)	
Stool consistency, median (min-maks)	2 (1-4)	3 (1-4)	3 (1-4)	0.610	3 (1-6)	4 (2-6)	4 (2-5)	0.000†
Painful defecation,*	21 (58.3)	19 (65.5)	25 (75.8)	0.308	14 (38.9)	7 (24.1)	9 (27.3)	0.385
Stool withholding,*	17 (47.2)	17 (58.6)	16 (48.5)	0.618	12 (33.3)	8 (27.6)	9 (27.3)	0.826
Fecal incontinence,*	5 (15.2)	11 (39.3)	4 (15.4)	0.045†	2 (6.1)	4 (14.3)	4 (15.4)	0.459
Rectal bleeding,*	9 (25)	4 (13.8)	5 (15.2)	0.430	5 (13.9)	1 (3.4)	2 (6.1)	0.269
Abdominal distention,*	11 (30.6)	13 (44.8)	15 (45.5)	0.362	12 (33.3)	8 (27.6)	7 (21.2)	0.531
Abdominal pain,*	22 (61.1)	19 (65.5)	25 (75.8)	0.418	17 (47.2)	13(44.8)	13 (39.4)	0.801
Nausea/vomiting *	8 (22.2)	7 (24.1)	9 (27.3)	0.887	6 (16.7)	4 (13.8)	2 (6.1)	0.388
Enuresis,*	9 (27.3)	7 (25)	5 (19.2)	0.767	5 (15.2)	4 (14.3)	4 (15.4)	0.993
Anorexia,*	25 (69.4)	9 (31)	23 (69.7)	0.002†	14 (38.9)	8 (27.6)	16 (48.5)	0.242
Anal fissure,*	17 (47.2)	21 (72.4)	21 (63.6)	0.105	6 (16.6)	8 (27.5)	4 (12.1)	0.276
Fecal impaction,*	19 (32.8)	17 (29.3)	22 (37.9)	0.244	-	-	-	-
Sodium phosphate enema*,	19 (32.8)	17 (29.3)	22 (37.9)	0.244	-	-	-	-

*n (%), †Values of p<0.05 were considered statistically significant and senna showed the significance.

characteristics of the study groups. Compared to lactulose and trimebutine groups, senna group had higher rates of fecal incontinence and fewer rates of anorexia (p=0.045 and p=0.002, respectively). Follow-up time was 6.27±4.73 months (min-max 2-24).

Efficacy of treatment

Treatment compliance was observed in 93.9% of children. The compliance of therapy in lactulose, senna, and trimebutine groups were 94.4%, 96.6% and 90.9%, respectively (p=0.768). Significant improvements in stool consistency as compared

Table IV: Efficacy and adverse events of lactulose, senna and trimebutine.

	Lactulose (n=36)	Senna (n=29)	Trimebutine (n=33)	p
Compliance to treatment,*	34 (94.4)	28 (96.6)	30 (90.9)	0.768
Clinical improvement,*	26 (72.2)	28 (96.6)	27 (81.8)	0.036 [†]
Flatulence,*	22 (61.1)	14 (48.3)	19 (57.6)	0.572
Taste problem,*	10 (27.8)	2 (6.9)	11 (33.3)	0.037 [†]

* (n(%)), [†]Senna showed the significance

Table V: Cost- Effective Analysis of Lactulose, Senna and Trimebutine.

	Mean cost per patient (€)	Drug success rate	Cost and effectiveness	Required cost for 1% success sensitivity (€)	Expected cost/expected cost effectiveness rate
Lactulose	8.4	0.72	6	0.11	11.7
Senna	1.9	0.96	1.82	0.02	1.97
Trimebutine	6.5	0.81	5.26	0.08	8.02

with initial data were achieved ($p < 0.001$) in all of the drugs. Lactulose increased defecation frequency ($p = 0.034$), decreased anal fissure, and anorexia significantly than the baseline ($p = 0.001$ and $p = 0.007$, respectively). Senna decreased fecal incontinence ($p = 0.039$), painful defecation ($p = 0.004$) and stool withholding ($p = 0.022$) significantly, while increased defecation frequency ($p = 0.001$) as compared with baseline. Trimebutine increased defecation frequency ($p = 0.025$), decreased abdominal pain ($p = 0.002$), painful defecation ($p < 0.001$), stool withholding ($p = 0.016$), abdominal distention (0.039), nausea/vomiting ($p = 0.039$) and anal fissure ($p = 0.021$) significantly as compared with baseline (Table II).

All parameters were also compared among three of the groups which are shown in Table III. Stool consistency improved significantly in the senna treated group as compared to the other 2 groups ($p < 0.001$). Clinical improvement was observed in 82.7% of the patients at the end of four weeks of treatment. Although clinical improvement was achieved in all three groups, the senna treated group had a significantly higher clinical improvement rate ($p = 0.036$).

Adverse events

There was no important difference between the 3 groups for flatulence. Drug taste problems developed the least in the senna treated group ($p = 0.037$). Table IV shows the efficacy and adverse effects of the drugs.

Pharmacoeconomic results

There was a positive correlation between patient age and drug cost due to the amount of the drug consumption. There was no significant difference between patient ages in all three groups, so we performed the mean cost of the drugs per patient. The effectiveness of drugs (clinical improvement) and drug costs were investigated together. Pharmacoeconomic evaluation as per patient cost showed 1.9€ for senna, 6.5€ for trimebutine, and 8.4€ for lactulose during four weeks of therapy. Senna

group had the highest success rate (0.96) as well as the lowest cost per patient (1.9€) and lowest cost and effectiveness score (1.82). Therefore, senna was found the most successful drug for the treatment.

A 1% increase in success rate needed as €0.02 for senna, €0.11 for lactulose and €0.08 for trimebutine, respectively. Senna had the lowest cost-effectiveness for a 1% increase in the success rate. Senna had the highest success for clinical improvement and the lowest cost per patient, and the most cost-effective drug for constipation treatment. Table V summarizes the cost-effective analysis of the drugs.

DISCUSSION

This retrospective, 4 weeks-follow-up study revealed that senna, lactulose, and trimebutine were all effective drugs in the treatment of children with functional constipation. Senna revealed the highest clinical improvement rate among them. However, the efficacy of each drug on clinical symptoms of constipation showed variability, which may be determinant of initial drug choice for the treatment of FC.

Senna is a stimulant laxative that increases bowel movements and leads to liquid and electrolyte secretion into small bowel and colon. Senna is suggested in the short term treatment of FC by North American Society for Pediatric Gastroenterology and Nutrition as well as NICE guidelines (3,17). There are only a few data in the literature about the use and effectiveness of senna in FC. Some studies found that senna was not effective in FC7-9. However, others found senna to be the most effective drug to increase stool consistency score (18). We also observed that senna led to the most remarkable increase in stool consistency and more softer stools compared to lactulose and trimebutine. Children in the senna group had higher rates of fecal incontinence than the other two groups. Consumption

of lower levels of fiber and more carbohydrates and fat may be responsible for the constellation of constipation and ultimately fecal incontinence (19). Senna decreased fecal incontinence from 39.3% to 14.3%, which was significantly higher than the lactulose and trimebutine. But senna is found only in tablet form for the treatment of functional constipation in our country which is difficult to use for children younger than 6 years old. Thus we gave triturated powdered form in this group and there was no compliance problem in them.

The other drug, trimebutine is effective in IBS with constipation or diarrhea. Trimebutine acts on GIS with dual effect and improves both hyper and hypomotility (20). There is only one adult study in the literature, evaluating the effect of trimebutine on chronic idiopathic constipation, and showed increased defecation frequency without significance (14). To the best of our knowledge, our study is the first report about trimebutine treatment in childhood FC. We showed that trimebutine increased defecation frequency, stool consistency score and decreased abdominal pain, painful defecation, stool withholding, abdominal distention, nausea/vomiting, and development of anal fissure. Trimebutine may be preferred especially in constipated children with abdominal pain, abdominal distention, and/or nausea and vomiting.

Lactulose is a disaccharide and its degradation products like CO₂, lactic and acetic acid pull water into the colon and soften the stool (15). Although lactulose is commonly used in the treatment of children with FC, data about its' effectiveness is controversial. Some studies showed that lactulose is effective in increasing bowel movements, while, others found lactulose is ineffective in the treatment of constipation (7,21-25). In our study, lactulose was effective in increasing stool consistency score and defecation frequency. Also, anorexia and anal fissure formation significantly decreased after lactulose therapy. Passage of softer stool may have contributed to the healing of anal mucosa. Lactulose can be the first line choice laxative in children with anorexia and anal fissure.

The outcome of treatment also depends on the compliance of the administrated drug. Several factors such as dosage forms, drug taste, and side effects may determine the compliance of the patients. Drugs administrated in tablet form may provide the advantage of small volume over the syrup forms. There was no significant difference in side effects among these drugs.

Constipation is a common problem and the duration of treatment may last for several months. Data about constipation and cost for treatment in children are limited. Liem O. et al. (26) showed children with constipation or prescribed a laxative consumed \$3.9 billion more in healthcare costs per year than those without constipation²⁶. Therefore, cost-effectiveness of the treatment should also be considered as well as clinical efficacy. Senna therapy was the most cost-effective compared with lactulose and trimebutine. It provides greater benefits at a lower cost compatible with literature (27).

Our study has several limitations. It was a retrospective, observational study, time of follow up was short, and the sample size was small. On the other hand, strong sides of our study were; a questionnaire form was completed for all patients, a standardized method (Bristol Stool Chart), and patients' defecation diaries were used to evaluate defecation frequency and stool consistency, objectively.

Although a retrospective study, to the best of our knowledge this is the first study comparatively evaluating effectiveness and cost-effectiveness of lactulose, senna, and trimebutine in childhood FC and FFI.

As a conclusion, our study showed that lactulose, senna, and trimebutine were all safe and effective for the treatment of childhood FC and FFI. However, treatment should be adjusted according to the predominant clinical symptoms. Senna may be the first choice of treatment with high cost-effectiveness and tolerable taste, trimebutine in patients with abdominal distention, abdominal pain, nausea/vomiting, or anal fissure and lactulose in patients with anorexia or anal fissure, respectively.

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