

REVIEW

Use of polyethylene glycol in functional constipation and fecal impaction

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ABSTRACT

Objective: The objective of this study was to evaluate in an analytical and descriptive manner the evidence published so far on the use of polyethylene glycol (PEG), with or without electrolytes, in the management of functional constipation and the treatment of fecal impaction.

Methodology: Search on MEDLINE, EMBASE and Cochrane databases until May 2016 of all publications adjusted to the following terms: *constipation AND/OR fecal impaction AND (PEG OR polyethylene glycol OR macrogol OR movicol OR idralax OR miralax OR transipeg OR forlax OR golytely OR isocolan OR mulytely) NOT colonoscopy*. Critical reading of selected articles (English or Spanish), sorting their description according to group age (adult/pediatric age) and within those, in accordance with study features (efficacy evaluation *versus* placebo, doses query, safety, comparison with other laxatives, observational studies and monographic review articles of polyethylene glycol or meta-analysis).

Results: Fifty-eight publications have been chosen for descriptive analysis; of them, 41 are clinical trials, eight are observational studies and nine are systematic reviews or meta-analysis. Twelve clinical trials evaluate PEG efficacy *versus* placebo, eight *versus* lactulose, six are dose studies, five compare polyethylene glycol with and without electrolytes, two compare its efficacy with respect to milk of magnesia, and the rest of the trials evaluate polyethylene glycol with enemas (two), *psyllium* (one), tegaserod (one), prucalopride (one), paraffin oil (one), fiber combinations (one) and *Descurainia sophia* (one).

Conclusions: Polyethylene glycol with or without electrolytes is more efficacious than placebo for the treatment of functional constipation, either in adults or in pediatric patients, with great safety and tolerability. These preparations constitute the most efficacious osmotic laxatives (more than lactulose) and are the first-line treatment for functional constipation in the short and long-term. They are as efficacious as enemas in fecal impaction, avoid the need for hospital admission and are well tolerated by patients (mainly when administered without electrolytes).

Key words: Functional constipation. Fecal impaction. Macrogol. Polyethylene glycol. PEG.

INTRODUCTION

Functional constipation (FC), defined by the Rome Criteria (1) as a chronic functional digestive condition, is a serious problem for adults and children due both to its prevalence and to the concomitant reduction in quality of life. In addition, it implies a high pharmaceutical cost.

Likewise, fecal impaction can lead to a situation that seriously compromises patient health, especially at extreme ages, causing sometimes a vital risk.

In order to treat these pathologies, a variety of resources has been employed, including pharmaceutical resources and others that directly impinge upon patient life habits. Among the aforementioned, the most outstanding and frequently utilized resource is the use of laxatives.

Laxatives are substances utilized since ancient times for different applications. Their main function is to provoke feces evacuation and/or bowel cleansing. Today, their use is indicated in different situations: colon preparation for surgery, certain pathologies requiring colon cleanse (i.e., liver encephalopathy), bowel cleansing for radiological or endoscopic examinations, and FC treatment non-responding to dietary hygienic measures.

There are laxatives of different types: bulk-forming, surfactant or softening, stimulating, and osmotic agents. The mechanism of action of osmotic laxatives is that they are able to increase water into the intestinal lumen by osmolarity or else, by preventing absorption of the liquid in which they are administered, decreasing feces consistency, increasing their volume, promoting intestinal peristalsis and thus, feces transit and evacuation.

Among the osmotic laxatives, there are different types: sodium citrate and phosphates, preferably administered rectally, lactitol, lactulose, magnesium salts, chlorine salts and polyethylene glycols (PEGs).

PEGs, which are the aim of this review, are high molecular weight, water-soluble polymers that can form hydro-

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gen bonds, in a ratio of 100 water molecules per one PEG molecule. In this way, the resulting colon hydration favors colon transit in a dose-dependent manner. Macrogol is the international common denomination (ICD) used for PEG. PEG (macrogol) can be utilized in two different preparations: PEG 3350 and PEG 4000. Likewise, PEG 3350 can be presented in two forms, pure PEG 3350 and PEG 3350 with electrolytes added (PEG + E), such as sodium bicarbonate, sodium chloride, potassium chloride, and sodium sulfate, in variable concentrations. This is intended to avoid possible dehydration caused by a severe diarrheal effect. We have performed a review of published articles on PEG, evaluating PEG efficacy on FC treatment in adults, as well as in children with FC or fecal impaction until 2016.

METHODOLOGY

Literature review

The databases used for the bibliographic search have been MEDLINE, EMBASE and Cochrane initiative databases. Search terms were: *constipation AND/OR fecal impaction AND (PEG OR polyethylene glycol OR macrogol OR movicol OR idralax OR miralax OR transipeg OR forlax OR golytely OR isocolan OR mulytely) NOT colonoscopy*. Studies performing constipation diagnosis have been selected according to the Rome I, II, or III criteria, or previously to them, based on clinical criteria that have excluded organic diseases (neurological, endocrine, etc.) or drugs (opioids) as causes, or association with irritable bowel syndrome. In addition, we have only

included studies on pediatric patients meeting diagnostic criteria of functional constipation and/or fecal impaction. The PEG use for colon preparation in any common procedure (surgery, endoscopy, radiology, etc.) has been specifically excluded. Only publications in either English or Spanish, excluding scientific meeting abstracts, have been evaluated. Since this is not a comparative analytical study of quantitative results (meta-analysis), in addition to randomized quantitative trials comparing PEG with placebo or laxatives, observational prospective or retrospective open studies of PEG efficacy, review articles and meta-analysis analyzing PEG efficacy for the treatment of functional constipation or fecal impaction in pediatrics have been evaluated.

Data extraction and analysis

The reviewers have performed in an independent manner the databases search and have followed the process illustrated in figure 1. This has led to the analysis of 58 articles (Table I) that have been critically read, evaluating the type of study design, number of subjects included in the intervention performed by the authors, measure instruments, and variables included in each study.

Adult age (Table II)

Twenty-six articles have been evaluated: 17 clinical trials, (2-16), four observational studies (17-20), two reviews (21,22) and three meta-analyses (23-25).

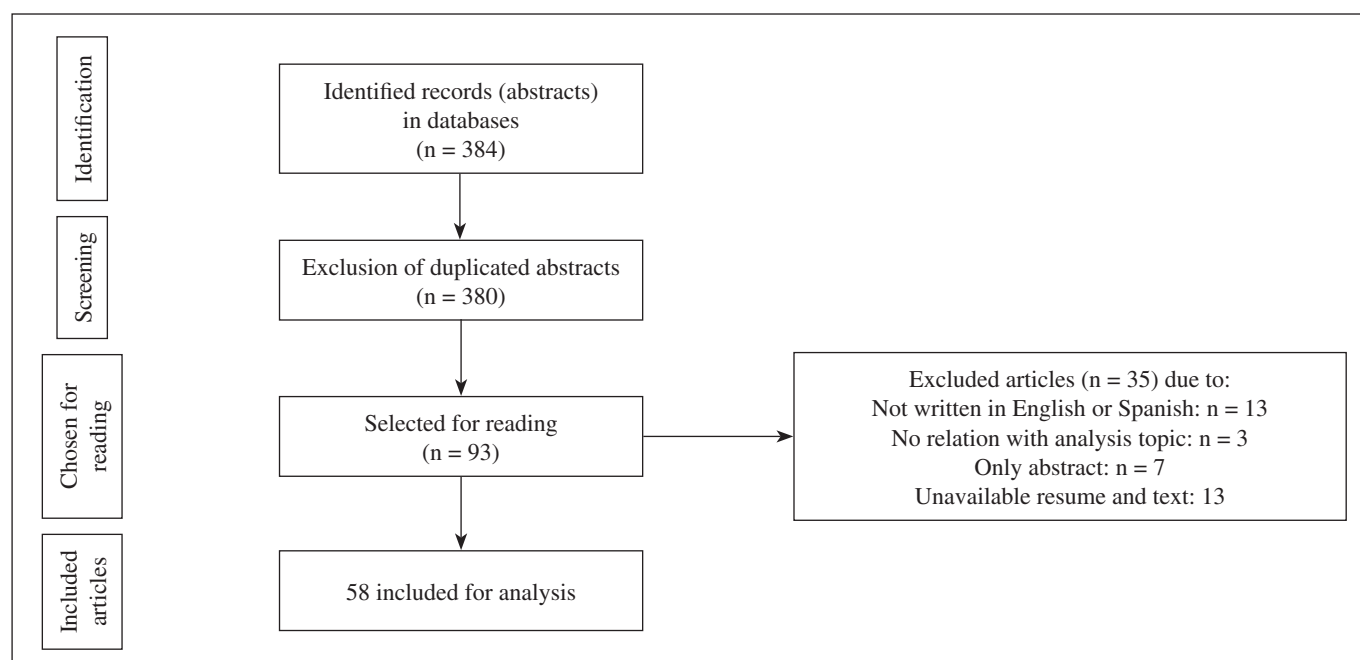


Fig. 1. Study selection flow.

Table I. Features of the selected studies

Comparison	Number of studies	Total of Patients	Patients with PEG	Patients Comparator	References
PEG or PEG + E/placebo*	12	1,099	799	551	(2-11,28,29)
PEG o PEG + E/lactulose	8	761	402	396	(26,27,30-35)
PEG/PEG + E	5	532	269	263	(12,13,36,37,58)
PEG/milk of magnesia	2	168	85	83	(38,39)
PEG + E/ <i>psyllium</i>	1	126	63	63	(14)
PEG/tegaserod	1	234	118	116	(15)
PEG + E/prucalopride	1	236	120	116	(16)
PEG/paraffin oil	1	158	80	78	(40)
PEG/ <i>Descurainia sophia</i>	1	120	60	60	(41)
PEG/enemas	2	169	83	86	(55, 56)
PEG/fibers	1	100	50	50	(42)
PEG doses comparison	6	604*	421	268	(6,10,12,43,44,57)
PEG o PEG + E observational	8	599	599	-	(17-20,33,47,48,59)
Reviews and meta-analysis	9				(21-25,51-54)

PE + E: PEG plus electrolytes. Some studies are crossover. Therefore, the total number does not always matches the sum of the comparative studies. *One of the studies compares different doses versus placebo.

All comparative studies with placebo (n = 10) were randomized (11), double-blind was used in nine of them (2-7,9-11), and crossover design in other five studies (2-4,6,9). The duration of the studies was highly variable (5 days-6 months), being less than 12 weeks (n = 7) in the majority of them. The two studies comparing PEG with lactulose were randomized (26,27), none of them was double-blind and the duration of both of them was four weeks. In the comparative analysis of PEG versus PEG + E both studies were randomized, double-blind and with an adequate description of the methodology used (12,13). In three studies, PEG is compared with tegaserod (15), prucalopride (16) and *psyllium* (14); the three studies are randomized, parallel, with good methodology description.

Pediatric age

Functional constipation (Table III)

Twenty eight articles have been evaluated, 17 clinical trials (28-44), six observational studies, four prospective studies (45-48) and two retrospective studies (49,50), as well as two reviews (51,52) and three meta-analysis (25,53,54). Only two clinical trials versus placebo have been evaluated (28,29), which are randomized, one double-blind and the other one a crossover trial (28). Six trials have compared PEG with lactulose, four double-blind (31-33,35) with different doses, formulas and durations. Two randomized, non-blinded trials compare PEG with milk

of magnesia (38,39). There are two comparative studies between PEG and PEG + E (36,37), one of them being a blind, randomized trial (36). Open observational studies have a variable duration (0-37 months), with methods in which doses variability stands out (45-50). One trial compares PEG efficacy with paraffin oil (40) and another one, with *Descurainia sophia* L. (41), none of them blinded.

Fecal impaction (Table IV)

Six articles have been evaluated, three clinical trials (55-57), three observational studies, one prospective (33) and two retrospective studies (58,59).

EFFICACY IN ADULT POPULATION

Papers analyzed in this age group show a great variability with respect to design, methodology, and sample size (Table II). Studies have been divided according to the existence or non-existence of a comparative drug.

PEG versus placebo

All studies that have evaluated PEG efficacy versus placebo, not without some heterogeneity, show a significant superiority regarding stool number, less straining, less need for rescue laxatives, and lower dropout number in patients taking PEG.

Table II. Studies with PEG/PEG + E in adult population with functional constipation

Authors/ref./year	Treatment/dose/day	Comparator/n	Duration	Design	Results
Andorsky and Goldner 1990 (2)	PEG + E/16/8-16 oz	Placebo/16	2 x 5 days	Double-blind/crossover, randomized	Higher number of stools/week, PEG versus placebo 7.75 ± 4.55 versus 4.88 ± 2.62 p < 0.01
Baldonado et al. 1991 (3)	PEG 3350 + E/34/30 g	Placebo/34	2 x 8 days	Double-blind/crossover, randomized	Higher number of stools/week, PEG versus placebo, 5.53 versus 12.13 p < 0.01
Klauser et al. 1995 (4)	PEG 4000/8/60 g	Placebo/8	2 x 6 weeks	Double-blind/crossover, randomized	Higher number of stools/week, PEG versus placebo, 3 versus 11 p < 0.01
Corazziari et al. 1996 (5)	PEG + E/25/29,2 g	Placebo/23	8 weeks	Multi-center, double-blind, randomized	Higher number of passing stools/week, PEG versus placebo, 4.8 ± 2.3 versus 2.8 ± 1.6 p < 0.002
Di Palma et al. 1999 (6)	PEG 3350/85 6 g 12 g 17 g 34 g	Placebo/50/35	3 x 10 days	Double-blind/crossover, randomized	Higher number of stools/week, PEG versus placebo, 3.2-5.6 versus 3.2-4.1
Corazziari et al. 2000 (7)	PEG + E/33/29.2 g	Placebo/37	20 weeks	Multi-center, double-blind, randomized	Higher number of stools/week, PEG versus placebo, 7.4 versus 5.4
Di Palma et al. 2000 (8)	PEG 3350/80/17 g	Placebo/71	2 weeks	Multi-center, blind, randomized	Higher number of stools/week, PEG versus placebo, 4.5 versus 2.7 p < 0.01
Cleveland et al. 2001 (9)	PEG 3350/23/17 g	Placebo/23	2 x 2 weeks	Double-blind crossover, randomized	Higher number of stools/week, PEG versus placebo, 7.0 versus 3.6 p < 0.0001
Di Palma et al. 2002 (10)	PEG 3350/18 different dosage 6: 51 g 6: 68 g 6: 85 g	Placebo/6	One control intake during 2 days	Double-blind, randomized	Shorter time to present first and second satisfactory defecation A dose of 68 g was more efficacious and satisfactory than the first one (14.8 ± 9.05) and second stool (19.2 ± 11.3)
Di Palma et al. 2007 (11)	PEG 3350/204/17 g	Placebo/100	6 months	Multi-center double-blind, randomized	Higher % of patients with more than 3 stools/week, in PEG versus placebo (52% versus 11%)
Attar et al. 1999 (26)	PEG 3350 + E/60/13-39 g	Lactulose/55	4 weeks	Multi-center, randomized	Number of stools/day PEG 1.3 ± 0.7/LC 0.9 ± 0.6 p < 0.005
Bouhnik et al. 2004 (27)	PEG 4000/32/10-30 g	Lactulose/33	4 weeks	Multi-center, randomized, parallel groups	Number of stools/week PEG 8.8/LC 7.8
Chaussade y Mimic 2003 (12)	PEG + E/137 AD: 11.8 g/69 BD: 5.9 g/65	PEG/132 AD: 20 g/67 BD: 10 g/65	4 weeks	Multi-center, double-blind, randomized, parallel groups	All groups improve regarding basal, without SD between them

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Table II (Cont.). Studies with PEG/PEG + E in adult population with functional constipation

Authors/ref./year	Treatment/in/dose day	Comparator/n	Duration	Design	Results
Seinela et al. 2009 (13)	PEG + E/32/6-24 g	PEG/30	4 weeks	Multi-center, double-blind, randomized, parallel groups	All groups improve regarding basal, without SD between them
Di Palma et al. 2007 (11)	PEG/118/17 g	Tegaserod/116	4 weeks	Multi-center, randomized, open, parallel groups	Number of stools/week PEG 10.4/TG 8.5 p < 0.01
Cinca et al. 2013 (16)	PEG + E/120/26 g	Prucalopride/116	4 weeks	Double-blind, masked, randomized, parallel groups	Number of stools/week PEG 3.2/PR 2.2 p < 0.01
Wang et al. 2004 (14)	PEG + E/63/27,6 g	Psyllium/63	2 weeks	Open, randomized, parallel groups	Number of stools/week PEG 8.5/PG 5.72 p < 0.005
Culbert et al. 1998 (17)	PEG + E/16/110 g/day	None	3 days	One-center, prospective, observational	Effective disimpaction in severe functionally constipated after 3 days of treatment 81.3%
Tran y Di Palma 2005 (19)	PEG/50/17 g	None	2 weeks of treatment and 4 weeks without treatment	One-center, open	PEG efficacy in achieving more than 3/stools week, in 83.4% after 14 days At 30 days without PEG, 61.7% of patients needed laxatives
Chen et al. 2005 (18)	PEG + E/56/110,4 g/day	None	3 days	Multi-center, prospective, observational	Effective disimpaction in severe functionally constipated after three days of treatment 89.3% (IC 95%: 75.3-94.4%)
Di Palma et al. 2007 (20)	PEG 3350/311/17 g	None	12 months	Multi-center, prospective observational	Efficacy and safety No electrolyte alterations in blood detected No tachyphylaxis Diarrhea, soft feces and nausea, more frequent secondary effects

PEG: Polyethylene glycol; N: Number of patients; LC: Lactulose; E: Electrolytes; D: Doses; SD: Significant differences; TG: Tegaserod; PR: Prucalopride; HD: High dose; LD: Low dose; CI: Confidence interval.

Table III. Studies with PEG/PEG + E in childhood with functional constipation

Authors/ref./year	Treatment/N /doses	Comparator/N	Duration	Design	Results
Thomson et al. 2007 (28)	PEG + E/51 Variable doses according to age and days between 6.9 g and 62.1 g	Placebo/51	2 weeks	Double-blind, multi-center, randomized, crossover	Number of stools per week Higher number of stools PEG + E 3.12 ± 2.05 versus placebo 1.45 ± 1.20 p < 0.001(week 2)
Nurko et al. 2008 (29)	PEG/79; 3 groups and 3 doses (0.2, 0.4,0.8 g/kg/day)	Placebo/24	2 weeks	Double-blind, multi-center, randomized, controlled, dose evaluation	Number of stools per week Higher number of stools in different doses PEG versus placebo, week 2
Savino et al. 2012 (36)	PEG + E/42/according to age 6.9-27.6 g/day	PEG/49/0.7 g/kg/day	2 months	Blind, randomized, controlled	Number of stools per week PEG versus PEG + E, 9.2 versus 7.8 p < 0.025
Llerena et al. 2015 (37)	PEG + E/32 Fecal impaction: 1.5-2 g/kg/day Constipation:0.4-1 g/kg/day	PEG/30 Fecal impaction: 1.5-2 g/kg/day Constipation: 0.4-1 g/kg/day	3 months	Open, observational, parallel groups	Number of stools per week PEG + E 5.45 ± 7 versus 4.67 ± 4 p = 0.28 (12 weeks)
Gremse et al. 2002 (30)	PEG/37/1.3/kg/day	Lactulose	2 weeks	Prospective, open, crossover	Number of stools per week PEG 14.8 ± 1.4 versus lactulose 13.5 ± 1.5 P NDS
Voskuil et al. 2004 (31)	PEG/46 6 months-6 years: 2.95 g/day > 6 years: 6 g/day	Lactulose/45	2 months	Double-blind, randomized, parallel groups	Number of stools per week Improvement in both vs basal p < 0.01 Improvement in % of efficacy in PEG group versus lactulose (56% vs 29%)
Dupont et al. 2005 (32)	PEG/51 4-8 g/day	Lactulose/45	3 months	Double-blind, multi-center, masked, randomized	Number of stools per week Improvement in both
Candy et al. 2006 (33)	PEG + E/27 Dose after disimpaction: 12.51 ± 5.65	Lactulose/26	3 months	Double-blind, randomized	Number of stools per week PEG + E 9.4 versus lactulose 5.9 p < 0.007
Wang et al. 2012 (34)	PEG 4000/105	Lactulose/11	2 weeks	Blind, randomized	Average of stools per week PEG 7 versus lactulose 6 SD
Treepongkaruna et al. 2014 (35)	PEG 4000/44 8 g/day	Lactulose/44	4 weeks	Double-blind, randomized	Number of stools per week PEG 1.1 ± 0.55 versus lactulose 0.8 ± 0.41
Loening-Baucke y Pashankar 2006 (38)	PEG/39 0.7 g/kg/day	Milk of magnesia/40	12 months	Randomized, open	Efficacy, safety and tolerance Number of stools per week No differences between treatments, better tolerance to PEG
Ratanamongkol et al. 2009 (39)	PEG 4000/46 0.5 g/kg/day	Milk of magnesia/43	4 weeks	Randomized, controlled	Percentage of patients that improve with PEG (91%) versus MM (65%) is higher and better tolerated p < 0.003

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Table III (Cont.). Studies with PEG/PEG + E in childhood with functional constipation

Authors/ref./year	Treatment/ /doses	Comparator/N	Duration	Design	Results
Rafati et al. 2011 (40)	PEG/80/1-1.5 g/kg/day	Paraffin oil (PO)/78	4 months	Prospective, randomized	Improvement with respect to basal in number of stools per week Both treatments equally effective with respect to basal Pre PEG 1.6 ± 0.8 PEG 7.0 ± 3.8 Pre PO 1.4 ± 0.5 AP 6.3 ± 3.1 More secondary effects in PO
Nimrauzi et al. 2015 (41)	PEG/53/0.4 g/kg/day	<i>Descurainia sophia</i> L. (<i>D. sophia</i>)/56	8 weeks	Prospective, randomized	Improvement with respect to basal in number of stools per week Both treatments equally effective with respect to basal PrePEG and pre <i>D. Sophia</i> , without SD between both laxatives
Quitadamo et al. 2012 (42)	PEG + E/50/0.5 g/kg/day	Combination (acacia fiber, <i>psyllium</i> fiber and fructose)/50	2 months	Randomized, parallel, controlled groups	Number of stools per week No differences between treatments PEG + E 1.9 ± 0.6 versus FAIF 1.7 ± 0.6 p = 0.427
Pashankar y Bishop 2001 (45)	PEG/24 Initial dose 1 g/kg/day, increasing until achieving two stools per day	None	2 months	Observational, prospective	Improvement with respect to basal in number of stools per week Pre-PEG 2.3 ± 0.4 versus PEG 16.9 ± 1.6 p < 0.0001 The average dose was 0.84 g/kg/day (range, 0.27-1.42 g/kg/day)
Pashankar et al. 2003 (46)	PEG/43 EF/31 EF and encopresis 0.8 g/kg/day	None	3-30 months	Observational, prospective	Improvement with respect to basal in number of stools per week Pre-PEG 3 ± 0.5 versus PEG 12.5 ± 1.5 p < 0.001
Loening-Baucke et al. 2004 (49)	PEG Short-term (CP)/71 Long-term (LP)/47 1 g/kg/day	None	1-4 months 6-37 months	Observational retrospective	Improvement with respect to basal in number of stools per week Pre PEG 4.2 ± 3.9 versus PEG (CP) 11.2 ± 6.8 p < 0.01; PEG (LP) 8.7 ± 3.3 p < 0.05
Michail et al. 2004 (50)	PEG/28 Initial average dose 0.88 g/kg/day (range, 0.26-2.14 g/kg/day) Effective maintenance dose 0.78 g/kg/day (range, 0.26-1.26 g/kg/day)	None	0-21 months	Observational retrospective	Improvement with respect to basal in number of stools per week Pre PEG 2.2 ± 1 versus PEG (CP) 8.4 ± 2.5 p < 0.001

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Table III (Cont.). Studies with PEG/PEG + E in childhood with functional constipation

Authors/ref./year	Treatment/N/doses	Comparator/N	Duration	Design	Results
Dupont et al. 2006 (32)	PEG 4000/4 groups by age (n = 96) 4 age groups, each group divided into single or double doses: 2.5 g or 5 g 4 g or 8 g 8 g or 16 g 16 g or 32 g	PEG 4000/different doses	3 months	Randomized (doses), prospective	Improvement with respect to basal in number of stools per week Pre PEG 2-3 vs PEG (CP) 9-11 p < 0.0001 Better single dose (0.5 g/kg/day)
Hardikar et al. 2007 (47)	PEG + E/68/doses by age: 2-6 years: 6.563 g 3 doses/day 7-11 years: 6.563 g 4 doses/day	None	12 weeks	Open, prospective, one-center, observational	Improvement with respect to basal in number of stools per week Pre PEG + E 1.4 ± 0.55 versus PEG + E 7.1 ± 3.45 p < 0.0001
Infante Pina et al. 2011 (48)	PEG + E/15 Average dose 0.44 g/kg/day	None	4 weeks	Prospective, observational	Improvement with respect to basal in number of stools per week Pre PEG + E 2.46 ± 0.71 versus PEG + E 5.29 ± 1.68 p < 0.001
Dziechciarz et al. 2015 (44)	PEG /45 0.3 g/kg/day	PEG/45 0.7 g/kg/day	6 weeks	Prospective, open, randomized	Improvement with respect to basal in number of stools per week Both doses equally effective with respect to prePEG

PEG: Polyethylene glycol; N: Number of patients; LC: Lactulose; E: Electrolytes; D: Doses; SD: Significant differences; NSD: Non-significant differences; MM: Milk of magnesia; AFPPF: Acacia fiber, psyllium fiber, and fructose; PO: Paraffin oil.

Table IV. Studies with PEG/PEG + E in childhood with fecal impaction

<i>Authors/ref./year</i>	<i>Treatment/n/doses</i>	<i>Comparator/n</i>	<i>Duration</i>	<i>Design</i>	<i>Results</i>
Youssef et al. 2002 (57)	PEG/40/different doses: 0.25, 0.5, 1, 1.5 g/kg/day	PEG different doses	3 days	Prospective, doubled-blind, randomized	Efficacy in fecal impaction resolution: PEG (HD) 95% <i>versus</i> PEG (LD) 55% p = 0.005
Candy et al. 2006 (33)	PEG + E/63 Doses: 2-4 years: 13.8- 55.2 g 5-11 years: 27.6- 82.8 g	None	Resolution of fecal impaction in 7 days	Prospective, open	Efficacy in fecal impaction resolution: 92%
Bekkali et al. 2009 (55)	PEG/44/1.5 g/kg/day, 6 days	Enemas/46	6 days	Prospective, randomized, open	Efficacy in fecal impaction resolution: PEG 68% <i>versus</i> enemas 80% p = 0.25
Miller et al. 2012 (56)	PEG/39	Enemas/40	3 days	Prospective, randomized, open	Efficacy in fecal impaction resolution: PEG 38% <i>versus</i> enemas 74% p = 0.05
Boles et al. 2015 (58)	PEG + E/23/> 0.8 g/kg/day 78% of patients needed nasogastric tube for administration	PEG/28/> 0.8 g/kg/day Any patient needed nasogastric tube	Resolution of fecal impaction	Retrospective, observational	Efficacy in fecal impaction resolution was similar PEG + E 87% <i>versus</i> PEG 86% Less secondary effects in PEG (p < 0.001)
Jordan-Ely et al. 2015 (59)	PEG + E/associated to sodium picosulfate in 44 patients Different doses, 7 days Day 1 induction with 78-103 g of PEG + E	None	Resolution of fecal impaction and evaluation in 8 months of follow-up	Retrospective, observational	Resolution of fecal impaction: 100% after 7 days

PEG: Polyethylene glycol; N: Number of patients; LC: Lactulose; E: Electrolytes; D: Doses; SD: Significant differences; HD: High dose; LD: Low dose.

Studies of short-term efficacy

Initially, efficacy was evaluated in short-term crossover studies (5-8 days), observing through daily bowel movements a significant increase in stool number and a decrease in feces consistency in the groups treated with PEG, without remarkable secondary effects (2,3). Similar results were obtained after two weeks of treatment with 17 g/day of PEG 3350 (8,9) and after four weeks (19). In addition, rapid loss of benefit after cessation of PEG treatment was observed.

High dose PEG efficacy to achieve fecal disimpaction in adult patients with FC has been shown in two studies with PEG + E 110 g/day during three consecutive days (17,18). After 72 hours, 81.3% (CI 95%, 77.4-95.6%) (17) and 89.3% (CI 95%, 75.3-94.4%) (18) of treated patients had achieved disimpaction without secondary effects, and the majority of them experienced improvement in the number, consistency and easiness of passing stools at day two.

Studies of long-term efficacy

Long-term efficacy and safety of PEG 3350 17 g/day was evaluated for six months in a multi-center, dou-

ble-blind, randomized, controlled study *versus* placebo in parallel groups (11), in which the main objective was treatment success after applying very specific Rome criteria for 50% of weeks of treatment. Hence, 52% of the PEG group *versus* 11% of the placebo group (p < 0.001) reached this endpoint. Throughout the study, it was observed that the difference favoring PEG already occurred during the first month, reached the maximum in the second month and was maintained at six months, improving the subjective perception of constipation and the stool number per week (satisfactory and spontaneous) (p < 0.001). The presence of nausea, diarrhea, liquid stools and flatulence was higher in the PEG-treated group (40% *versus* 25%, p < 0.01), and no changes were detected in the analytical blood parameters analyzed. In a one-year open multi-center study, the same work group (20) obtained similar results and concluded that the drug is safe in prolonged treatments and that response is maintained over time.

PEG *versus* lactulose

In 1999, Attar et al. (26) analyzed the efficacy of PEG 3350 with electrolytes *versus* lactulose in a multi-center,

randomized, non-blind study, in which 60 patients were treated with PEG (13 g) and 55 patients with lactulose (10 g) for four weeks. The PEG group presented a higher number of stool per week (1.3 *versus* 0.9, $p < 0.005$) with respect to lactulose and a significant decrease in straining (0.5 *versus* 1.2, $p < 0.0001$). In addition, the degree of satisfaction was also higher in the PEG group (7.4 *versus* 5.2, $p < 0.01$). Tolerance was similar in both groups, but flatulence was lower in the PEG group (3.8 *versus* 9.2, $p = 0.01$). In the last two weeks of the study (when the patients could adjust the dose) the number of PEG intakes (1.6 as average) was lower than the number of lactulose intakes (2.1 as average), $p < 0.001$.

Afterwards, in 2004, Bouhnik et al. (27) published a prospective, randomized study with parallel groups, comparing PEG 4000 efficacy and tolerance ($n = 32$) *versus* those of lactulose ($n = 33$). The study design was complex. In the first week patients took a fixed dose of 20 g of PEG or lactulose; in the second week, depending on efficacy and tolerability, patients could choose to change the dose from 10 to 30 g, and in the last two weeks they had to take the same dose they had chosen in the second week. Furthermore, feces samples were collected for bacteriological studies on days 1, 21 and 28. No differences were observed in relation to frequency of stools, their features, or symptoms perceived by the patient between both groups, and from the bacteriological point of view, it was detected that lactulose was behaving as a prebiotic and that PEG diminished colonic fermentation.

PEG *versus* tegaserod

A multi-center, randomized, non-blinded trial from 2007 (15) compared the efficacy and safety of PEG 3350 at a 17 g/day dose (118 patients) with tegaserod at a dose of 6 mg/twice a day (116 patients) for four weeks. PEG was more efficacious than tegaserod with respect to the primary endpoint (improvement $\geq 50\%$ of Rome Criteria during the weeks of treatment); 50% PEG *versus* 31% tegaserod, $p < 0.003$. Patients taking PEG presented more weekly stools than those taking tegaserod (7.7 *versus* 4.9, $p < 0.01$) and five patients abandoned tegaserod treatment *versus* none with PEG. Main secondary effect observed in the tegaserod group was headache (6%). Tegaserod was withdrawn from the market in several countries due to the onset of cardiovascular secondary effects.

PEG + E *versus* prucalopride

The only published study is a single-center, double-blind, double-masked, randomized clinical trial, which compared PEG 3350 + E at a dose of 26 g/day (120 patients) with prucalopride at a dose of 1-2 mg (116 patients) for 28 days in women with FC (16). The primary

endpoint of the study was to evaluate the ratio of patients presenting more than three complete spontaneous bowel movements in the last week of treatment. The analysis of results showed that in the 4th week, 66.7% of the PEG group and 56% of the prucalopride group fulfilled the improvement criteria ($p = 0.13$), the differential being about 10% in favor of the PEG group. However, in a three-week analysis, the PEG group had a significantly higher response than the prucalopride group. Moreover, in the secondary endpoints, the weekly analysis showed that the PEG group showed less straining, less sensation of incomplete evacuation and that feces' Bristol stool scale value was higher than in the prucalopride group. The colonic transit time was reduced in both groups without significant differences.

PEG + E *versus* psyllium (ispaghula husk)

The only clinical trials analyzing the comparative efficacy in both preparations was a randomized, non-blinded study of two parallel groups (63 patients in each group), taking PEG + E 13.8 g/twice daily or psyllium 3.5 g/twice a day for two weeks (14). Patients that took PEG + E increased the mean weekly defecation rate with respect to baseline, significantly more than the psyllium group (from 1.18 ± 0.77 to 7.95 ± 3.49 *versus* 1.33 ± 0.68 to 5.33 ± 2.81) in the first week, and up to 8.48 ± 3.55 *versus* 5.71 ± 2.49 the second week ($p < 0.001$). After two weeks, 87.3% of patients on PEG + E have normalized their defecations *versus* 66.7% of patients on psyllium. No adverse effects or changes in blood test results were observed in any of both groups.

PEG with electrolytes *versus* PEG without electrolytes

Two studies analyze the efficacy of both PEG presentations. The first study, from 2003, is a multi-center, double-blind, randomized study in two parallel groups of outpatients with FC, administered with 5.9-11.8 g of PEG 3350+E, or 10-20 g of PEG 4000 for one month (12). No significant differences were obtained between both preparations. Another study compared PEG 4000 *versus* PEG + E in elderly patients with FC (admitted to ten institutions in Finland) during four weeks at variable doses (from 12 g twice a day to 12 g in alternative days). It was observed that both preparations were equally effective, safe and well tolerated and that patients could change from one preparation to the other without loss of efficacy. The only non-significant difference was found in the taste evaluation, so that 31% of patients of the isotonic preparation group considered the suspension taste as bad or very bad, with respect to 12% of the group treated with the hypotonic preparation ($p < 0.1$).

Analysis of review articles and meta-analysis

Five review articles that assess high quality clinical trials, performed in adults with PEG up to their publication date, have been evaluated.

The first article is a systematic review by Ramkumar and Rao in 2005 (21), in which eight studies that fulfilled the inclusion criteria of being randomized clinical trials in adult patients are analyzed. The authors evaluated and ranked the articles with grade of recommendation and level of evidence (USPSTF). Five of the studies analyzed were PEG *versus* placebo trials, one *versus* lactulose, another one evaluated lactulose and PEG in constipation induced by opioids, and the last two compared two PEG formulations (PEG *versus* PEG + E). The review concluded that PEG administration in FC is efficacious with few secondary effects, and slightly better than lactulose, being more cost-effective than the latter. Therefore, the authors granted a grade of recommendation 1 and level of evidence A.

In a Cochrane review from 2010, Lee-Robichaud et al. analyze in a meta-analysis clinical trials published between 1997 and 2007 that comparatively evaluate PEG solutions with lactulose for FC treatment (23). They review ten trials (four in adults) that included a total 868 patients. They conclude that PEG is superior to lactulose regarding the increment in the number of stool passages/week, form of the stool, decrease in bowel pain, and reduction in the need of associated laxatives.

In 2010, using the main databases, Belsey compiled a total of 63 studies, reduced to 20 with inclusion criteria filters, all of them in adults (24). This paper performed a quantitative meta-analysis with different evaluations, based on the quality of the studies analyzed. The analysis determined that patients treated with PEG had an increment in the number of defecations per week with respect to placebo of 1.98 stools/week ($p < 0.0003$) (all the studies), 2.34 stools/week in high quality studies ($p < 0.0001$). With respect to lactulose, patients had one stool/week in all the studies and 1.65 stools/week regarding high quality studies ($p < 0.02$). He concluded the reinforcement of the hypothesis that PEG is more effective than placebo and lactulose in patients with FC, although the comparative studies between both drugs are scarce.

In 2014, Paré and Fedorak published a systematic literature review and analyzed PEG efficacy in chronic constipation derived from 19 studies, three of them being meta-analysis (22). These authors concluded that, in spite of the methodological variety of the studies, it is clear that PEG is more efficacious than placebo and that PEG without electrolytes is preferred to the one with electrolytes, due to patients' greater acceptance of drug taste.

Recently (2016), Kateralis et al. have evaluated 19 clinical trials (25) that fulfill the required criteria needed to perform a quantitative analysis (meta-analysis) until April 2015. The main endpoint of this study was to evaluate the efficacy of PEG + E or PEG without electrolytes in the

treatment of FC in adults, between themselves, or *versus* placebo, lactulose, prucalopride, tegaserod, and *psyllium* (ispaghula). The analysis shows that differences between PEG or PEG + E and placebo are significant, increasing the average number of defecations per week with respect to placebo, 1.8 times PEG and 1.9 times PEG + E. Likewise, PEG + E increased 1.9 times the number of stool passages *versus* lactulose, 1.3 with respect to tegaserod, 1.4 to prucalopride and 2.6 to *psyllium*. In the safety analysis, they do not observe alterations of relevance in any study and therefore, they conclude that both PEG and PEG + E, without any difference, are efficacious and safe for the treatment of FC in adults.

EFFICACY IN CHILDHOOD

The articles analyzed in this age group show a great variability with regard to design, methodology and sample size (Table III).

PEG *versus* placebo

Two studies evaluate (according to age) different doses of PEG + E (28) and PEG (29). The multi-center, double-blind, randomized and crossover clinical trial by Thomson et al. (28) tries to evaluate the efficacy and safety of PEG + E in 51 children (age 2-11) with FC, administering different doses (from one to six daily doses of a PEG + E sachet with 6.9 g), adjusted to age and symptoms during two weeks, or of placebo. Later, and after two weeks without any drug administration, the groups were crossed and the group that had previously received placebo was administered PEG + E during two more weeks. The main intention-to-treat efficacy variable (number of complete defecations/week) was observed to be significantly higher in the PEG + E treated group (3.12 *versus* 1.45, $p < 0.001$). Moreover, it was detected that PEG + E produced a significantly higher number of total defecations/week ($p < 0.003$), less pain and straining during defecation ($p < 0.04$ and $p < 0.001$, respectively) and less stool consistency ($p < 0.001$). The secondary effects related to treatment were similar in both groups (41% PEG and 45% placebo).

Subsequently, Nurko et al. (29) performed a multi-center, double-blind, randomized and controlled trial in 103 children (4-16 years old) with different PEG doses (0.2, 0.4, 0.8 g/kg/day) or placebo during two weeks. The efficacy percentage (presence of \geq three stools/week in the second week) in patients taking PEG was significantly higher than in those taking placebo (77% with 0.2 g/kg, 74% with 0.4 g/kg and 73% with 0.8 g/kg *versus* 42% with placebo; $p < 0.04$). Stool consistency and straining significantly improved with 0.4 g/kg and 0.8 g/kg ($p < 0.003$), with higher frequency in bowel pain and fecal incontinence, however, after high doses.

PEG *versus* lactulose

Five studies compare the efficacy, tolerability and secondary effects of PEG *versus* lactulose with different results.

In 2002, Gremse et al. (30) analyzed in an open, randomized and crossover study the efficacy of PEG 3350 (10 g/m²/day) *versus* lactulose (1.3 g/kg/day in two intakes) in 37 children (2-16 years old) for two weeks and, subsequently, treatments were crossed over for another two weeks. In addition, the number and features of the stools, colonic transit time and grade of satisfaction perceived by health care providers and physicians were evaluated. They did not observe significant differences between treatment groups in any parameter analyzed.

In 2004, Voskuijl et al. (31) analyzed PEG 3350 (n = 46) *versus* lactulose (n = 45) for an eight-week period in a double-blind, randomized clinical trial of parallel groups, constituted by children from six months to 15 years of age. Children younger than six years took 2.95 g/sachet/day of PEG or 6 g/sachet/day of lactulose and children older than six years took 5.9 g/day *versus* 12 g/day (2 sachets), respectively. The dose was increased another 2.95 g of PEG or 6 g of lactulose if the effect was considered as insufficient, or it was reduced 50% if diarrhea appeared. The percentage of success (number of patients presenting \geq three stools per week and \leq one episode of encopresis every two weeks) was higher in the group with PEG (56% *versus* 29%, p < 0.02) than in the group with lactulose, in both PEG doses. Moreover, in this group an improvement in abdominal pain, effort and pain during bowel movement with regard to lactulose was also observed.

Dupont et al. (32) analyze the efficacy and biological changes in PEG treatment with PEG 4000 (4-8 g/day) *versus* lactulose (3.33-6.66 g/day) in 96 children with FC (ages six months to three years) in a randomized, double-blind and multi-center study, during three months of treatment. Different blood parameters (proteins, albumin, iron, electrolytes, folic acid, vitamins A and D) were evaluated on days 1 and 84. In the intermediate (day 42) and final analyses (day 84) of the study, no differences were detected in the stool number per week or in biological parameters between both groups. The group treated with PEG needed the use of rescue enemas less frequently and, additionally, presented better stool consistency and better appetite.

Candy et al. (33) analyzed the long-term (three months) efficacy to avoid new impaction episodes and to increase the number of defecations/week after a fecal disimpaction treatment in 27 children (2-11 years old). In the lactulose group, 23% of patients suffered impaction, compared to 0% in the PEG-treated group (p < 0.01), and the number of weekly stools was significantly higher than in the PEG-treated group (9.4 *versus* 5.9, p = 0.007, 95% CI 1.0-6.0).

In 2012, Wang et al. (34) evaluated the efficacy and safety of PEG 4000 in children (n = 105) (20 g/day, during

14 days) *versus* lactulose (n = 111) (10 g/day during three days and 6.7 g/day during 11 days) in a blind, randomized and multi-center study. Clinical remission was considered when patients presented more than three stools per week and their consistency had a 4-6 value in the Bristol stool scale. Moreover, 72.38% of patients treated with PEG achieved remission, compared to 41.44% of patients treated with lactulose; the average frequency of stools in the PEG-treated group increased from 2 to 7, with respect to a 2 to 6 increase in the lactulose-treated group, and stool consistency during the second week was better in the PEG-treated group.

In 2014, Treepongkaruna et al. (35) compared PEG 4000 *versus* lactulose in 88 children of 1-3 years of age affected by FC during a period of one month in a randomized, double-blind study (8 g per day of PEG 4000 and 3.3 g of lactulose). The average change in the stool frequency/day in both groups was of 0.51 stools/day in the PEG group, compared to 0.15 stools/day in the lactulose group. Furthermore, stools consistency and ease of stool passage were significantly better in the PEG-treated group.

Comparison of different PEG preparations

Two studies compare different types of PEG. In the first study, from 2012 (36), PEG 3350 at a dose of 0.7 g/kg/day (n = 49) was compared with PEG 3350 + E at a dose of 6.9 g/day (n = 42). Although there were no significant differences between both groups, the efficacy in constipation improvement and fecaloma resolution was slightly higher in the PEG 3350 + E group. In the second study (37), PEG 3350 (0.4-1 g/kg/day split in two doses up to a maximum of 20 g/day) (30 children) was compared to PEG 3350 + E (0.4-1 g/kg/day split in two doses up to a maximum of 27.6 g/day) (32 children) during three months. Efficacy, safety and degree of clinical and biological tolerance were evaluated. No differences in efficacy were observed between both preparations and a slight hyponatremia was detected in the group treated with PEG without electrolytes.

PEG *versus* milk of magnesia

Loening-Baucke and Pashankar (38) evaluated PEG efficacy (0.7 g/kg/day) in 39 children *versus* milk of magnesia (2 ml/kg/day) in 40 children in a randomized, open study for health care providers, children and physicians. The doses could be adjusted upwards or downwards, provided that children passed one daily stool of normal consistency and had no incontinence. Clinical controls were established at 1, 3, 6, and 12 months of treatment. The main endpoint was to achieve \geq of three defecations per week, \leq of two incontinence episodes per month, and absence of abdominal pain. A significant improvement was achieved in both groups in all the parameters ana-

lyzed regarding the basal period, not finding any differences between them. Furthermore, 5% of patients refused PEG intake, *versus* 35% that refused milk of magnesia ($p < 0.001$). To conclude, albeit the efficacy and safety of both preparations was similar, children accepted PEG intake much better. Ratanamongkol et al. (39) analyzed a short-term, randomized study (four weeks) in 1-4 year-old children, 39 of them in the PEG 4000 group (0.5 g/kg/day) and 43 of them treated with milk of magnesia (0.5 ml/kg/day, 400 mg/5 ml). He observed that 91% of patients on PEG had an improvement in week 4, compared to 65% of patients taking milk of magnesia ($p < 0.003$), and that the degree of acceptance was significantly higher in the PEG group (89% *versus* 72%, $p = 0.04$).

PEG *versus* other laxatives

In a randomized study with children of 2-12 years of age (40), the efficacy of PEG 3350 (1-1.5 g/kg/day) ($n = 80$) was compared to paraffin oil (1-1.5 ml/kg/day) ($n = 78$) during four months. Patients treated with PEG presented a higher percentage of improvement ($95.3 \pm 3.7\%$) than paraffin oil ($87.2 \pm 3.7\%$), although differences were not significant. All adverse reactions (nausea, vomiting, meteorism, abdominal pain, and dehydration) were detected with higher frequency in the paraffin oil group ($p < 0.05$), observing a subsequent percentage of dropouts, significantly higher than in the PEG group.

Nimrauzi et al. (41) evaluated in a randomized study of parallel groups (children of 2-12 years of age) the efficacy of PEG (0.4 g/kg/day) ($n = 53$) *versus* *Descurainia sophia* L. (2-3 g/day, depending on being under or over four years of age) ($n = 56$), an herb used in the Iranian traditional medicine as a laxative. No differences were observed regarding frequency of stools or secondary effects at the end of the study between both products, whereas PEG was better accepted.

A study compares PEG + E (0.5 g/kg/day) with a mixture of acacia fiber, *psyllium*, and fructose (AFPF) (42) (16.8 g/day) in two groups of 50 children (2.7-6.5 years old) during two months. No significant differences were found in terms of efficacy and safety, albeit PEG 3350 + E was better tolerated.

Observational studies

In 2001, Pashankar and Bishop (45) evaluated in an observational two-month study that the effective average dose of PEG was 0.84 g/kg/day. In a classic study from 2003 (46), the same group proved the efficacy of PEG 3350, using a dose of 0.8 g/kg/day in 74 children (all of them older than two years) that suffered FC and encopresis. In spite of its limitations, this work is considered to be a baseline study for the utilization of PEG in pediatrics

(children over two years of age). In 2004, the same group published a retrospective study (49) with PEG 3350 in 75 children under two years of age. The analysis was carried out according to follow-up time; 71 children completed the study in a range of 1-4 months (average dose of 0.82 g/kg/day) and 47 completed the study in 6-37 months (average dose of 0.67 g/kg/day). The effectiveness of the treatment was 85% (short-term treatment) and 91% (long-term treatment). Adverse effects, including diarrhea, were mild and disappeared after decreasing the dose administered. This study emphasizes the efficacy and safety of PEG without electrolytes in children under two years of age after short- and long-term treatments. Similar results were obtained by Michail et al. (50).

A multi-center, prospective and randomized study (43) from 2006 analyzed the most effective dose of PEG 4000 that allowed a normal bowel movement habit in 96 children divided into four groups, according to age (6-12 months, 13 months-3 years, 4-7 years, and 8-15 years of age). The authors observed that a dose of 0.5 g/kg/day is effective in 90% of children between six months and 15 years of age. Accordingly, another multi-center, randomized, double-blind, placebo-controlled study, searching for doses (29), determined that the most effective PEG 3350 dose for long-treatment in children between 3.1-8.5 years is 0.4 g/kg/day.

The efficacy of two doses of PEG + E according to age (2-6 years old: 6.563 g x 3; 7-11 years old: 6.563 g x 4) was analyzed in an open, multi-center and prospective study (48) performed in 68 children. The efficacy regarding the increment in the number of stool passages and decrease of abdominal pain with respect to the basal period was demonstrated.

Safety at the renal and digestive level of PEG + E (measuring natriuria, urinary osmolarity, immediate principles in stool and hydrogen breath tests) was evaluated in a study from 2011 in a small group of patients ($n = 15$) with ages ranging from two to nine, to whom PEG + E was administered during four weeks at 0.44 g/kg/day (48).

Lastly, in 2015, a randomized, prospective, open study of PEG 4000 comparing two groups of 2-4 year old children treated with high (0.7 g/kg/day) and low (0.3 g/kg/day) doses during six weeks was published. It was concluded that both doses were efficacious and safe for FC treatment, without any differences between them.

Review and meta-analysis articles

In 2013, two extensive and well documented review articles were published. In the first article (51), aspects of PEG use in children, such as biochemistry, efficacy, safety, acceptance and even pharmaco-economic features were analyzed. The conclusions were that PEG is equally effective than other laxatives during long-term treatments, such as milk of magnesia or mineral oil, and is more effective

than lactulose. Likewise, its acceptance rate is better than that of other laxatives and presents a high safety, without significant adverse effects. However, in this review article it was acknowledged that further studies comparing the use of PEG with and without electrolytes are necessary. The other study is an extensive Cochrane review (53) in which 1,643 pediatric patients were included. The combined analyses suggest that PEG preparation can be superior to placebo, lactulose and milk of magnesia in child FC. However, it is indicated that the general quality of the studies to demonstrate the primary endpoint (number of bowel movements/week) was low or very low, due to the paucity and heterogeneity of the data and the high risk of bias in the pooled analysis studies.

In 2014, a meta-analysis was published (54) on 10 articles out of 231 identified articles. It was concluded that PEG is safe during childhood and more efficacious than other laxatives for fecal disimpaction. Adverse effects were minimal and well tolerated. Nevertheless, the authors specify that further randomized studies are needed in order to determine optimal doses, routes of administration and PEG type.

In 2015, Kuizenga-Wessel et al. (52) questioned and evaluated throughout the literature the criteria utilized in order to regard FC as such in children younger than four years old. Out of 1,115 articles analyzed, they found only five that fulfilled the inclusion criteria established and, out of these five articles, only two articles utilized the Rome criteria III. Two studies compared PEG 4000 with lactulose or milk of magnesia, one compared probiotics efficacy and other two articles, new formulas. The authors concluded that further clinical trials are needed that will present greater uniformity in study design and definitions for evaluating FC in small children.

Use of PEG in fecal disimpaction

We have found six publications referring to this topic, although they present very different features (Table IV).

In 2002, Youssef et al. (57) analyzed in a prospective, double-blinded, randomized study the efficacy of different doses of PEG (0.25, 0.5, 1, 1.5 g/kg/day) during three days to achieve disimpaction in children between 3.3 and 13.1 years of age. The authors concluded that high doses (1 and 1.5 g/kg/day) were significantly more efficacious ($p < 0.005$, 95% of success) than lower doses (55%). In 2006, Candy et al. (33) evaluated in a prospective, open study of PEG + E the efficacy of stepwise doses during seven days, according to age (2-4 years: 13.8-55.2 g/day; 5-11 years: 27.6-82.8 g/day), in order to achieve disimpaction in children between two and eleven years of age. The first day, the dose was always low, whereas in days 6 and 7, the doses achieved the maximum level. Then, 89% of the 28 2-4 year-old children and 94% of the 5-11 year-old children achieved disimpaction between days 3 and 7.

Two studies comparatively analyze the efficacy of PEG with enemas (55,56). The most detailed study, by Bekkali et al. (55), evaluates PEG doses of 1.5 g/kg/day ($n = 44$ children) versus enemas ($n = 46$ children). The efficacy after six days was similar (68% in PEG and 80% in enemas), but patients with PEG presented a higher number of episodes of anal incontinence. Interestingly enough, after analyzing the behavior towards treatment (fear of such treatment), the authors did not observe significant differences between both groups (95% enemas, 81% PEG).

In a retrospective, observational study (58), comparing the usefulness of PEG + E ($n = 23$) with PEG 3350 ($n = 28$) in fecal impaction, it was observed that the efficacy was similar with both preparations (87% PEG + E versus 86% PEG). Nevertheless, the PEG + E-treated group presented more mild/moderate secondary effects (nausea, vomiting, abdominal cramps and electrolyte alterations) (11/24 versus 1/28, $p < 0.01$). Furthermore, it was necessary to use a nasogastric tube for its administration in 78% (18/23) of patients, which did not happen in any subject on PEG 3350 ($p < 0.01$).

Recently, another retrospective, observational study performed in 44 outpatients (2-17 years old) (59) treated with a combination of PEG + E with sodium picosulfate during seven days has been published. The first day, only high doses of PEG + E 78-103 g/day were administered, distributed in 6-8 doses. The second day, 52-78 g/day of PEG + E plus 15-20 drops of picosulfate (7.5-10 mg) were administered, and on days 5-7, 13 g of PEG + E plus 5-10 drops of picosulfate (2.5-5 mg) were, in turn, administered. The first defecation took place during the first 12 hours and the maximum number of stools was observed on the second day. All patients achieved disimpaction without hospital admission.

CONCLUSION

The studies reviewed show a great variability in the design, methodology, analyzed factors and sample size. Thus, it is almost impossible to perform a comparative study of them. Therefore, we have to restrict ourselves to point out those conclusions that, regardless of the study type, seem to be drawn from them.

1. PEG is a first choice drug for short- and long-treatment of FC, both in adult and pediatric populations, as well as for prevention and resolution of fecal impaction.
2. PEG presents a similar efficacy to other laxatives, such as milk of magnesia, paraffin oil or sodium phosphate, and in the majority of the studies where it is compared to lactulose PEG performs better.
3. PEG is a safe drug with low incidence of secondary mild effects, which are well controlled with dose adjustment.

4. In the majority of studies, acceptance and tolerability from patients is higher than to the rest of drugs analyzed.
5. No significant differences seem to exist on the use of different PEG types (PEG without electrolytes, PEG + E and PEG 4000), although comparative studies between them are limited and further studies are needed.
6. Doses employed are very variable, without a standard measure. According to the results, recommended doses in adults are 6-12 g/day of PEG + E and 10-20 g/day of PEG. In children, recommended doses are around 0.5-0.7 g/kg/day.

CONFLICT OF INTEREST

This review has been promoted by the SEPD. Both this organization and the authors have acted with full scientific independence and declare no conflict of interest regarding the present work, albeit some authors (MM, ALH) and the SEPD itself have received in several occasions funding from industry related to PEG and constipation treatments.

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