Comparison of the Low Dose Polyethylene Glycol with Lactulose and Magnesium Hydroxide in Constipated Children. A Multicentric Randomized Clinical trial.

Shahsanam Gheibi[1], Mohammad Hadi Imanieh[2], Mahmood Haghighat[2], Hossein Niknahad[3], Mohammad Sadegh Sayyafan[3], Farzaneh Moatamed[4], Mohammad Hussein Saneian[5], Hasan Karami[6], Mohammad Reza Esmaeili Dooki[7]

[1.] Department of Pediatrics, Urmia University of Medical Science, I.R.Iran. drgheibi@yahoo.com
[2.] Department of Pediatrics, Shiraz University of Medical Science, I.R. Iran
[3.] Department of Pharmacy, Shiraz University of Medical Science, I.R. Iran.
[4.] Department of Pediatrics, Tehran University of Medical Science, I.R. Iran
[5.] Department of Pediatrics, Isfahan University of Medical Science, I.R. Iran
[6.] Department of Pediatrics, Sari University of Medical Sciences, I.R. Iran
[7.] Department of Pediatrics, Babul University of Medical Sciences, I.R. Iran

Abstract: This study was designed to compare the efficacy and safety of very low dose of polyethylene glycol 3350 (PEG) with magnesium hydroxide (MOM) and lactulose in functional constipation of children. A total number of 468 patients 1-15 year old with chronic constipation entered a randomized comparative multicenteric trial. Subjects were healthy outpatients who had hard, painful or $\leq$ 3 stools per week. Their parents were given a teaching pamphlet about constipation, diet and toilet training. The patients were allocated to 3 treatment groups; lactulose (70%) 1ml/kg/day/BID, MOM (400mg/5ml) 1ml/kg/day/BID, and PEG (40%) 1ml/kg/day/BID. The dose was adjusted up to three times depending on responding. Treatment scheduled for two months and data were collected on 2ed, 4th and 8th weeks. 354 patients completed the trial. After eight weeks, patients in the PEG groups had higher number of bowel movement (Pv< 0.001) and low straining at stool (Pv <0.001) than patients in two others groups. Patient's adherences with PEG were better than lactulose and magnesium hydroxide (Pv<0.001). Soiling and blood on stool declined significantly in three groups (Pv<0.001) without differences among. There were no serious adverse effects. Thus low dose of polyethylene glycol 3350 was more effective than lactulose and similar to M.O.M for the treatment of functional constipation and better tolerated without any significant adverse events in children.
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1. Introduction:

Constipation, defined as a delay or difficulty in defecation, is a extremely common pediatric problem(Gordon et al. 2012, Ahmed, Pai and Reynolds 2012), estimated to occur in 3(Tabbers et al. 2011) to 10% of children (Leung, Chan and Cho 1996) and 12% to 35% of the general population.(Youssef 2007, De Giorgio et al. 2011) The incidence appears to be increasing, possibly because of changes in diet, reduced fluid intake and lack of exercise.(Hardikar, Cranswick and Heine 2007) Beyond the neonatal period, about 95% of constipations has a functional cause and can result in fecal impaction, fecal soiling and abdominal pain.(Dupont et al. 2006, Tabbers et al. 2011) Functional constipation most commonly is due to painful bowel movements with resultant voluntary withholding of feces by a child who wishes to avoid an unpleasant defecation.(Baker et al. 1999) Specific evidence-based standards for evaluation and treatment are lacking.(Miller, Dowd and Fraker 2007, Burgers et al. 2012) The recommended approach is to empty the constipated bowel and keep it empty.(Candy, Edwards and Geraint 2006, Biggs and Dery 2006) The successful management of chronic constipation involves several aspects, including an increase in dietary fiber(Schmulson Wasserman et al. 2008) and fluid intake(Bae, Son and Lee 2010), the introduction of regular toilet sits after the main meals,(Loening-Baucke 1993, Bautista Casasnovas et al. 2011) behavioral modification(Bell and Wall 2004), counseling and the use of various laxatives and stool softeners (Pashankar and Bishop 2001) and, above all, close follow-up.(Croffie JM 2004) The long-term outcome in children with chronic idiopathic constipation, with or without encopresis, is not well established. Many children do not respond to medication and continue to have chronic problems.(Nurko 2000) Treatment success rate reported between 50 to 90% with various laxatives.(Davidson, Kugler and Bauer 1963, Staiano et al. 1994) Recently, low dose polyethylene glycols have been suggested as safe and effective alternative treatments for constipation. Polyethylene glycols

(PEG) laxatives, whose osmotic properties enable softening of stools and promoting bowel transit (Andorsky and Goldner 1990), have clearly demonstrated their efficacy and tolerance for the treatment of chronic constipation, not only in adults but also in children.(Dupont et al. 2006, Wang et al. 2012, Horn, Mantione and Johanson 2012) Electrolyte-free PEG 3350 (MiraLax,) has been used as a laxative for short term(Pashankar and Bishop 2001, Gremse, Hixon and Crutchfield 2002, Dupont et al. 2005) and long term(Loening-Baucke 2002, Pashankar, Bishop and Loening-Baucke 2003, Pashankar, Loening-Baucke and Bishop 2003, Michail et al. 2004, Erickson et al. 2003, Loening-Baucke and Pashankar 2006, Voskuijl et al. 2004) in constipated children. The safety and efficacy of 0.63 to 1.5g/kg/day of electrolyte-free PEG to treat constipation have been recently demonstrated in children.(Erickson et al. 2003, Pashankar and Bishop 2001, Rafati et al. 2011) We have used small daily doses (0.4g/kg/day) of PEG 3350 solution in our clinical practice and have found it to be a safe, effective and palatable laxative. We then carried out a prospective, comparative, multicenteric, controlled trial examining efficacy and dosing of PEG in constipated children.

2. Materials and methods

This comparative, randomized and controlled trial was conducted between October 2007 and September 2008 in 5 tertiary care centers in I.R.Iran. Because we were not able to produce the three remedies in one shape, the study was not blinded. The trial was approved by the Shiraz University of Medical Science Ethics Committee. Sample size of 354 patients was calculated for showing a difference at least 15% between three groups. One hundred eighteen children were assigned randomly to receive one of medications. According to plurality of research centers and probability of high attrition we decided to enroll about 500 cases; 150 subjects in Shiraz, 100 patients in Tehran and Isfahan and 75 patients in Sari and Babul each one, but study was finished with completion of determined sample size. Systematic randomization was used for allocation of the patients and prepared dossiers and PEG solution were sending from Shiraz to other centers, all of which used the same investigational protocol (Figure.1). In spite of using systematic randomization for allocation of the patients, for ethical considerations we decided in each group, if the patients had been tried the same therapies previously, and had refractory problem, they were assigned to afterwards schedule, although we anticipated that the number of patients in three groups were not equal. Functional constipation was defined by a duration of ≥8 weeks and ≥2 of the following characteristics: frequency of bowel movements of <3 stools per week, >1 episode of fecal incontinence per week, large stools noted in the rectum or felt during abdominal examination, passing of stools so large that they obstructed the toilet, and retentive posturing (withholding behavior).

Exclusion criteria were impossibility to access the subject (no phone), hirschsprung's disease, anorectal malformations, history of abdominal surgery, no use medication and any systemic illness that could lead to constipation. Baseline evaluations included history, physical examinations and collection of demographic data before initiation of the study. Before the first appointment, parents have been expounding about the pathophysiology of constipation and the rationale of therapy. In addition to, we had made ready a teaching pamphlet consisting of five sections: 1) introduction to constipation, 2) diet, 3) toilet training, 4) enema and 5) therapy, and had given them. Children of appropriate developmental status were advised to sit on the toilet for 5-10 minutes after each meal. Written informed consent was obtained for all participating patients.

Then the children who fulfilled the selection criteria were randomly allocated to 3 therapeutic groups: lactulose (70%) 1ml/kg/d/BID, magnesium hydroxide (400mg/5ml) 1ml/kg/d/BID, and polyethylene glycol 3350 (40%) 1ml/kg/d/BID. The polyethylene glycol 3350 (solution 40% with no added salts) was supplied to the investigator in 40g/L. For preparation of 40% PEG (3350) solution; sodium benzoate (0.1%, w/v) and sugar (25%) were dissolved in an adequate amount of water preheated to 80°C. The required amount of PEG 3350 for preparing 40% (w/v) solution is added to the adequate amount of water preheated to 80°C, and the sodium benzoate/sugar solution is added to the PEG mixture during stirring and then stirred to complete dissolution. Adequate amount of orange essence and an orange color was added to the solution after complete dissolution of the mixture.

Study was scheduled for an 8-week period and treatment efficacies were evaluated at days 14, 28, and 56. Clinical efficacy and tolerance were assessed using a questionnaire which included the administered drug and dose, number of stools and soiling and presence of the following symptoms: straining at stool, blood on stool, abdominal pain, vomiting, bloating and flatus.

If the treatment was to be considered to be having insufficient effect (persisting symptoms), the administered dose could be increased 0.5 to 1ml/kg/d per visit up to 3ml/kg/d. However, if the diarrhea was reported (defined as; more than 3 stools/d) the original dose was reduced by 50%. If the subjects unable to return to clinic for follow up, history was obtained by

phone contact. After the initial phase, the patients with history of prolonged constipation duration beforehand were asked to continue cooperation with investigators for an additional 16 weeks. Symptoms recorded with outpatients clinical follow up at 16 and 24 weeks.

Primary Outcomes

Improvement was defined as ≥ 3 bowel movements per week, ≤ 2 episodes of fecal incontinence per month, and no abdominal pain, with or without laxative therapy.

Statistical analysis

It was estimated that a total sample of 354 patients would be adequate to show a difference of at least 15% more success at 2 months using PEG compared with lactulose and MOM (alpha risk= 0.05 and power=80%). For each patient the clinical efficacy and tolerance variables were analyzed for the first and second two weeks and the last four weeks as well as for the eight weeks of the study. Mean values were calculated for the number of stools, dosage of drugs taken and soiling per month between groups. Subjective criteria were using χ^2 with continuity correction and Pearson correlation. Quantitative mean data were compared by one-way ANOVA. A value $p<0.05$ was consider statically significant.

3. Result

A total numbers of 468 patients with functional constipation were enrolled the study in 5 centers in I.R. Iran and 354 (186 female and 168 male) patients completed the 8 week period of the study. The subjects were 164 patients in Shiraz because the study was designed here and started earlier, but the numbers of cases were 93 patients in Tehran and 80, 69 and 60 patients in Isfahan, Sari and Babul, respectively.

Since the most of patients had been used several different therapies (i.e. lactulose and M.O.M) previously, if the patients had refractory problem, they were assigned to afterwards schedule, thus the number of patients in three groups were unequal. Because lactulose and M.O.M had been used routinely in Iran formerly, and PEG were used for the first time, therefore there were 154 children in PEG group, 94 receiving lactulose and 106 receiving MOM.

The three treatments groups were well matched for all baseline clinical characteristics (table 1). Mean age was 4±2.26 (range, 1 to 13 years). Mean duration of constipation was 2.04±1.7 years (range, 6month to 7 years). Mean age at start constipation was 1/95±1.59 years (1 to 11 years) and in 76% start before 2 years. Mean weight was 15.43±5.56 kilograms.

The mean PEG treatment dose at the 2-month follow-up evaluation was 0.46 ± 0.11 g/kg body weight daily, the mean MOM and lactulose daily doses at the 2-month follow- up evaluation were 1.05 ± 0.38 ml/kg and 1.07 ± 0.33 mL/kg body weight, respectively. Results of the 8-week follow-up are shown in table 2. Throughout the eight week period, the mean stool frequency was higher in the PEG than MOM than lactulose groups (PV=0.0001).

Table 1. Baseline patient's characteristics

Groups / Variables	PEG (n=154)	Lactulose (n= 94)	MOM (n= 106)	Pv
Sex (F/M)	86/68	56/38	64/42	0.24
Age, mean ± SD (yr)	4 ± 2.26	3.77 ± 2.3	4.29 ± 2.36	0.24
Weight, mean ± SD (kg)	15.1 ± 4.7	14.76 ± 4.8	16 ± 7.3	0.22
Mean duration of constipation	1.82 ± 1.54	2.15 ± 1.42	2.27 ± 2.08	0.09
Mean age at start constipation± D(yr)	2.1 ± 1.49	1.6 ± 1.68	2 ± 1.62	0.06
Mean stool/week	2.08 ±0.98	1.8 ± 0.98	2.04 ± 1	0.28
Withholding (%)	118 (75.6%)	80 (85.1%)	86 (85.1%)	0.18
Abdominal pain(%)	55 (35.3%)	30 (31.9%)	38 (35.8%)	0.81
Painful defecation(%)	133 (85.3%)	86 (91.5%)	94 (88.7%)	0.33
Positive family history (%)	59 (37.8%)	40 (42.6%)	42 (39.6%)	0.76
Fecal impaction (%) (Disimpaction)	88 (56.4%)	54 (57.4%)	58 (54.7%)	0.92
Soiling (%)	33 (21.2%)	14 (14.9%)	28 (26.4%)	0.13
Blood on stool (%)	65 (41.7%)	36 (38.3%)	32 (30.2)	0.16

Abdominal pain, soiling and bloody stool decreased significantly within groups (PV=0.0001) but no significant differences between three groups were seen (PV=0.2, 0.13 and 0.16 respectively), and there were no new abnormal findings on follow up examination.

Straining at the stool was seen in the majority of patients before treatment (91.5% in lactulose, 90.4% in MOM and 85.3% in PEG) and significantly decreased within groups after treatment (lactulose 51.1%, MOM 28.3% and PEG 18.6%). There was significant differences between groups (P=0.0001).

As can been seen in table 2, this study demonstrates that PEG and MOM are more effective than lactulose in treating childhoods functional constipation over an 8-wk period and improvement rates were 90.4% with PEG, 88.7% with MOM and 70.2% with lactulose (PV=0.001). Adverse events leading to drug withdrawal were recorded during the study; twelve (12.5%) of children interrupted lactulose (because of abdominal pain, diarrhea and flatulence) whereas five (4.7%) cases discontinue MOM (because of diarrhea and intolerance) before to be cured, but fifteen (9.6%) cases refused PEG (because of worry) despite primary agreement and informed consent. Failure rate with intent to treat was 29.8% with lactulose and 9.6% and 11.3% with PEG and MOM respectively. (PV=0.0001).

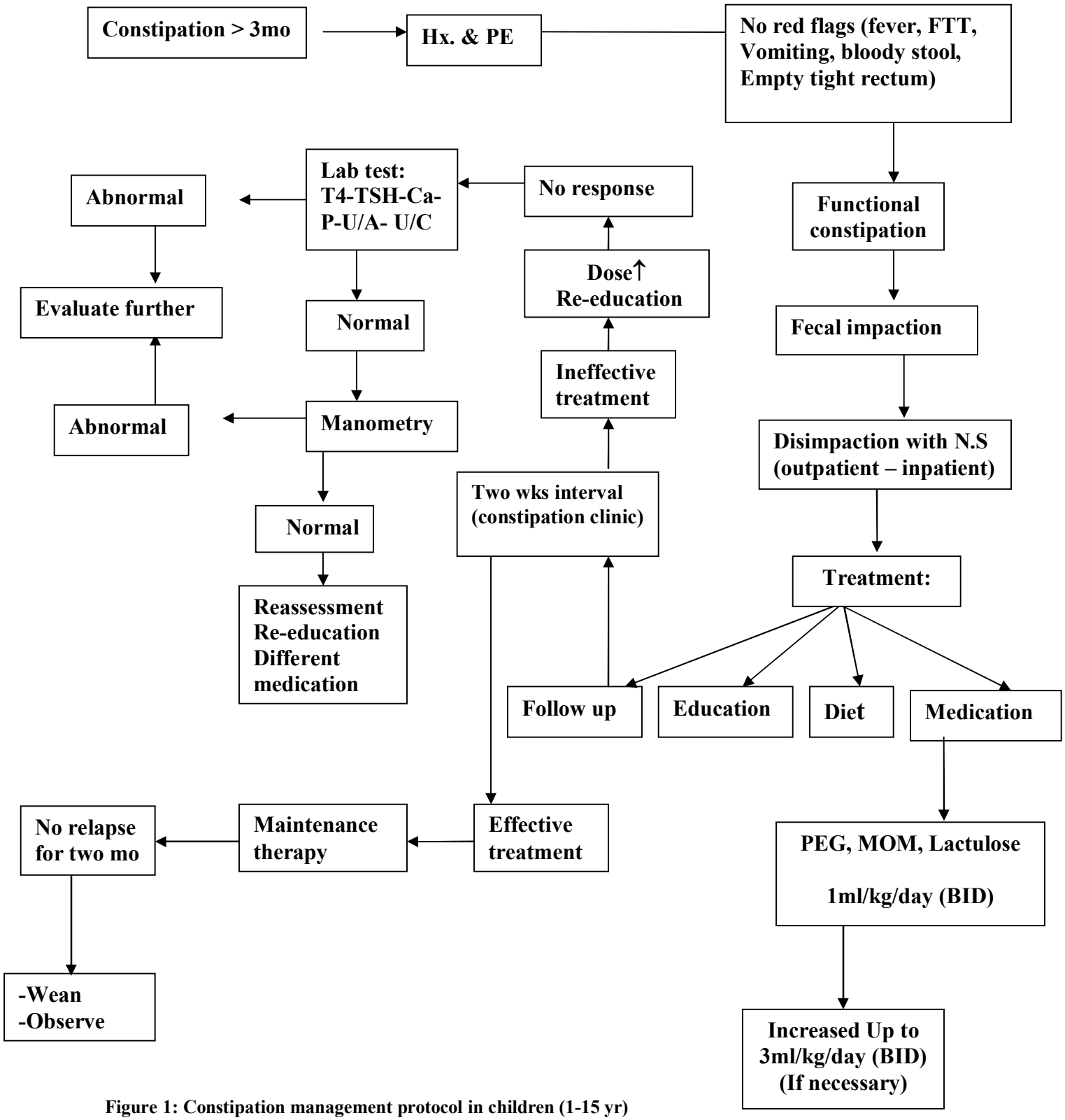

Figure 1: Constipation management protocol in children (1-15 yr)

Table 2. Comparing childhood constipation response to different medications.

Groups / Variables	Lactulose (n=94)	Magnesium Hydroxide (n=106)	Polyethylene glycol (n=154)	Pv
Mean doses (ml/kg)	1.07 ± 0.33	1.05 ± 0.38	1.08 ± 0.27	0.84
Mean stool/2nd wk	4.7 ± 2.06	5.7 ± 1.7	6.1 ± 1.7	0.001
Mean stool/4th wk	5.3 ± 2.03	5.79 ±1.77	6.15 ± 1.71	0.002
Mean stool/8th wk	5.09 ± 2.07	5.67 ± 1.77	6.07 ± 1.77	0.0001
Abdominal pain (%)	20 (21.3%)	34 (32.1%)	31 (19.9%)	0.05
Painful defecation (%)	48 (51.1%)	30 (28.3%)	29 (18.6%)	0.0001
Soiling (%)	8 (8.5%)	14 (13.2%)	8 (5.1%)	0.06
Blood on stool (%)	8 (5.1%)	10 (10.6%)	12 (11.3%)	0.13
Improvement: n (%)	66 (70.2%)	94 (88.7%)	141 (90.4%)	0.001
Failure /stop: n (%)	28 (29.8%)	12 (11.3%)	15 (9.6%)	0.0001

4. Discussion

This is the first large-scale prospective randomized and multicenteric study designed to compare PEG 3350 with two other commonly used laxatives (magnesium hydroxide and lactulose) in children with functional constipation. We found that all three resulted in a significant increase in defecation frequency and a significant decrease in encopresis frequency after eight weeks of treatments. However, PEG and MOM were more effective than lactulose.

PEG 3350 without added electrolytes is a new non-absorbable, tasteless, odorless(Humphreys and Reinberg 2005) and chemically inert polymer(Loening-Baucke and Pashankar 2006) and has been introduced as a new laxative in recent years.(DiPalma et al. 2000, Cleveland et al. 2001, Herve et al. 2001, Hudziak et al. 1996, Youssef et al. 2002, Benninga, Candy and Taminiau 2005)

Since the use of laxatives alone had low success rate,(Abrahamian and Lloyd-Still 1984, Loening-Baucke 1990) and 50% of treated patients experience a relapse within 1 year (van Ginkel et al. 2003, Staiano et al. 1994) it is suggested that toilet training, dietary advice and regular use of laxatives should be combined to prevent future impaction and to ensure a prolonged period of painless defecation, which is essential to provide the confidence necessary for promoting regular bowel habits,(Dupont et al. 2006) thus we made ready a teaching pamphlet about constipation, diet, toilet training, enema and therapy, and gave the patients parents.

The findings of this study are shown that PEG 3350 without electrolytes was safe and well tolerated, and significantly more effective than lactulose in the treatment of chronic constipation in children over an 8-wk period, but with similar efficacy to MOM. Similar to our study, previous studies could not demonstrate superior efficacy of PEG over MOM(Loening-Baucke 2002, Loening-Baucke and Pashankar 2006, Loening-Baucke 2005, Gomes, Duarte and Melo Mdo 2011), whereas in other controlled studies PEG has been shown to be more effective than lactulose (Candy et al. 2006, Voskuijl et al. 2004, Gremse et al. 2002, Rendeli et al. 2006, Dupont et al. 2005, Wang et al. 2012, Lee-Robichaud et al. 2010).

Because of multiplicity of research centers, we could not collecting data after approved two months period. Since, by reason of good results from PEG therapy and users satisfaction, after completion of research, some investigators change other medications of their patients to PEG, whenever, the majority of patients continued for months. No significant side effects or tolerances were reported by any researchers for PEG after six months, only one patient needs to rising the total dose of PEG up to 1gr/kg/day (2.5ml/kg/day) in Esfahan. The low adverse reaction of PEG may be due to low dose utilization comparing to other studies with high dose and high adverse reactions.(Youssef et al. 2002, Andorsky and Goldner 1990, Loening-Baucke 2002, Pashankar and Bishop 2001)

Limitations of this study include short follow up and choice of an open-label design; because we were not able to prepare three medications in a similar shape and color needy for an actual controlled trial. Also, although systematic randomization was used for allocation of the patients but if the patients had been used the ready records medication previously, and had refractory problem, they were assigned to receive the drug of subsequent ready file. Thus the numbers of patients in three groups were not equal, and because of widespread using of lactulose and MOM for pediatrics constipation beforehand, these groups making smaller population than PEG group.

In conclusion, we can say that low dose PEG is more effective and safe for treating childhood's functional constipation but double blinded clinical trial with long term follow up is required for confirmations.

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Corresponding Author:
Dr Shahsanam Gheibi
Department of Pediatrics Gastroenterology,
Associate Professor of Pediatrics
Urmia University of Medical Sciences, I.R.Iran
Email: drgheibi@yahoo.com

References:

1. Gordon M, Naidoo K, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database Syst Rev 2012;7:CD009118.
2. Ahmed M, Pai B, Reynolds T. Use of polyethylene glycol in children less than 3 years of age. J Coll Physicians Surg Pak 2012:22:267-268.
3. Tabbers MM, Boluyt N, Berger MY, Benninga MA. Clinical practice : diagnosis and treatment of functional constipation. Eur J Pediatr 2011:170:955-963.
4. Leung AK, Chan PY, Cho HY. Constipation in children. Am Fam Physician 1996:54:611-618, 627.
5. Youssef NN. Childhood and Adolescent Constipation: Review and Advances in Management. Curr Treat Options Gastroenterol 2007:10:401-411.
6. De Giorgio R, Cestari R, Corinaldesi R, Stanghellini V, Barbara G, Felicani C, Di Nardo G, et al. Use of macrogol 4000 in chronic constipation. Eur Rev Med Pharmacol Sci 2011:15:960-966.
7. Hardikar W, Cranswick N, Heine RG. Macrogol 3350 plus electrolytes for chronic constipation in children: a single-centre, open-label study. J Paediatr Child Health 2007:43:527-531.
8. Dupont C, Leluyer B, Amar F, Kalach N, Benhamou PH, Mouterde O, Vannerom PY. A dose determination study of polyethylene glycol 4000 in constipated children: factors influencing the maintenance dose. J Pediatr Gastroenterol Nutr 2006:42:178-185.
9. Baker SS, Liptak GS, Colletti RB, Croffie JM, Di Lorenzo C, Ector W, Nurko S. Constipation in infants and children: evaluation and treatment. A medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1999:29:612-626.
10. Miller MK, Dowd MD, Fraker M. Emergency department management and short-term outcome of children with constipation. Pediatr Emerg Care 2007:23:1-4.
11. Burgers R, Bonanno E, Madarena E, Graziano F, Pensabene L, Gardner W, Mousa H, et al. The care of constipated children in primary care in different countries. Acta Paediatr 2012:101:677-680.
12. Candy DC, Edwards D, Geraint M. Treatment of faecal impaction with polyethelene 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.
13. Biggs WS, Dery WH. Evaluation and treatment of constipation in infants and children. Am Fam Physician 2006:73:469-477.
14. Schmulson Wasserman M, Francisconi C, Olden K, Aguilar Paiz L, Bustos-Fernandez L, Cohen H, Passos MC, et al. [The Latin-American Consensus on Chronic Constipation]. Gastroenterol Hepatol 2008:31:59-74.
15. Bae SH, Son JS, Lee R. Effect of fluid intake on the outcome of constipation in children: PEG 4000 versus lactulose. Pediatr Int 2010:52:594-597.
16. Loening-Baucke V. Chronic constipation in children. Gastroenterology 1993:105:1557-1564.
17. Bautista Casasnovas A, Arguelles Martin F, Pena Quintana L, Polanco Allue I, Sanchez Ruiz F, Varea Calderon V. [Guidelines for the treatment of functional constipation]. An Pediatr (Barc) 2011:74:51 e51-57.
18. Bell EA, Wall GC. Pediatric constipation therapy using guidelines and polyethylene glycol 3350. Ann Pharmacother 2004:38:686-693.
19. Pashankar DS, Bishop WP. Efficacy and optimal dose of daily polyethylene glycol 3350 for treatment of constipation and encopresis in children. J Pediatr 2001:139:428-432.
20. Croffie JM FJ: Idiopatic constipation. In: Walker WA, Sherman PM, Goulet O, Shnider BI, Kleinman RE, Sanderson IR, eds. Pediatric Gastrointestinal Disease. 4 th ed. Hilton BC Decker, 2004:1000-1016.
21. Nurko S. Advances in the management of pediatric constipation. Curr Gastroenterol Rep 2000:2:234-240.
22. Davidson M, Kugler MM, Bauer CH. Diagnosis and management in children with severe and protracted constipation and obstipation. J Pediatr 1963:62:261-275.
23. Staiano A, Andreotti MR, Greco L, Basile P, Auricchio S. Long-term follow-up of children with chronic idiopathic constipation. Dig Dis Sci 1994:39:561-564.
24. Andorsky RI, Goldner F. Colonic lavage solution (polyethylene glycol electrolyte lavage solution) as a treatment for chronic constipation: a double-blind, placebo-controlled study. Am J Gastroenterol 1990:85:261-265.
25. Wang Y, Wang B, Jiang X, Jiang M, Xu C, Shao C, Jia L, et al. Polyethylene glycol 4000 treatment for children with constipation: A randomized comparative multicenter study. Exp Ther Med 2012:3:853-856.
26. Horn JR, Mantione MM, Johanson JF. OTC polyethylene glycol 3350 and pharmacists' role in managing constipation. J Am Pharm Assoc (2003) 2012:52:372-380.
27. Gremse DA, Hixon J, Crutchfield A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. Clin Pediatr (Phila) 2002:41:225-229.
28. Dupont C, Leluyer B, Maamri N, Morali A, Joye JP, Fiorini JM, Abdelatif A, et al. Double-blind randomized evaluation of clinical and biological

tolerance of polyethylene glycol 4000 versus lactulose in constipated children. J Pediatr Gastroenterol Nutr 2005:41:625-633.
29. Loening-Baucke V. Polyethylene glycol without electrolytes for children with constipation and encopresis. J Pediatr Gastroenterol Nutr 2002:34:372-377.
30. Pashankar DS, Bishop WP, Loening-Baucke V. Long-term efficacy of polyethylene glycol 3350 for the treatment of chronic constipation in children with and without encopresis. Clin Pediatr (Phila) 2003:42:815-819.
31. Pashankar DS, Loening-Baucke V, Bishop WP. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. Arch Pediatr Adolesc Med 2003:157:661-664.
32. Michail S, Gendy E, Preud'Homme D, Mezoff A. Polyethylene glycol for constipation in children younger than eighteen months old. J Pediatr Gastroenterol Nutr 2004:39:197-199.
33. Erickson BA, Austin JC, Cooper CS, Boyt MA. Polyethylene glycol 3350 for constipation in children with dysfunctional elimination. J Urol 2003:170:1518-1520.
34. Loening-Baucke V, Pashankar DS. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. Pediatrics 2006:118:528-535.
35. Voskuijl W, de Lorijn F, Verwijs W, Hogeman P, Heijmans J, Makel W, Taminiau J, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. Gut 2004:53:1590-1594.
36. Rafati M, Karami H, Salehifar E, Karimzadeh A. Clinical efficacy and safety of polyethylene glycol 3350 versus liquid paraffin in the treatment of pediatric functional constipation. Daru 2011:19:154-158.
37. Humphreys MR, Reinberg YE. Contemporary and emerging drug treatments for urinary incontinence in children. Paediatr Drugs 2005:7:151-162.
38. DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterol 2000;95:446-450.
39. Cleveland MV, Flavin DP, Ruben RA, Epstein RM, Clark GE. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double-blind, placebo-controlled study. South Med J 2001:94:478-481.
40. Herve S, Leroi AM, Mathiex-Fortunet H, Garnier P, Karoui S, Menard JF, Ducrotte P, et al. Effects of polyethylene glycol 4000 on 24-h manometric recordings of left colonic motor activity. Eur J Gastroenterol Hepatol 2001:13:647-654.
41. Hudziak H, Bronowicki JP, Franck P, Dubos-Berogin C, Bigard MA. [Low-dose polyethylene glycol 4000: digestive effects. Randomized double-blind study in healthy subjects]. Gastroenterol Clin Biol 1996:20:418-423.
42. Youssef NN, Peters JM, Henderson W, Shultz-Peters S, Lockhart DK, Di Lorenzo C. Dose response of PEG 3350 for the treatment of childhood fecal impaction. J Pediatr 2002:141:410-414.
43. Benninga MA, Candy DC, Taminiau JA. New treatment options in childhood constipation? J Pediatr Gastroenterol Nutr 2005:41 Suppl 1:S56-57.
44. Abrahamian FP, Lloyd-Still JD. Chronic constipation in childhood: a longitudinal study of 186 patients. J Pediatr Gastroenterol Nutr 1984:3:460-467.
45. Loening-Baucke V. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. J Pediatr 1990:116:214-222.
46. van Ginkel R, Reitsma JB, Buller HA, van Wijk MP, Taminiau JA, Benninga MA. Childhood constipation: longitudinal follow-up beyond puberty. Gastroenterology 2003:125:357-363.
47. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. J Pediatr 2005:146:359-363.
48. Gomes PB, Duarte MA, Melo Mdo C. Comparison of the effectiveness of polyethylene glycol 4000 without electrolytes and magnesium hydroxide in the treatment of chronic functional constipation in children. J Pediatr (Rio J) 2011:87:24-28.
49. Rendeli C, Ausili E, Tabacco F, Focarelli B, Pantanella A, Di Rocco C, Genovese O, et al. Polyethylene glycol 4000 vs. lactulose for the treatment of neurogenic constipation in myelomeningocele children: a randomized-controlled clinical trial. Aliment Pharmacol Ther 2006:23:1259-1265.
50. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus Polyethylene Glycol for Chronic Constipation. Cochrane Database Syst Rev 2010:CD007570.

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