CHAPTER II

REVIEW OF RELATED LITERATURES

There have been many studies investigating the efficacy of polyethylene glycol (PEG) in management of childhood constipation. These mainly increase stool frequency and reduce fecal incontinence episodes. Furthermore, some studies also reported adverse effects.

The studies about polyethylene glycol (PEG) in childhood constipation are summarized in Table 1.

Table 1: The studies about polyethylene glycol (PEG) in childhood constipation

Author, country	Study group	Study type	Outcome	Key results	comments
Attar et al (1999), USA (26)	115 children with chronic constipation received low dose PEG or lactulose for 4 weeks 91 patients complete the trial	Multicentre RCT	Stool frequency Adverse effects	PEG group had a higher number of stools and a lower median daily score for straining at stool than patients in the lactulose group. Clinical tolerance was similar in the two groups, but flatus was less frequently in the PEG group, no serious adverse events and no significant change in laboratory tests in either group.	
Pashankar et al (2001), USA (18)	24 children (18 months-12 years) with chronic constipation treated with PEG3350 for 8 weeks at an initial dose 1 g/kg/d. The dose was adjusted every 3 days to achieve 2 soft stools / day. 20 children completed the study		Efficacy Stool consistency Soiling events (9 children) Optimal dose Tolerance	Increased from 2.3 ± 0.4 /wk to 16.9 ± 1.6 /wk ($p < .0001$) Score (from 1 to 5) increased from 1.2 ± 0.1 to 3.3 ± 0.1 ($p < .0001$) Decreased from 10.0 ± 2.4/wk to 1.3 ± 0.7/wk ($p = 0.003$) Range 0.27–1.42 g/kg/day (mean 0.84 g/kg/day) No significant adverse effects besides dose related diarrhea. No subject discontinued treatment	Open labelled trial No control

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Youssef et al (2002), USA (27)	4 doses of PEG 3350: 0.25 g/kg/day, 0.5 g/kg/day, 1 g/kg/day, and 1.5 g/kg/day were given for 3 days in 41 children with constipation for >3 months and evidence of faecal impaction	Individual double blind RCT	Disimpaction Symptoms Adverse effects	Disimpaction achieved in 30 children (75%). 95% of higher dose patients (1–1.5 g/kg/day) achieved disimpaction vs 55% of low dose patients (0.25–0.5g/kg/day) Less straining and looser consistency was noticed with increasing doses, with no statistically significant difference noted between the dose groups in any of the stool characteristics Diarrhea and bloating was more common in higher dose group. No patient had clinically significant abnormal laboratory values	Demonstrated the use of PEG 3350 for disimpaction and dose response relation
Gremse et al (2002), USA (14)	37 patients (2 -16 years) with constipation received either PEG 3350 or lactulose for 2 wks followed by the other agent for 2 wks	Unblinded, RCT , crossover design	Stool frequency Stool consistency Colonic transit time Palatability and efficacy (as reported by child and parent)	Increased from 1.7±0.8/wk to14.8±1.4/wk for PEG 3350 and 13.5±1.5/wk for lactulose Similar for both laxatives Total transit time was 47.6±2.7 h (mean ±SE) for PEG 3350 and 55.3+2.4 h for lactulose (p = 0.038) PEG 3350 was effective in 31/37 patients (84%; 95%CI 68% - 94%) and lactulose was effective in 17/37 (46%; 95%CI 30% - 63%) (p =0.002). PEG 3350 was preferred by 27/37 respondents (73%) compared to lactulose	No wash out period during crossover
Loening-Baucke (2002), USA (13)	28 children (4.1-17.5 years) with constipation treated with PEG (0.5–1 g/kg/day) were compared with 21 children treated with milk of magnesia (1–2.5 ml/kg/day)	Individual case-control study	Efficacy Side effects Compliance	On 3 monthly F/U for a year, BM freq. increased and soiling freq. decreased significantly in both groups. Those on PEG were soiling > MOM (p,0.01) and fewer had improved (p,0.01) at the 1 month F/U Difference disappeared at subsequent F/U More diarrhea seen in PEG group but no dehydration None refused PEG, 3% refused MOM	Not randomized. Demonstrated a high level of compliance to PEG

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Erickson et al (2003), USA (22)	46 children with constipation and dysfunctional voiding were given PEG 3350 to evaluate efficacy, compliance and side-effects	Case series	Stool frequency Dysfunctional Voiding Voided volume Post-void residual volume Side effects	Increased from 0.42 ± 0.2/day to 1.25 ± 0.42/day (p = 0.0001) 18 (39%) children became dry, 26 (56.5%) had decreased wetting and 2 showed no improvement Increased from 146 ml to 210 ml (p,0.0001) Post-void residual volume decreased from 92 ml to 48 ml (p,0.0001) 9/46 had diarrhea and 1 stopped treatment	Addressed efficacy in those with constipation and resulting disorders in micturition
Pashankar et al (2003), USA (23)	74 children (2-12.8 years) with chronic constipation (31 also had encopresis) were given PEG for 3–30 mth (mean 8.4 mth) to assess long-term efficacy	Case series	Efficacy in constipation Efficacy in constipation and encopresis	Average dose 0.78 g/kg/day. Stool frequency increased from 2.9 ± 0.3/wk to 9.9 ± 0.7/wk (p,0.001). Stool consistency score (from 1 to 5) increased from 1.4 ± 0.1 to 3.1 ± 0.1 (p,0.001). Also significant improvement in signs and symptoms of constipation. Good daily compliance in 93% Average dose 0.69 g/kg/day. Stool frequency increased from 3.0 ± 0.5/wk to 12.5 ± 1.5/wk (p,0.001). Stool consistency score (from 1 to 5) increased from 1.4 ± 0.1 to 3.1 ± 0.1 (p,0.001). Soiling events decreased from 11.0 ± 1.6/wk to 1.8 ± 0.5/wk (p,0.001). Also significant improvement in signs and symptoms of constipation. Good daily compliance in 90%	Efficacy and compliance over long term was studied
Pashankar et al (2003), USA (20)	83 children (2-16.9 years) with chronic constipation (39 also had encopresis) were given PEG for 3–30 mth (mean 8.7 mth) to assess safety profile of long-term therapy	Case series	Clinical adverse effects Biochemical Changes Patient Acceptance	Dose-related diarrhea in 10%, flatulence and bloating in 6% and abdominal pain in 2% Nine subjects had transient mild elevation in ALT and 3 in AST which self-corrected in 11 later. Thought to be unrelated to PEG Good daily compliance in 90%.Caretaker reported improvement in 91% and liked by 73% of children	Long-term compliance and safety for PEG were studied Transient liver enzyme elevation not seen in subsequent studies

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Voskuijl et al (2004), Netherland (15)	100 children (6 months–15 years) with constipation received PEG 3350 or lactulose for 8 weeks. They were then asked to continue in an open-label assessment for an additional 18 weeks. 91 completed the study	Multicentre double blind RCT	Clinical efficacy at 8 weeks Adverse effects	Significant increase in the mean defecation frequency/ wk. and a significant decrease in the mean encopresis frequency /wk. were found in both groups. 56% (95% CI 39-70) in PEG group were successfully treated compared to 29% (95% CI 16- 44) in lactulose group No serious adverse effects recorded. Those taking lactulose reported significantly more adverse events like flatulence	Used PEG 3350 (with electrolytes) in lower doses than used in other studies
Thomson (2004), UK (28)	51 children aged 2–11 years (mean 5 y) entered a double blind treatment phase and were randomized to receive either PEG 3350 or matching placebo for first 2 weeks. After a 2 week washout period cross-over to receive alternative treatment was done for another 2 weeks	Double blind RCT with crossover	Stool frequency Soiling events Symptoms Adverse effects	Mean 3.59/wk. in PEG group vs 1.58/wk. in placebo group (p,0.001) after first 2 weeks Mean 4.65/week in PEG group vs 4.7/wk. in control group (p = 0.685) Pain on defecation, straining on defecation and stool consistency significantly better on PEG. Abdominal pain similar in both groups Frequency of adverse effects similar to placebo	Used PEG with electrolytes. Adequate wash-out before crossover.
Loening-Baucke et al (2004), USA (29)	75 children from age 1–24months (mean age 17 mth) with constipation were started on PEG3350; average dose of 1 g/kg/day	Case series	Stool frequency Effective dose Adverse effects	Increased from 3.7± 3.2/wk to 12.4 ± 7.0/wk in the initial 4 months and then8.6 ± 3.1/wk over long term. Also significant improvement in signs and symptoms of constipation. Constipation relieved in 85% with short-term and 91% with long-term therapy Average effective dose was 1.1 g/kg/day over short term and 0.8 /kg/day over long term 5 had diarrhea which improved on decreasing the dose. PEG was not stopped in anyone	Demonstrated the efficacy, tolerability and safety of PEG use for constipation in < 2 year olds

Author, country	Study group	Study type	Outcome	Key results	Comments
Michail et al (2004), USA (25)	28 patients younger than 18 months (range 7 weeks to 17 months) with constipation were started on PEG and mean duration of therapy was 6.2 ± 5 months	Case series	Dose Efficacy Side effects	Mean initial dose was 0.88 kg/day Mean effective maintenance dose was 0.78 kg/day Mean stool frequency increased from 2.2 ± 0.1/wk to 8.4 ±2.5/wk (p,0.001). Mean stool consistency score increased from 1.7 ±0.5 to 3.8 ±0.8 (p,0.001). PEG relieved constipation in 97.6% of patients 1 (3.6%) infant had flatulence and 4(14.3%) had transient diarrhea which resolved after dose adjustment	Demonstrated the efficacy, tolerability and safety of PEG use for constipation in <18 month olds
Dupont et al (2005), France (16)	96 constipated children (6months-3 years) received PEG 4000 or lactulose for 3 months Total protein, albumin, iron, electrolytes, and vitamins B9, folates, A and D ($25OHD_3$) were measured in blood before and after treatment (day 84)	Multicentre double blind RCT.	Efficacy Biological tolerance Clinical tolerance	Higher improvements in PEG gr. regarding stool consistency, appetite, fecaloma and use of additional laxatives. No treatment-related changes in serum iron, electrolytes, total protein, albumin, vit. A or D and folates Diarrhea (5 episodes in 2 children in both treatment gr.) and anorexia (1 child in the lactulose group) Vomiting and flatulence, higher with lactulose. No serious adverse effects	This study confirmed the long-term tolerance of PEG 4000 in pediatrics
Dupont et al (2006), France (30)	96 children (6-months- 15 yrs) with a history of functional refractory constipation Allocated to 4 groups 6–12 mo. 13 mo.–3yrs 4–7 yrs 8–15 yrs They were received PEG 4000 for 3 months	Multicentre study	Dose range Efficiency	Median (interquartile) effective daily doses were by groups 3.75 (2.5–5.0) g 6.00(4.00–7.43) g 11.71 (7.0–6.00)g and 16.0(16-24) g respectively (around 0.50 g/day/kg) More than 90% of the children, regardless of age group, had normal bowel habits at the end of the study	First large - scale dose determination study Recommend daily dose of PEG 4000 in children from 6 mo -15 yrs is 0.50 g/kg/d, with a potential influence of the starting dose on the maintenance dose.

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Loening-Baucke et al (2006), USA (17)	79 children(≥ 4 years)with chronic constipation and fecal incontinence were randomized to receive PEG 3350 (n=39) or MOM(n=40) for 12 months Follow up visits at 1,3,6,and 12 months	Unblinded, RCT	Efficacy Safety Acceptance	*After 12 months,* 62% of PEG treated children. and 43% of milk of magnesia-treated children exhibited improvement 33% of PEG treated children. and 23% of milk of magnesia-treated children had recovered. 1 child was allergic to PEG No significant adverse effects with either PEG or MOM except for transient diarrhea which disappeared with dose reduction Several children complained about the taste of PEG and MOM 2 children (5%) continued to refuse PEG, 14 children (35%) refuse MOM during the 12 months of the study ($P < .001$)	High dropout rate in this study because of loss to follow up monitoring and refusal of medication
Michael et al (2007), UK (31)	51 children (24 months - 11 years) with chronic constipation from six UK pediatric OPD were randomized to receive either PEG +E or matching placebo for first 2 weeks. After a 2 week washout period cross-over to receive alternative treatment was done for another 2 weeks 47 children completed the double blind treatment.	Multicentre double blind placebo controlled crossover trial	Efficacy	The mean number of complete defaecations/ wk. was significantly higher for children on PEG+E than for children on placebo (3.12 (SD 2.05) *vs* 1.45 (SD 1.20), respectively; $p < 0.001$)	Used PEG with electrolytes. Adequate wash-out before crossover.

The comparison between these studies using polyethylene glycol (PEG) in the treatment of childhood constipation is difficult, as different inclusion criteria and successful outcomes were used.

Furthermore, there were still limited studies regarding commonly used laxatives such as milk of magnesia, senna, or stool softeners in treatment of childhood constipation.

Only two studies as the followings, were reported to compare between polyethylene glycol and milk of magnesia in the treatment of childhood constipation.

Loening-Baucke, et al conducted a randomized trial compared polyethyleneglycol (PEG) with milk of magnesia (MOM) in 49 children aged 4.1-17.5 years, with functional constipation and encopresis. Follow-up at 1, 3, 6, and 12 months revealed similar effectiveness in increasing bowel movement frequency, decreasing soiling episodes, and decreasing abdominal pain. It also revealed that PEG was more palatable and better tolerated than milk of magnesia (33% of children refused to take milk of magnesia, whereas none refused PEG). No side effects from PEG were reported. (13)

Another study, also by Loening-Baucke, et al., compare polyethylene glycol and milk of magnesia, evaluating the efficacy, safety, acceptance, and 1-year outcomes. Thirty-nine children (aged $\geq$ 4 years) were assigned randomly to receive polyethylene glycol and 40 to receive milk of magnesia. At each follow up visit, significant improvement was seen in both groups, with significant increases in the frequency of bowel movements, decreases in the frequency of incontinence episodes, and resolution of abdominal pain. Compliance rates were 95% for polyethylene glycol and 65% for milk of magnesia. After 12 months, 62% of polyethylene glycol treated children and 43% of milk of magnesia-treated children exhibited improvement,and 33% of polyethylene glycol-treated children and 23% of milk of magnesia-treated children had recovered. They concluded that, polyethylene glycol and milk of magnesia were equally effective in the long-term treatment of children with constipation and fecal incontinence (17).

Therefore, we conducted this study to compare the effectiveness, adverse effects and patient compliance of polyethylene glycol without electrolytes (PEG 4000; an orange-grapefruit flavoured, gentle acting osmotic laxative, neither absorbed nor

metabolized) with milk of magnesia (MOM; a cheap, and commonly used laxative) for the treatment of functional constipation in infants and children aged 1 to 4 years. We selected this age group as the treatment response to osmotic laxative(s), in constipated children younger than 4 years (infants and preschool children), will be better than in older age, who may have already been affected by colon inertia or chronic colon dilatation due to prolong stasis of feces. Furthermore, the prognosis will be better if treatment is started earlier (29, 32). To date, no randomized controlled trial comparing these two laxatives was reported in this age group.