

Comparison of effectiveness between polyethylene glycol 4000 and lactulose in the treatment of pediatric functional constipation

Çocuklarda fonksiyonel konstipasyon tedavisinde polietilen glikol 4000 ve laktuloz etkinliklerinin karşılaştırılması

Meryem Keçeli Başaran¹

¹ Gaziosmanpaşa Training and Research Hospital,
Department of Pediatric Gastroenterology,
Hepatology and Nutrition, Istanbul, Turkey

ORCID ID of the author(s)
MKB:0000-0001-8362-8618

Abstract

Aim: Functional constipation is a common illness in children that requires close follow-up and long-term treatment. This study aims to compare the effectiveness of lactulose and PEG 4000 in the treatment of pediatric functional constipation.

Methods: One hundred and twenty-three patients included in this cross-sectional study were all diagnosed with functional constipation according to Rome IV criteria. The ages of the patients, who were all referred to the pediatric gastroenterology outpatient clinic between November 2017 and May 2018, ranged between 8 months and 4 years. Patients with accompanying organic diseases were excluded from the study. Children treated with Lactulose were included in the LAC group and those treated with PEG 4000 were included in the PEG group. The number of bowel movements, Bristol Stool Form Scale (BSFS), pain during bowel movements, formation of anal fissures and fecal impaction at diagnosis and during follow-up were noted from the patient files. A comparison was then made in 1st and 3rd months between the diagnostic findings and follow-up of patients in both groups.

Results: There were no age or gender-based differences between the two groups. Sixty-two (50%) patients received lactulose and the remaining 61 patients (50%) received PEG 4000 as treatment. At the end of the third month, patients had improved significantly more in the PEG group in terms of number of daily bowel movements, the presence of pain during bowel movement and median BSFS score ($P<0.001$).

Conclusion: While lactulose and PEG 4000 are both effective in the treatment of functional constipation in children, PEG 4000 is a more effective and successful treatment option compared to lactulose without increased side effects.

Keywords: Child, Polyethylene glycol 4000, Lactulose, Constipation

Öz

Amaç: Fonksiyonel konstipasyon çocukluk çağında sık görülen ve yakın takip gerektiren bir hastalıktır. Tedavide PEG 4000 tedavisinin daha etkili olduğu düşünülmektedir. Bu çalışmada fonksiyonel konstipasyonu olan çocuklarda PEG 4000 ve laktuloz tedavilerinin etkinliklerini karşılaştırmayı amaçladık.

Yöntemler: Çalışma Roma 4 kriterlerine göre fonksiyonel konstipasyon teşhisi konulan çocukları içermektedir. Bu çalışma karşılaştırmalı ve kesitsel bir çalışmadır. Çocuk Gastroenteroloji polikliniğine Kasım 2017 ve Mayıs 2018 tarihleri arasında başvuran 123 hasta dahil edilmiştir. Eşlik eden organik hastalığı saptanan hastalar çalışma dışı bırakılmıştır. Laktuloz tedavisi verilen çocuklar LAC grup, PEG 4000 tedavisi verilen çocuklar PEG grup olarak tanımlandı. Hastaların tanı ve takipte bağırsak hareketlerinin sayısı, Bristol Stool Score Form Ölçeği (BSFS), bağırsak hareketleri sırasında ağrı, anal fissür oluşumu ve fekal inkontinans kaydedildi. Daha sonra sırasıyla LAC grup ve PEG grup hastaların takibi arasında 1. ve 3. aylarda karşılaştırma yapılmıştır.

Bulgular: Çalışmaya 123 hasta alındı. 62 hastaya (%50) laktuloz ve geri kalan 61 hastaya (%50) tedavi olarak PEG 4000 verildi. Yaş ve cinsiyet açısından iki grup arasında fark saptanmadı. Üçüncü ayın sonunda, PEG grup çocuklarda iyileşme, günlük bağırsak hareketlerinin sayısı, bağırsak hareketi sırasında ağrı varlığı ve medyan BSFS skoru açısından laktuloz tedavisi gören hastalardan anlamlı olarak farklılık saptandı ($P<0,001$).

Sonuç: Hem laktuloz hem de PEG 4000, çocuklarda fonksiyonel konstipasyonun tedavisinde etkili olsa da, PEG 4000 tedavisi yan etkileri arttırmayan, laktuloza kıyasla daha etkili ve başarılı bir tedavi seçeneğidir.

Anahtar kelimeler: Çocuk, Polietilenglikol 4000, Laktuloz, Konstipasyon

Corresponding author/Sorumlu yazar:
Meryem Keçeli Başaran

Address/Adres: Gaziosmanpaşa Eğitim ve Araştırma Hastanesi, Çocuk Gastroenterolojisi, Hepatoloji ve Beslenme Bölümü, İstanbul, Türkiye
E-mail: meryem.keceli07@yahoo.com

Ethics Committee Approval: This study was approved by the Ethics Committee of Gaziosmanpaşa Taksim Training and Research Hospital (5/30/2018-54). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Etik Kurul Onayı: Bu çalışma Gaziosmanpaşa Taksim Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylanmıştır (30.05.2018-54). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 7/13/2020
Yayın Tarihi: 13.07.2020

Copyright © 2020 The Author(s)
Published by JOSAM

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and build upon the work provided it is properly cited. The work cannot be used commercially without permission from the journal.



Introduction

Constipation is a common digestive problem, which accounts for 3-5 % of all admissions to pediatric service and 25% of pediatric gastroenterological disorders [1]. In children, constipation can be defined as a decrease in the frequency of bowel movements, hard stool, and pain during bowel movement. While 95% of the patients do not have an organic cause, metabolic or endocrine disorders, anorectal anomalies or Hirschsprung's disease may cause constipation in the rest of the cases [2,3]. Functional constipation (FC) is the most common cause of childhood constipation. The diagnosis of functional constipation is made according to the ROME IV criteria [4].

Constipation influences the emotional well-being, appetite, and life quality of the affected children. Traditional therapies for constipation include bowel retraining, fiber-rich diet, more water intake, physical exercise and the use of various laxatives and stool softeners.

Lactulose, a semisynthetic disaccharide, is an osmotic laxative used in the treatment of constipation. Although the treatment outcome is usually favorable, drug compliance and treatment success are negatively affected due to gastrointestinal side effects and drug intolerance [5].

Polyethylene glycol 4000 (PEG 4000) is a non-toxic, water-soluble, high-molecular polymer which is not absorbed in the gastrointestinal tract after oral administration. PEG 4000 acts as an osmotic agent that increases the water content of the stool. Several clinical trials have indicated that PEG 4000 is effective in treating constipation in adults and children [6,7].

The objective of this study is to determine the effectiveness of the frequently used osmotic laxatives and PEG 4000 in the treatment of functional constipation in children and to compare their advantages.

Materials and methods

Patients

This study included a total of 123 patients aged between 8 months and 4 years, who were referred to the pediatric gastroenterology outpatient clinic of Gaziosmanpaşa Taksim Training and Research Hospital between November 2017 and May 2018. Information about patients were obtained from patient files. All had functional constipation per Rome IV criteria. Displaying at least two of the following problems defines functional constipation: Two bowel movements or fewer per week for at least 2 months, painful bowel movement, hard stool, large and lumpy stool, and the presence of fecal mass in rectum. The patients who had previous gastrointestinal surgery, an underlying endocrine disease (hypothyroidism, diabetes mellitus), cerebrospinal disease, cerebral palsy, food allergy, celiac disease, pediatric psychiatric disorders, oncological diseases as well as those who had constipation due to other primary diseases were excluded from the study. Informed consent forms were obtained from the parents of all patients at the beginning of the study.

Study design

Patients were started on lactulose (1 g/kg/day, 2 doses) or PEG 4000 (0.5 g/kg/day, 2 doses) for treatment. The patients were assigned to either treatment group based on their outpatient

clinic application number, where those with odd numbers received lactulose (LAC group) and those with even numbers were given PEG 4000 (PEG group). The patients and the parents were called for controls during the second week, and in the 1st and 3rd months of treatment. In the second week of the treatment, the participants received an interview about compliance concerning their treatment as well as an examination for underlying organic diseases. During each of these controls, the number of bowel movements, stool type based on the Bristol Stool Form Scale (ASFS), pain during bowel movements, the formation of anal fissures and fecal impaction were analyzed and subsequently noted in the patient files.

The diagnostic and follow-up findings of patients who were on Lactulose and PEG 4000 treatment were compared.

Statistical analysis

The normality of numerical variables was analyzed with the Kolmogorov Smirnov test. Pearson's chi-square test was carried out to compare the differences between categorical variables. Independent Samples t-test and Mann Whitney U test were deployed for normally and non-normally distributed independent variables, respectively. Descriptive statistics were presented as median (interquartile range, IQR). Friedman Test was used for more than two dependent variables. The differences between the measurements were compared with the Wilcoxon test and evaluated with Bonferroni correction ($P=0.05/3=0.017$). In statistical analyses, Jamovi Project (2017, Version 0.8, www.jamovi.org) was used, and the level of statistical significance (P -value) was set at 0.05. The required sample size was calculated as 96 patients, as determined by the statistical program, considering 30% difference between the groups. The sample size was calculated with StatsDirect software version 2.7.9 (StatsDirect Ltd., England, UK).

Results

A total of 123 patients with a mean age of 27.5 (12) months were included in the study. There were 62 females (50%). Sixty-two patients (50%) received lactulose and the remaining 61 (50 %) received PEG 4000 as treatment. There were no age and gender-based differences between the groups. In the LAC group, the duration of complaints prior to treatment and the presence of anal fissures were significantly lower ($P=0.002$, $P<0.001$, respectively) (Table 1).

The analysis of patients' response to treatment suggests that both treatment groups posted significant improvement in the number of daily bowel movements and the BSFS score at the end of the 3rd month in comparison to baseline values ($P<0.001$, $P<0.001$ and $P<0.001$, $P<0.001$, respectively) (Table 2).

The comparison of the number of bowel movements, pain during bowel movements, the BSFS score, and soiling at baseline and in the 1st and 3rd months for both treatment groups are presented in Table 3. The differences in terms of median BSFS score ($P=0.002$) and frequency of soiling ($P=0.003$) were statistically significant. The BSFS score at baseline was significantly higher in LAC group (median 2; range: 1-2) than the PEG group (median 1; range: 1-2), while PEG group treatment was found to have a higher frequency of soiling at baseline (45.9 %) compared to the LAC group (20.97 %).

At the end of the first month, both the median number of daily bowel movements and median BSFS score in PEG 4000 group (median 4; range 3-4) was significantly higher than that in the LAC group (median 3; range 3-4) ($P=0.033$, $P=0.042$, respectively). On the other hand, there were no significant differences between the groups in terms of pain during bowel movement and soiling at the end of the first month ($P=0.156$ and $P=0.473$, respectively) (Table 3). PEG group displayed significantly better results in number of daily bowel movements, presence of pain during bowel movement and median BSFS score as opposed to patients who received lactulose treatment at the end of the 3rd month ($P<0.001$, $P=0.001$, $P<0.001$, respectively) (Table 3).

Table 1: Comparison of the groups in term of general characteristics at baseline

	Groups		P-value
	LAC group	PEG group	
n (%)	62	61	
Age mean (standard deviation)	26.53 (12.54)	29.23(11.98)	0.225*
Gender			
Male	32(51.61 %)	29(47.54 %)	0.652**
Female	30(48.39 %)	32(52.46 %)	
Anal Fissure			
Absent	46(74.19 %)	26(42.62 %)	<0.001**
Present	16(25.81 %)	35(57.38 %)	
Mean duration of the complaint (months)	6(4-8)	8(5-12)	0.002***

LAC: lactulose, PEG: Polyethylene glycol, * Independent samples t test, ** Chi-Square test, *** Mann Whitney U test

Table 2: Comparison of number of daily bowel movements and the Bristol Stool Form Scale score at baseline and at the end of 1st and 3rd months in treatment groups

Treatment method	Variables	Baseline	1st month	3rd month	P-value*
LAC group	Number of daily bowel movements	2(2-2)	3(3-4)	4(3-4)	<0.001
	Bristol Stool Form Scale Score	2(1-2)	3(2-3)	3(3-3)	<0.001
PEG group	Number of daily bowel movements	2(1-3)	4(3-4)	5(5-6)	<0.001
	Bristol Stool Form Scale Score	1(1-2)	3(3-3)	4(3-4)	<0.001

LAC: lactulose, PEG: Polyethylene glycol, * Friedman test

Table 3: The comparison of groups in terms of the number of daily bowel movements, BSFS score, presence of soiling, and presence of pain during bowel movement at baseline and at the 1st and 3rd months

Time	Baseline	Variables	Groups		P-value
			LAC group	PEG group	
1st month	Number of daily bowel movements Pain during bowel movement (n, %) Absent Present BSFS score Soiling (n, %) Absent Present	Number of daily bowel movements	2 (2-2)	2 (1-3)	0.907*
		Pain during bowel movement (n, %)			
		Absent	8 (12.9 %)	5 (8.2 %)	0.396**
		Present	54 (87.1 %)	56 (91.8 %)	
		BSFS score	2 (1-2)	1 (1-2)	0.002*
		Soiling (n, %)			
		Absent	49 (79.03 %)	33 (54.1 %)	0.003**
		Present	13 (20.97 %)	28 (45.9 %)	
		Number of daily bowel movements	3 (3-4)	4 (3-4)	0.042*
		Pain during bowel movement (n, %)			
		Absent	16 (25.81 %)	23 (37.7 %)	0.156**
		Present	46 (74.19 %)	38 (62.3 %)	
3rd month	Number of daily bowel movements Pain during bowel movement (n, %) Absent Present BSFS score Soiling (n, %) Absent Present	Number of daily bowel movements	4 (3-4)	5 (5-6)	<0.001*
		Pain during bowel movement (n, %)			
		Absent	43 (69.35 %)	57 (93.44 %)	0.001**
		Present	19 (30.65 %)	4 (6.56 %)	
		BSFS score	3 (3-3)	4 (3-4)	<0.001*
		Soiling (n, %)			
		Absent	62 (100 %)	61 (100 %)	n/a
		Present	0 (0 %)	0 (0 %)	
		Number of daily bowel movements	4 (3-4)	5 (5-6)	<0.001*
		Pain during bowel movement (n, %)			
		Absent	43 (69.35 %)	57 (93.44 %)	0.001**
		Present	19 (30.65 %)	4 (6.56 %)	
BSFS score	3 (3-3)	4 (3-4)	<0.001*		
Soiling (n, %)					
Absent	62 (100 %)	61 (100 %)	n/a		
Present	0 (0 %)	0 (0 %)			

LAC: lactulose, PEG: Polyethylene glycol, BSFS: Bristol Stool Form Scale, * Mann Whitney U test, ** Chi-Square test, n/a: not applicable

Discussion

The pathophysiology of FC is yet to be fully understood. It is likely to be multifactorial. In the United States, 99% of pediatric gastroenterologists were aware of the Rome criteria for FC. However, only 45% of them were using these criteria in clinical practice [7,8]. In this study, Rome IV criteria were used. A recent multicenter study including 465 infants in Italy reported that 11.6%, 13.7%, and 10.7% of the infants

fulfilled Rome III criteria for FC at 3, 6, and 12 months following birth.

One of the most important causes of constipation in children is stool withholding due to painful and difficult bowel movement [8]. The presence of fecal mass in the rectum can also lead to fecal incontinence and hospital visits because of involuntary bowel evacuation. Lactulose and PEG 4000 are among the laxative treatment alternatives in patients with constipation [9]. Lactulose is not digested in the intestines, and through osmotic effects, it softens the feces, facilitates gas formation via intestinal bacteria, reduces stool pH and increases intestinal peristalsis. Therefore, bloating, indigestion and gas problems are highly likely during the treatment [10]. Lactulose is frequently prescribed for children in pediatric clinics, but its effectiveness is lower than that of liquid paraffin and PEG 4000, and hence, it often requires additional treatment [11,12].

Similarly, PEG, a polymer of linear structure, is an osmotic laxative that holds water through hydrogen bonds. PEG is minimally (1%) metabolized and absorbed in the intestines [13]. PEGs are named by their molecular weights such as PEG 3350 and PEG 4000 with molecular weights of 3350 and 4000 g/mol, respectively. Iso-osmotic PEGs rather than hypo-osmotic types are more popular since they do not cause electrolyte imbalance [14]. Both lactulose and PEG 4000 treatments need to be used with care to avoid electrolyte imbalance and fluid loss and provide parents with necessary and adequate information. In a study conducted by Dupond et al. [15], PEG group had no change in the levels of serum electrolytes, total protein, folate, vitamins A and D, and iron for 3 months contrary to the LAC group.

In this study, fecal impaction rates increased in both PEG and LAC groups as their BSFS score decreased. This finding supports the pathophysiology of constipation. In other words, as the stiffness of the stool increases, the child withholds the stool in the rectum due to painful bowel movement, which results in fecal impaction [16,17]. In this study, there was no significant difference between the treatment groups in terms of either soiling or pain during bowel movement at the end of the first month. This rate is likely to be lower in families who practice psychological and supportive treatments. On the other hand, differences between the treatment methods were statistically significant in terms of the number of bowel movements, pain during bowel movement and median BSFS score at the end of the third month: The median number of weekly bowel movements in PEG group was significantly higher. We considered that this might be linked with the better softening of the stool in PEG 4000 treatment. Voskuijl et al. [18] reported that PEG group had better stool consistency and less fecal impaction than LAC group. In a study of pediatric patients with functional constipation, Poddar et al. [19] found that both PEG and lactulose were equally effective. However, they added that a significantly higher number of children in LAC group had to be switched over to PEG treatment due to a lack of effectiveness in the LAC group. Chen et al. [20] found that PEG was more effective than other laxatives including lactulose. Candy et al. [21] reported a significant increase in the number of weekly bowel movements in PEG-treated children in comparison to lactulose-treated children, indicating a higher efficacy for

PEG. Loening-Baucke [22] reported a higher success rate when PEG was used compared to other laxatives. Gremse et al. [23] found a significantly higher level of success in PEG treatment compared to lactulose. Jarzębicka et al. [24] noted a significantly higher number of bowel movements per week in the patients using PEG in comparison to lactulose.

In a meta-analysis, Candy and Belsey [25] stated that PEG was either more or equally efficient in constipated children, and they did not find any evidence indicating lower effectiveness of PEG in comparison to other laxatives. They also found more side effects in lactulose-users. Bae et al. [26] reported that constipated pediatric patients using PEG 4000 had benefited from additional fluid intake, which was related to bowel movements and stool consistency. Wang et al. [27] also reported that PEG 4000 was safe and more effective than lactulose for the treatment of constipation in children. Treepongkaruna et al. [28] found that PEG 4000 had higher effectiveness than lactulose for the treatment of chronic constipation in young children and it was well tolerated. It has been stated in Cochrane reviews 2018 as well as in ESPGHAN- NASPGHAN 2014 guideline that PEG is more effective and superior in the treatment of FC in children [29,30].

In this study, both lactulose and PEG 4000 treatment were found to be effective in FC in accordance with the literature information. PEG 4000 treatment was more effective and superior than lactulose treatment without increased side effects.

PEG 4000 should be used as the first option for FC treatment in children. In cases where PEG 4000 is not feasible, lactulose treatment may serve as a suitable alternative.

Limitations

A double-blind placebo-controlled study would yield more objective results in terms of demonstrating drug efficacy. PEG and LAC group are not homogeneously distributed in clinical findings. However, PEG treatment appears more effective, although the symptoms of constipation are more severe. Furthermore, the education level of the family and the child behavior in withholding stool are both significant. Another limitation of the study is the omission of taking sociocultural level of the patients' family into account.

Conclusions

PEG 4000 is more effective than lactulose with fewer side effects in the treatment of functional constipation in children. We think that it may be preferable in cases where lactulose therapy is ineffective. Family education on diet and toilette training also plays a significant role in the treatment, along with medical therapy.

References

1. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2006;130:1527-37.
2. Castiglia PT. Constipation in children. *J Pediatr Health Care* 2001;15:200-2.
3. Wang MG, Wang BX. Initial therapy of constipation in children. *J Appl Clin Pediatr*. 2006;7:446-8.
4. Corazzari E, Badiali D, Habib FI, Reboa G, Pitto G, Mazzacca G, et al. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. *Dig Dis Sci*. 1996;41:1636-42.
5. Gordon M, Naidoo K, Akobeng AK, Thomas AG. Cochrane review: osmotic and stimulant laxatives for the management of childhood constipation. *Evid Based Child Health*. 2013;8:57-109.
6. Pashankar DS, Bishop WP. Efficacy and optimal dose of daily polyethylene glycol 3350 for treatment of constipation and encopresis in children. *J Pediatr*. 2001;139:428-32.
7. Sood MR, Di Lorenzo C, Hyams J, Miranda A, Simpson P, Mousa H, et al. Beliefs and attitudes of general pediatricians and pediatric gastroenterologists regarding functional gastrointestinal disorders: a survey study. *Clin Pediatr (Phila)*. 2011;50:891-6.
8. Schurman JV, Hunter HL, Friesen CA. Conceptualization and treatment of chronic abdominal pain in pediatric gastroenterology practice. *J Pediatr Gastroenterol Nutr*. 2010;50:32-7.

9. Mugie SM, Di Lorenzo C, Benning MA. Constipation in childhood. *Nat Rev Gastroenterol Hepatol*. 2011;8:502-11.
10. McKeown C, Hisle-Gorman E, Eide M, Gorman GH, Nylund CM. Association of constipation and fecal incontinence with attention deficit/hyperactivity disorder. *Pediatrics*. 2013;132:e1210-5.
11. Hoekman DR, Benning MA. Functional constipation in childhood: current pharmacotherapy and future perspectives. *Expert Opin Pharmacother*. 2013;14:41-51.
12. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database Syst Rev*. 2010;(7):CD007570.
13. Brady CE, DiPalma JA, Morawski SG, Santa Ana CA, Fordtran JS. Urinary excretion of polyethylene glycol 3350 and sulfate after gut lavage with a polyethylene glycol electrolyte lavage solution. *Gastroenterology*. 1986;90:1914-8.
14. Youssef N, Di Lorenzo C. Childhood constipation: Evaluation and treatment. *J Clin Gastroenterol*. 2001;33:199-205.
15. Dupont C, Leluyer B, Maamri N, Morali A, Joye JP, Fiorini JM, et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. *J Pediatr Gastroenterol Nutr*. 2005;41:625-33.
16. Loening-Baucke V. Chronic constipation in children. *Gastroenterology*. 1993;105:1557-64.
17. Leung AK, Chan PH, Cho HY. Constipation in children. *Am Fam Physician*. 1996;54:611-8.
18. Voskuil W, de Lorijn F, Verwijs W, Hogeman P, Heijmans J, Mäkel W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut*. 2004;53:1590-4.
19. Poddar U, Singh S, Pawaria A, Srivastava A, Yachha SK. An etiological spectrum, clinical differentiation and efficacy of polyethylene glycol over lactulose in children with constipation: Experience of 316 cases. *J Paediatr Child Health*. 2018 Jun 26. [Epub ahead of print]
20. Chen SL, Cai SR, Deng L, Zhang XH, Luo TD, Peng JJ, et al. Efficacy and complications of polyethylene glycols for treatment of constipation in children: a meta-analysis. *Medicine (Baltimore)*. 2014;93:e65.
21. Candy DC, Edwards D, Geraint M. Treatment of faecal impaction with polyethylene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy. *J Pediatr Gastroenterol Nutr*. 2006;43:65-70.
22. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. *J Pediatr*. 2005;146:359-63.
23. Gremse DA, Hixon J, Crutchfield A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. *Clin Pediatr (Phila)*. 2002;41:225-9.
24. Jarzębicka D, Sieczkowska-Golub J, Kierkus J, Czubkowski P, Kowalczyk-Kryston M, Pelc M, et al. PEG 3350 Versus Lactulose for Treatment of Functional Constipation in Children: Randomized Study. *J Pediatr Gastroenterol Nutr*. 2019 Mar;68(3):318-24.
25. Candy D, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. *Arch Dis Child*. 2009;94:156-60.
26. Bae SH, Son JS, Lee R. Effect of fluid intake on the outcome of constipation in children: PEG 4000 versus lactulose. *Pediatr Int*. 2010;52:594-7.
27. Wang Y, Wang B, Jiang X, Jiang M, Xu C, Shao C, et al. Polyethylene glycol 4000 treatment for children with constipation: A randomized comparative multicenter study. *Exp Ther Med*. 2012;3:853-6.
28. Treepongkaruna S, Simakachorn N, Pienvichit P, Varavithya W, Tongpenyai Y, Garnier P, et al. A randomised, double-blind study of polyethylene glycol 4000 and lactulose in the treatment of constipation in children. *BMC Pediatr*. 2014;14:153.
29. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD009118. DOI: 10.1002/14651858.CD009118.pub3.
30. Tabbers MM, Di Lorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014 Feb;58(2):258-74. doi: 10.1097/MPG.0000000000000266.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.