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Bowel preparation for elective procedures in Children: A Systematic Review

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What is known about the subject

- Bowel preparation is vital to imaging and surgery in young people, but it is key to consider tolerability as well as efficacy in these patients
- Previous systematic reviews have only considered preparation for imaging and limit the age range, despite paediatricians often caring for children till older.

What this study adds

- Despite many trials, there is much clinical heterogeneity and risk of bias concerns with the evidence base, as well as poor safety and tolerability reporting.
- There is evidence that PEG regimens are effective. However, when compared, sodium picosulphate appeared better tolerated with no difference in efficacy.
- Future research needs to address these key methodology issues and also consider safety and tolerability, as well as efficacy.

Abstract

Objective: Adequate bowel preparation is crucial for both surgery and imaging in young people. Whilst systematic reviews have considered preparation for colonoscopy, they do not consider surgical interventions and to the age of 16, despite it being normal practice for paediatric gastroenterologists to care for transitioning children till older. We carried out a systematic review investigating the optimum bowel preparation agents for all indications in children and young people.

Design: A Cochrane format systematic review of randomised controlled trials (RCTs). Data extraction and assessment of methodological quality were performed independently by two reviewers. Methodological quality was assessed using the Cochrane risk of bias tool.

Patients: Young people requiring bowel preparation for any elective procedure, as defined by the primary studies.

Interventions: RCTs comparing bowel preparation with placebo or other interventions.

Main outcome measures: Adequacy of bowel preparation, tolerability and adverse events.

Results: The search yielded 2124 results and 15 randomised controlled studies (n = 1435), but heterogeneity limited synthesis. Meta-analysis of 2 studies comparing PEG with sodium phosphate showed no difference in the quality of bowel preparation (RR 1.27 [95% CI, 0.66-2.44]). Two studies comparing sodium picosulphate / magnesium citrate with PEG found no difference in bowel preparation, but significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS (RR 0.04 [95% CI, 0.01-0.18]). Meta-analysis of 3 studies (n = 241) found no difference between PEG and Sennasoids (RR 0.73 [95% CI, 0.31-1.71]).

Conclusions: The evidence base is clinically heterogeneous and methodologically at risk of bias. There is evidence that all regimens are equally effective. However, sodium picosulphate was better tolerated than PEG. Future research is needed with all agents and should seek to consider safety and tolerability, as well as efficacy.

Background:

Bowel imaging is a crucial modality in the diagnosis and monitoring of Inflammatory Bowel Disease (IBD), as well as surgery frequently being required in such patients. Multiple studies have suggested that bowel preparations must be individually tailored according to patient age, size and clinical status.[1] However, currently there is no internationally recognised gold standard regimen for paediatric bowel preparations.[2] Several regimens have been tried with the aim of identifying the safest, efficacious and tolerable combination, with varying success.[3]

Bowel preparation regimens can be based on lavage (bowel clean out) or cathartics (agents that accelerates defecation). Examples included; large volume of polyethylene glycol-electrolyte (PEG-ELS) lavage solution, sodium phosphate (an oral, low-volume, hyperosmotic agent), sodium pico-sulphate, bisacodyl and dietary measures, such as diet packs or clear liquid diets (often in combination with other agents).

Adequate bowel preparation prior to such procedures is crucial to ensure complete visualisation of the colonic mucosa (thus successful diagnostic and therapeutic colonoscopy, endoscopy and capsule endoscopy) and to minimize the risk of possible contamination during surgery. Administration of the agents is much more problematic in children compared to adults who manage to take the agents readily. In un-cooperative children, use of a naso-gastric tube to administer the agents has been reported to be an effective method to guarantee bowel wash out.[4] Reduced tolerance can result in poor outcomes due to inadequate preparation, increased rate of complications, extended procedural time and missed lesions.[3] Additionally, side effects have previously been noted, such as hyperphosphataemia in children who receive sodium phosphate.[4]

Whilst previous reviews have considered preparation for colonoscopy[3], they do not always consider surgical interventions and often limit their populations at the age of 16, despite it being normal practice for paediatric gastroenterologists over several years to adult services.[5]

We carried out an up to date systematic review using the Cochrane collaboration format to summarise the available evidence investigating the optimum bowel preparation agents for all indications in children and young people.

Methods:

The objectives of this review were to evaluate the efficacy and safety of different bowel preparation for young people for any indication. A full protocol for the study was completed by the authors prior to commencement of the study and is available on request.

Criteria for considering studies for this review

RCTs were included in this systematic review. Participants were aged 0 to 21 years. This age range was selected after a scoping search and discussion with local stakeholders confirmed that it can be normal practice in pediatric gastroenterology for these patient groups to have variable transition to adult services, but 21 years was agreed as an absolute cut off and reflected several studies that would otherwise be excluded. Studies compared bowel preparation with another bowel preparation or placebo, with all forms and dosing regimens considered. The primary outcome measure for the studies was the number of adequate bowel preparations, as defined by the included studies. Secondary outcomes included: tolerability, Duration of procedure, Missed lesions due to inadequate bowel preparation and occurrence of any adverse events.

Search methods for identification of studies

Electronic searches (search strategy not limited by language) were completed of MEDLINE, The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and CINAHL (Inception- 15 July 2016), Appendix 1. References of included trials were also searched. Manufacturers were contacted to identify further negative and unpublished research. Abstracts were considered for inclusion if full details to judge inclusion were offered or available from the authors after contact by the study team.

Data extraction and assessment of methodological quality of included studies were independently performed by 2 authors and disagreements solved with involvement of the third author.

Data collection and analysis

All identified abstracts and results from searches were reviewed by the authors. If the reference appeared relevant, a full copy of the study was obtained. After reading the full texts, each author independently assessed the eligibility of all trials identified based on the inclusion criteria above.

Disagreement among authors was discussed and agreement reached by consensus. If the data to judge inclusion were unclear, attempts were made to contact the authors.

A data extraction form was developed and piloted to extract information on relevant features and results of all primary and secondary outcomes of included studies. The two reviewers separately extracted and recorded data on the predefined checklist, with disagreement discussed and consensus reached.

The risk of bias of selected trials was assessed independently by the authors using the Cochrane risk of bias tool with disagreement once again resolved by reaching consensus. Study authors were contacted for further information when insufficient information was offered to judge risk of bias or data were missing for primary outcomes. Analysis was completed using Revman (Review Manager 5.2, V.5.2.9, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2012).

The primary outcome—efficacy of bowel preparation agents—was assessed using the mean difference (MD) with 95% CI. The secondary outcomes were assessed by calculating the risk ratio (RR) and 95% CI or the MD with 95% CI, as indicated. The authors of included studies were again contacted to supply any missing data. Heterogeneity among trial results was assessed by inspection of graphical presentations and by calculating the $\chi 2$ test of heterogeneity (a p value of 0.10 was regarded as statistically significant). We also used the I2 statistic to quantity the effect of heterogeneity.12 A random-effects model was used, with a sensitivity analysis with the fixed-effects model, to identify differences in results that would suggest heterogeneity.

Results:

The electronic database search identified 2124 studies that were screened for inclusion. Of these, 15 studies (n = 1435) were judged to be potentially relevant and subjected to full text review (Figure 1). Experts were contacted, but no extra reports were received and no further studies were identified from drug companies.

Description of studies

Nine reports were excluded for failing to meet the inclusion criteria. Five were not solely with patients under 21 years of age, three were not RCTs and one was an abstract with insufficient data to judge inclusion. The 15 RCTs included described various regimens and comparative agents (Table 1). Four studies compared various different regimens and combinations of PEG, Two compared polyethylene glycol (PEG) with oral sodium phosphate, two compared PEG with Normal Saline, three compared multiple combinations of PEG, sennasoids and sodium picosluphate, two diet kits with sodium phosphate, one study compared sodium picosulphate with phosphate enemas and one sodium picospulphate with PEG.

Risk of bias of included studies

Seven studies were rated as low risk for random sequence generation (selection bias) because these studies employed computer-generated randomisation. The remaining studies described themselves as randomised but, with no further details given or available from authors, were rated as unclear risk of bias.

Five studies were rated as low risk of bias for allocation concealment (selection bias). Nine remaining studies were rated as unclear risk of bias for allocation concealment as the methods were not clearly described in the manuscripts. One described the allocated researcher as performing colonoscopies and was rated as high risk.

Ten studies were blinded and were judged to be at low risk of bias for blinding of personnel (performance bias) for such an intervention. Four studies described themselves as blinded, but gave no further details so was rated as unclear risk of bias. One study was open-label and judged to be at high risk of bias for blinding.

Eight studies reported full and appropriate data and satisfactorily documented withdrawals and dropouts and were therefore judged to be at low risk of bias for incomplete outcome data (attrition bias) and nine were judged as low risk for selective reporting (reporting bias). Two studies did not record full data for all patients and were judged high risk of bias for attrition bias. Four studies did not offer outcome data regarding side effects and tolerability so were judged at high risk for reporting bias.

All studies were judged to be at low risk for other sources of bias. However, the small sample sized of many of these studies is concerning, suggesting they were pilot or similarly underpowered studies, raising a further concern regarding bias. Details are summarised in Table 1.

The 15 studies present significant clinical and methodological heterogeneity (Table 1) and this severely limits the scope for synthesis.

PEG vs Sennasoids

Meta-analysis of 3 studies (n = 241) [6,7,8] found no difference between polyethylene glycol (PEG) and Sennasoids in adequate bowel preparation (RR 0.73 [95% CI, 0.31-1.76], Figure 2). Data regarding tolerability and safety was not presented to allow synthesis.

Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS)

Within these two studies versus PEG-ELS[9,10], equivocal adequacy of bowel preparation was seen (RR 0.99 [95% CI, 0.89-1.11], Figure 3). PEG's acceptability was reportedly poorer than sodium picosulphate in both studies. Meta-analysis of two PEG-ELS studies using the random effects model found a significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS group than the sodium picosulphate group (RR 0.04 [95% CI, 0.01-0.18], Figure 4).

One patient in the PEG-ELS group and one in the sodium picosulphate group in the two studies were assessed as dehydrated and required intravenous (IV) fluids. For the PEG-ELS patient, a 10-year-old girl is reported who required intravenous fluid for 6 hours because of lethargy and dehydration (dryness of the oral mucosa and orthostatic hypotension) with serum electrolyte and glucose serum levels within the normal range. For the child in the sodium picosulphate group, a 12-year-old girl is reported that required intravenous fluids for 2 hours due to mild lethargy post procedure and was discharged well thereafter. Her vital signs were always within normal limits, but her serum osmolality

was 316 mosm/L; she had drunk only two glasses of apple juice during the entire duration of the bowel cleanout. No other serious adverse events were noted.

PEG vs Normal Saline

Meta-analysis of 2 studies (n = 125) comparing PEG with normal saline[11,12] found no difference in rate of adequate bowel preparation (RR 0.95 [95% CI, 0.87-1.04], Figure 5). Adverse events were not reported homogenously to allow analysis, but occurred in both groups, including abdominal pain and vomiting.

PEG vs Sodium phosphate

There were two studies concerning 63 participants.[4,13] Meta-analysis of 2 studies using the random-effect model found no difference in the adequacy of bowel preparation (RR 1.27 [95% CI, 0.66-2.45], Figure 6). One of the studies needed to insert a nasogastric tube in all patients receiving PEG, while in the remaining study, 53% of participants in the PEG group were unable to finish taking the solution whilst all the patients in the sodium phosphate group could complete the medication. As these were reported differently, no meta-analysis was performed. No serious adverse events were reported.

Other studies

Within the remaining studies[1, 14-18] no meta-analysis was possible. However, no individual study found any different in adequacy of bowel preparation or adverse events. Tolerability was not well reported across studies. Whilst secondary outcome analysis for further items were planned, data was not presented to allow this to take place.

Discussion:

Despite the common requirement for bowel preparation in young people, the results of this review have highlighted a very poor evidence base. A mixture of clinical heterogeneity related to multiple agent regimens and methodological heterogeneity limiting the ability for meta-analysis has significantly limited synthesis. In multiple small analyses, PEG-ELS, Senna, Normal Saline, Sodium phosphate and Sodium picosulphate / Magnesium citrate found no difference in adequacy of bowel preparation. This was similar across the remaining individual studies. As such, despite the significant weaknesses of the evidence base, it is worth noting that no difference in adequacy of bowel preparation has been reported in any included study. This was also the case with adverse events, although it must be noted these were reported in an extremely heterogeneous fashion, with individual minor, major and patient overall recording of events across studies.

Of note, there was a significant difference in favour of sodium pico-sulphate and magnesium citrate regarding tolerability, specifically the need for a nasogastric tube to complete the bowel preparation. This is a particularly interesting finding, as the primary studies highlighted that whilst tolerability of PEG was extremely poor, smaller volumes than planned appeared to have little impact on efficacy. This raises the question of the need for the nasogastric tube at all and so this may need further investigation in the future. Sodium pico-sulphate was also compared to bisacodyl and a phosphate enema in a single study with equivocal preparation, tolerability and safety reported.

PEG appeared to be the least tolerable agent across all studies - with a number of the patients requiring a nasogastric tube insertion, but this is from qualitative synthesis of individual studies, with this outcome reported in heterogeneous fashion so meta-analysis was not possible. Oral sodium phosphate was well tolerated in individual studies. Despite the satisfactory tolerability and safety profile of sodium phosphate, it should be noted that care must be taken when using this agent as it can cause significant electrolyte imbalances. As such, it should not be used in patients with deranged baseline electrolytes, suboptimal renal and hepatic function, as it poses a risk of acute kidney injury and phosphate nephropathy.[19]

With all the agents studied the occurrence of minor adverse events such as abdominal pain, bloating, faecal incontinence, nausea, vomiting, headaches and anal irritation was comparable. No serious adverse events were reported in any of the studies.

The evidence base for this review covers a large number of trials with a reasonable number of patients, but is severely limited due to clinical and methodological heterogeneity, as well as concerns with risk of bias. As such, the findings of this review should be interpreted with extreme caution as it is difficult to draw firm conclusions for any of the investigated agents. it must also be noted that for the primary outcome, successful bowel preparation was 'as defined' by primary studies, with several different scoring systems and criteria used. This also limits the appropriateness of meta-analysis in this context. This is also true of adverse events, which were reported in a sporadic and inconsistent manner that prevented comment on even simple complaints, such as nausea or vomiting.

Considering the small sample sizes, the high degree of heterogeneity and a wide variation in the regimen of each cleansing agent; the findings of this review cannot be reliably used to inform clinical practise, but most usefully should inform future research. In particular, as the question of adequacy of bowel preparation has been established as essentially equivocal amongst all study agents, a shift of focus for future studies is needed. Given the unique needs of a paediatric population, considering the issue of tolerability as a primary outcome is vital and looking at the lower volume options presented as enteral agents could offer potential practical advantages and need a high quality study to investigate them.

Conclusions:

The publishing evidence base investigating this issue is large, but is clinically heterogeneous and at risk of bias. All regimens appear equivocal for adequacy of bowel preparation. However, when compared with sodium pico-sulphate, sodium pico-sulphate is better tolerated. Future research should seek to consider safety and tolerability, as well as efficacy, given the key importance of these issues in a childhood population.

Figure legend

Fig 1: Patient flow diagram

Fig 2: Forest plot for PEG vs Senna, adequacy of bowel preparation

Fig 3: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), adequacy of bowel preparation

Fig 4: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), Tolerability of agent

Fig 5: Forest plot for PEG vs Normal Saline, adequacy of bowel preparation

Fig 6: Forest plot for PEG vs Sodium Phosphate, adequacy of bowel preparation

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Study	Year	No	Age	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Context	Randomisation	Allocation Concealment	Blinding	Incomplete Outcomes	Selective reporting	Other
Gremse et al	1996	34	3 years - 17 years	Sodium Phosphate	PEG	N/A	N/A	Elective Colonoscopy	Unclear - one of the authors randomised patients into groups	One of the authors assigned the patients to their groups, also perform colonoscopies	Appear Single Blind	Unclear, no ITT	High – Details of adverse events not given	None
Sinha et al	2007	126	Mean 3 years	Sodium Chloride	PEG	Ringer Lactate	N/A	Elective surgery	Unclear	Unclear	Appear Single Blind	Low risk	Unclear risk	None
Kierkus et al	2013	240	10 years – 18 years	BPEG	PEG	Sennosides	N/A	Elective colonoscopy	List Created by independent person using block	Yes	Single Blind	Low risk	Low Risk	None
El-Baba et al	2006	62	4 years – 18 years	Pre-packaged food kit, magnesium citrate	Sodium Phosphate	N/A	N/A	Elective colonoscopy	Computer random number generator	Unclear	Single Blind	Unclear	Low risk	None apparent
Turner et al	2009	83	4 years – 18 years	Pico-Salax	PEG-ELS	N/A	N/A	Elective colonoscopy	Computer-generated list in blocks of 6	Yes	Single Blind	Yes	Low risk	Funded by pharma but not involved in study
Trautwein et al	1996	140	5 years – 18 years	X-Pep and Sodium Phosphate	Magnesium citrate and Sodium phosphate	N/A	N/A	Elective colonoscopy	Unclear	Unclear	Unclear	Unclear	Unclear Risk	None apparent
Kumar et al	2013	30	1 month – 7 years	Normal Saline	PEG	N/A	N/A	Various surgical procedures	Unclear	Unclear	Unclear	Low risk	Low	None apparent
Pinfield et al	1999	63	18 months - 16 years	Picolax	Bisacodyl + Phosphate enema	N/A	N/A	Elective colonoscopy	Unclear	Sealed envelopes	Single blind	High Risk – only adverse events	High risk	None apparent
Di Nardo et al	2014	299	2 years – 18 years	PEG-ELS with simethicone	PEG with citrate and bisacodyl	PEG 3350 with ascorbic acid	Sodium picosulphate, Magesium oxide and citric acid	Elective colonoscopy	Computer generated list	Opaque sealed signed envelop	Unblind	Low Risk	Low risk	None apparent
Elitsur et al	2013	93	Mean 10yrs	4-day protocol PEG 3350	2-day protocol PEG 3350 + bisacodyl	N/A	N/A	Elective Colonoscopy	Computer generated random list	unclear	unclear	unclear	High risk	None apparent

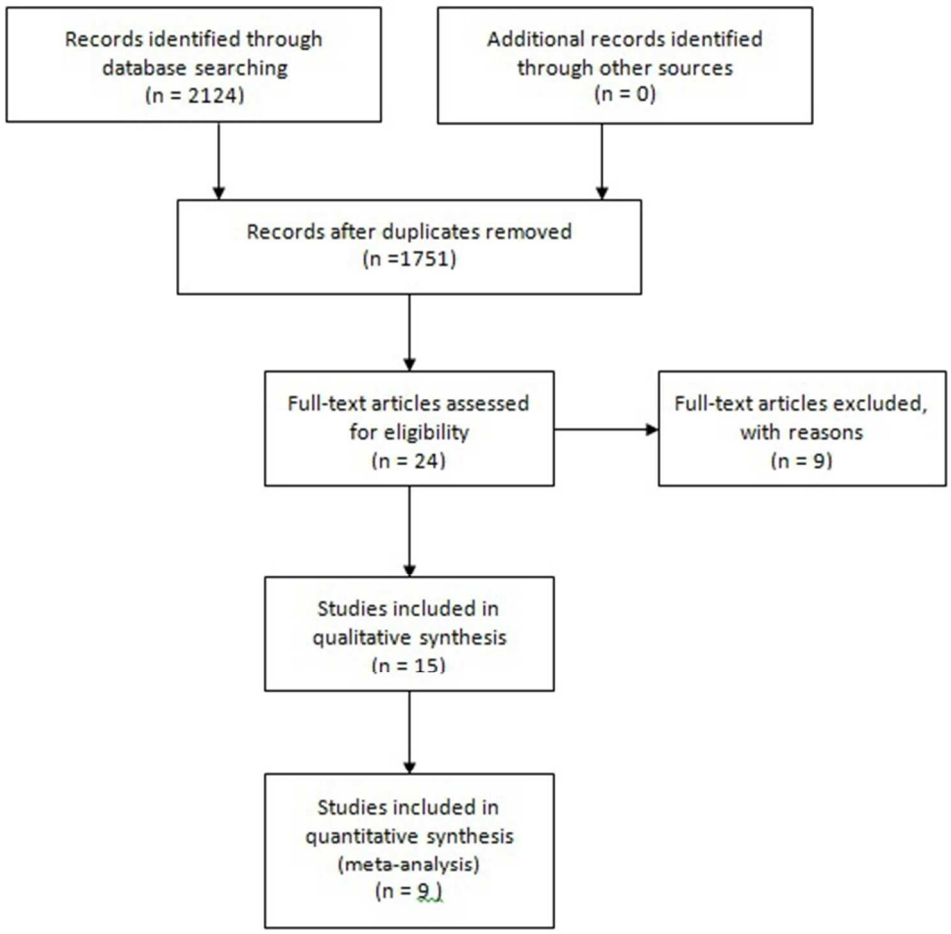
Sorser et al	2014	32	2 years – 21 years	3 day PEG 3350 Max 255g	3 day PEG 3350 max 85g/day	N/A	N/A	Elective Colonoscopy	No detail given	unclear	Single blind	Low risk	Low risk	None apparent
Najafi et al	2015	100	2 years – 14 years	1-day 2g/kg PEG + Bisacodyl Suppository	2-day 1.5g/kg PEG + Bisacodyl suppository	N/A	N/A	Elective Colonoscopy	Computer generated random numbers	A technician randomly assign	Single blind	Low Risk	Low Risk	None apparent
Dahsan et al	1999	70	3 years – 20 years	Magnesium citrate with X-prep	Dulcolax and Fleet Enema	Golytely (PEG)	N/A	Elective Colonoscopy	No detail given	unclear	Single blind	Low Risk	Low risk	None apparent
Terry et al	2013	33	6 years – 21 years	PEG-P	Senna	N/A	N/A	Elective Colonoscopy	Randomly chosen preparation packet	A nurse administer – no further details	Single Blind	Low risk	Low Risk	None apparent
Da Silva et al	1997	30	3 years – 14 years	Sodium Phosphate	PEG	N/A	N/A	Elective Colonoscopy	Computer generated randomly assigned	Unclear Risk	Unclear Risk	Unclear	High Risk	None apparent

BPEG: PEG combined with bisacodyl

PEG: Polyethylene glycol

PEG-ELS Polyethylene glycol –electrolyte lavage solution

PEG – P Polyethylene glycol without electrolytes



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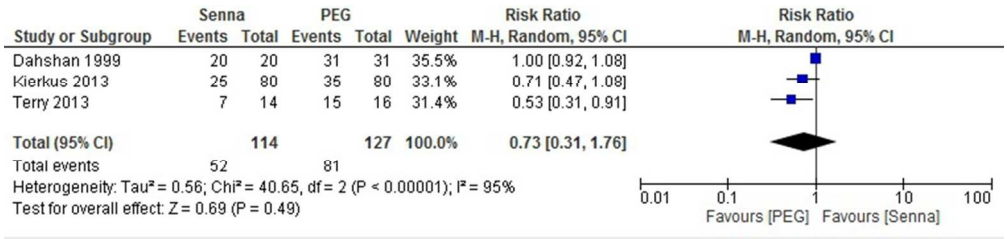

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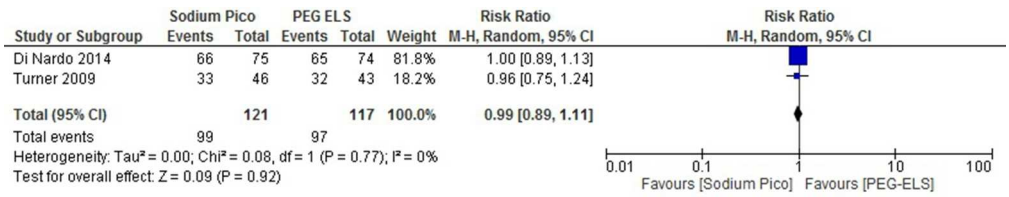

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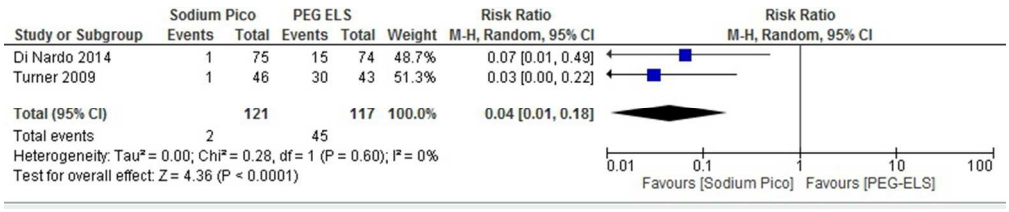

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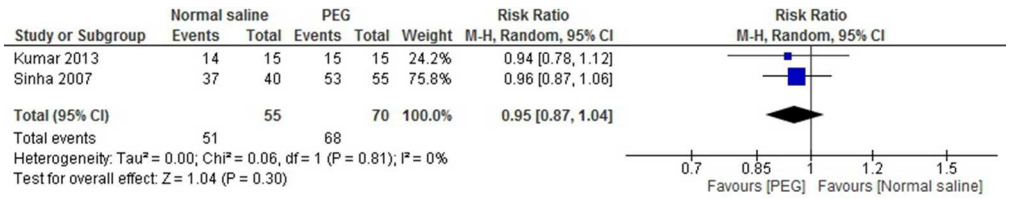

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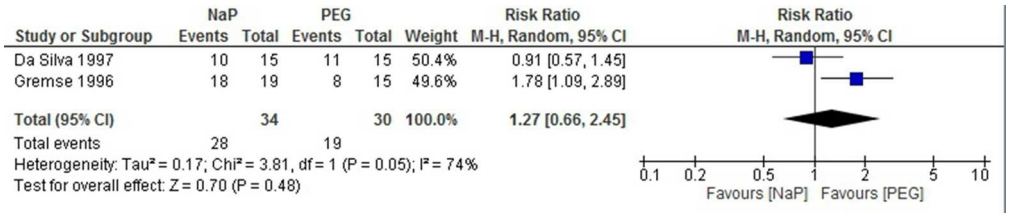

201x41mm (96 x 96 DPI)

Appendix 1 - Search strategy

vid EMBASE 1974 to 16 July 2016

1. exp colonoscopy/ OR colonoscop*.mp.
2. Surgery OR procedure
3. 1 or 2
4. infant/
5. child/
6. school child/
7. adolescent/
8. (infant* or child* or pediatric* or paediatric* or adolescent* or neonat* or toddler or young).mp.
9. 4 or 5 or 6 or 7 or 8
10. colon lavage/
11. intestine preparation/
12. exp laxative/
13. exp macrogol derivative/
14. exp phosphate/
15. exp citric acid/
16. exp magnesium oxide/
17. exp bisacodyl/
18. exp organometallic compound/
19. exp sulfate/
20. exp anthraquinone derivative/
21. exp enema/
22. (cathartic* or polyethylene glycol* or laxative* or phosphate* or citrate* or magnesium oxide* or bisacodyl or organometallic compound* or sulfat* or anthraquinone* or enema or bowel preparation or bowel cleansing or PEG-ELS or macrogol* or senna or docusate sodium or Sodium picosulphate or Cascara or casanthranol or Buckthorn or senokot or Aloe Vera or aloin Phenolphthalein or Dulcolax or stimulant or osmotic).mp.
23. (Miralax or Transipeg or Movicol or Forlax or Idrolax or GoLytely or PMF-100 or Golitely or Nulitely or Fortans or TriLyte or Colyte or lactulose or disaccharide or Apo-Lactulose or Chronulac or lactitol or sorbitol or Generlac or Cephulac or Cholac or Constilac or Enulose or Cilac or Heptalac or Actilax or Duphalac or Kristalose or Citroma or Osmoprep or Visicol).mp.
24. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 3 and 9 and 24
26. CROSSOVER PROCEDURE.sh.
27. DOUBLE-BLIND PROCEDURE.sh.
28. SINGLE-BLIND PROCEDURE.sh.
29. (crossover* or cross over*).ti,ab.
30. placebo*.ti,ab.
31. (doubl* adj blind*).ti,ab.
32. allocat*.ti,ab.
33. trial.ti.
34. RANDOMIZED CONTROLLED TRIAL.sh.
35. random*.ti,ab.
36. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)

38. 36 not 37
39. 25 and 38

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Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis

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Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis

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What is known about the subject

- Bowel preparation is vital to imaging and surgery in young people, but it is key to consider tolerability as well as efficacy in these patients
- Previous systematic reviews have only considered preparation for imaging and limit the age range, despite paediatricians often caring for children till older.

What this study adds

- Despite many trials, there is much clinical heterogeneity and risk of bias concerns with the evidence base, as well as poor safety and tolerability reporting.
- There is evidence that PEG regimens are effective. However, when compared, sodium picosulphate was better tolerated than PEG
- Future research needs to address these key methodology issues and also consider safety and tolerability, as well as efficacy.

Abstract

Objective: Adequate bowel preparation is crucial for both surgery and imaging in young people. Whilst systematic reviews have considered preparation for colonoscopy, they do not consider surgical interventions and to the age of 16, despite it being normal practice for paediatric gastroenterologists to care for transitioning children till older. We carried out a systematic review investigating the optimum bowel preparation agents for all indications in children and young people.

Design: A Cochrane format systematic review of randomised controlled trials (RCTs). Data extraction and assessment of methodological quality were performed independently by two reviewers. Methodological quality was assessed using the Cochrane risk of bias tool.

Patients: Young people requiring bowel preparation for any elective procedure, as defined by the primary studies.

Interventions: RCTs comparing bowel preparation with placebo or other interventions.

Main outcome measures: Adequacy of bowel preparation, tolerability and adverse events.

Results: The search yielded 2124 results and 15 randomised controlled studies (n = 1435), but heterogeneity limited synthesis. Meta-analysis of 2 studies comparing PEG with sodium phosphate showed no difference in the quality of bowel preparation (RR 1.27 [95% CI, 0.66-2.44]). Two studies comparing sodium picosulphate / magnesium citrate with PEG found no difference in bowel preparation, but significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS (RR 0.04 [95% CI, 0.01-0.18]). Meta-analysis of 3 studies (n = 241) found no difference between PEG and Sennasoids (RR 0.73 [95% CI, 0.31-1.71]).

Conclusions: The evidence base is clinically heterogeneous and methodologically at risk of bias. There is evidence that all regimens are equally effective. However, sodium picosulphate was better tolerated than PEG. Future research is needed with all agents and should seek to consider safety and tolerability, as well as efficacy.

Background:

Bowel imaging is a crucial modality in the diagnosis and monitoring of Inflammatory Bowel Disease (IBD), as well as surgery frequently being required in such patients. Multiple studies have suggested that bowel preparations must be individually tailored according to patient age, size and clinical status.[1] However, currently there is no internationally recognised gold standard regimen for paediatric bowel preparations.[2] Several regimens have been tried with the aim of identifying the safest, efficacious and tolerable combination, with varying success.[3]

Bowel preparation regimens can be based on lavage (bowel clean out) or cathartics (agents that accelerates defecation). Examples included; large volume of polyethylene glycol-electrolyte (PEG-ELS) lavage solution, sodium phosphate (an oral, low-volume, hyperosmotic agent), sodium pico-sulphate, bisacodyl and dietary measures, such as diet packs or clear liquid diets (often in combination with other agents).

Adequate bowel preparation prior to such procedures is crucial to ensure complete visualisation of the colonic mucosa (thus successful diagnostic and therapeutic colonoscopy, endoscopy and capsule endoscopy) and to minimize the risk of possible contamination during surgery. Administration of the agents is much more problematic in children compared to adults who manage to take the agents readily. In un-cooperative children, use of a naso-gastric tube to administer the agents has been reported to be an effective method to guarantee bowel wash out.[4] Reduced tolerance can result in poor outcomes due to inadequate preparation, increased rate of complications, extended procedural time and missed lesions.[3] Additionally, side effects have previously been noted, such as hyperphosphataemia in children who receive sodium phosphate.[4]

Whilst previous reviews have considered preparation for colonoscopy[3], they do not always consider surgical interventions and often limit their populations at the age of 16, despite it being normal practice for paediatric gastroenterologists to look after such patients for a number of years before transition to adult services.[5]

We carried out an up to date systematic review using the Cochrane collaboration format to summarise the available evidence investigating the optimum bowel preparation agents for all indications in children and young people.

Methods:

The objectives of this review were to evaluate the efficacy and safety of different bowel preparation for young people for any indication. A full protocol for the study was completed by the authors prior to commencement of the study and is available on request. This set out the procedure for the search, study screening, data extraction, risk of bias evaluation and analysis.

Criteria for considering studies for this review

RCTs were included in this systematic review. Participants were aged 0 to 21 years. This age range was selected after a scoping search and discussion with local stakeholders (tertiary centres) confirmed that it can be normal practice in pediatric gastroenterology for these patient groups to have variable transition to adult services, but 21 years was agreed as an absolute cut off and reflected several studies that would otherwise be excluded. Studies with adults included that did not allow analysis of this Paediatric age range were excluded. Studies compared bowel preparation with another bowel preparation or placebo, with all forms and dosing regimens considered. The purpose of bowel clearance was for colonoscopy or elective surgery. Studies were excluded if the purpose was to treat faecal impaction or encopresis. The primary outcome measure for the studies was the number of adequate bowel preparations, as defined by the included studies. Secondary outcomes included: tolerability (the propoprtion of children who could take the given therapy without the need for support through a nasogastric tube or incomplete dosing), Duration of procedure, Missed lesions due to inadequate bowel preparation and occurrence of any adverse events.

Search methods for identification of studies

Electronic searches (search strategy not limited by language) were completed of MEDLINE, The Cochrane Central Register of Controlled Trials, EMBASE and CINAHL (Inception- 15 July 2016), Appendix 1. References of included trials were also searched. Manufacturers were contacted to identify further negative and unpublished research. Abstracts were considered for inclusion if full details to judge inclusion were offered or available from the authors after contact by the study team.

Data extraction and assessment of methodological quality of included studies were independently performed by 2 authors and disagreements solved with involvement of the third author.

Data collection and analysis

All identified abstracts and results from searches were reviewed by the authors. If the reference appeared relevant, a full copy of the study was obtained. After reading the full texts, each author independently assessed the eligibility of all trials identified based on the inclusion criteria above. Disagreement among authors was discussed and agreement reached by consensus. If the data to judge inclusion were unclear, attempts were made to contact the authors.

A data extraction form was developed and piloted to extract information on relevant features and results of all primary and secondary outcomes of included studies. The two reviewers separately extracted and recorded data on the predefined checklist, with disagreement discussed and consensus reached.

The risk of bias of selected trials was assessed independently by the authors using the Cochrane risk of bias tool with disagreement once again resolved by reaching consensus. Study authors were contacted for further information when insufficient information was offered to judge risk of bias or data were missing for primary outcomes. Analysis was completed using Revman (Review Manager 5.2, V.5.2.9, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2012).

The primary outcome—efficacy of bowel preparation agents—was assessed using the Risk Ratio (RR) with 95% CI. The secondary outcomes were assessed by calculating the risk ratio (RR) and 95% CI or the MD with 95% CI, as indicated. The authors of included studies were again contacted to supply any missing data. Heterogeneity among trial results was assessed by inspection of graphical presentations and by calculating the $\chi 2$ test of heterogeneity (a p value of 0.10 was regarded as statistically significant). We also used the I2 statistic to quantity the effect of heterogeneity.[12] A result of less than 25% was defined as low, upto 75% moderate and above 75% high heterogeneity. A random-effects model was used, with a sensitivity analysis with the fixed-effects model, to identify differences in results that would suggest heterogeneity.

Results:

The electronic database search identified 2124 studies that were screened for inclusion. Of these, 15 studies (n = 1435) were judged to be potentially relevant and subjected to full text review (Figure 1). Only 12 papers needed consideration of a third author (less than 1%) to reach consensus, with one included and 11 excluded. Experts were contacted, but no extra reports were received and no further studies were identified from drug companies.

Description of studies

Excluded studies

Nine reports were excluded for failing to meet the inclusion criteria. Five were not solely with patients under 21 years of age, three were not RCTs and one was an abstract with insufficient data to judge inclusion.

Included studies

The 15 RCTs included described various regimens and comparative agents (Table 1). Four studies compared various different regimens and combinations of PEG, Two compared polyethylene glycol (PEG) with oral sodium phosphate, two compared PEG with Normal Saline, three compared multiple combinations of PEG, sennasoids and sodium picosluphate, two diet kits with sodium phosphate, one study compared sodium picosulphate with phosphate enemas and one sodium picospulphate with PEG.

Study	Year	No	Age	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Context	Randomisation	Allocation Concealment	Blinding	Incomplete Outcomes	Selective reporting	Other
Gremse et al	1996	34	3 years - 17 years	Sodium Phosphate	PEG	N/A	N/A	Elective Colonoscopy	Unclear - one of the authors randomised patients into groups	One of the authors assigned the patients to their groups, also perform colonoscopies	Appear Single Blind	Unclear, no ITT	High – Details of adverse events not given	None
Sinha et al	2007	126	Mean 3 years	Sodium Chloride	PEG	Ringer Lactate	N/A	Elective surgery	Unclear	Unclear	Appear Single Blind	Low risk	Unclear risk	None
Kierkus et al	2013	240	10 years – 18 years	BPEG	PEG	Sennosides	N/A	Elective colonoscopy	List Created by independent person using block	Yes	Single Blind	Low risk	Low Risk	None
El-Baba et al	2006	62	4 years – 18 years	Pre-packaged food kit, magnesium citrate	Sodium Phosphate	N/A	N/A	Elective colonoscopy	Computer random number generator	Unclear	Single Blind	Unclear	Low risk	None apparent
Turner et al	2009	83	4 years – 18 years	Pico-Salax	PEG-ELS	N/A	N/A	Elective colonoscopy	Computer-generated list in blocks of 6	Yes	Single Blind	Yes	Low risk	Funded by pharma but not involved in study
Trautwein et al	1996	140	5 years – 18 years	X-Pep and Sodium Phosphate	Magnesium citrate and Sodium phosphate	N/A	N/A	Elective colonoscopy	Unclear	Unclear	Unclear	Unclear	Unclear Risk	None apparent
Kumar et al	2013	30	1 month – 7 years	Normal Saline	PEG	N/A	N/A	Various surgical procedures	Unclear	Unclear	Unclear	Low risk	Low	None apparent
Pinfield et al	1999	63	18 months - 16 years	Picolax	Bisacodyl + Phosphate enema	N/A	N/A	Elective colonoscopy	Unclear	Sealed envelopes	Single blind	High Risk – only adverse events	High risk	None apparent
Di Nardo et al	2014	299	2 years – 18 years	PEG-ELS with simethicone	PEG with citrate and bisacodyl	PEG 3350 with ascorbic acid	Sodium picosulphate, Magesium oxide and citric acid	Elective colonoscopy	Computer generated list	Opaque sealed signed envelop	Unblind	Low Risk	Low risk	None apparent
Elitsur et al	2013	93	Mean 10yrs	4-day protocol PEG 3350	2-day protocol PEG 3350 + bisacodyl	N/A	N/A	Elective Colonoscopy	Computer generated random list	unclear	unclear	unclear	High risk	None apparent

Sorser et al	2014	32	2 years – 21 years	3 day PEG 3350 Max 255g	3 day PEG 3350 max 85g/day	N/A	N/A	Elective Colonoscopy	No detail given	unclear	Single blind	Low risk	Low risk	None apparent
Najafi et al	2015	100	2 years – 14 years	1-day 2g/kg PEG + Bisacodyl Suppository	2-day 1.5g/kg PEG + Bisacodyl suppository	N/A	N/A	Elective Colonoscopy	Computer generated random numbers	A technician randomly assign	Single blind	Low Risk	Low Risk	None apparent
Dahsan et al	1999	70	3 years – 20 years	Magnesium citrate with X-prep	Dulcolax and Fleet Enema	Golytely (PEG)	N/A	Elective Colonoscopy	No detail given	unclear	Single blind	Low Risk	Low risk	None apparent
Terry et al	2013	33	6 years – 21 years	PEG-P	Senna	N/A	N/A	Elective Colonoscopy	Randomly chosen preparation packet	A nurse administer – no further details	Single Blind	Low risk	Low Risk	None apparent
Da Silva et al	1997	30	3 years – 14 years	Sodium Phosphate	PEG	N/A	N/A	Elective Colonoscopy	Computer generated randomly assigned	Unclear Risk	Unclear Risk	Unclear	High Risk	None apparent

Table 1. Characteristics of included studies and risk of bias
(BPEG: PEG combined with bisacodyl; PEG: Polyethylene glycol; PEG-ELS Polyethylene glycol –electrolyte lavage solution; PEG – P Polyethylene glycol without electrolytes)

Risk of bias of included studies

Seven studies were rated as low risk for random sequence generation (selection bias) because these studies employed computer-generated randomisation. The remaining studies described themselves as randomised but, with no further details given or available from authors, were rated as unclear risk of bias.

Five studies were rated as low risk of bias for allocation concealment (selection bias). Nine remaining studies were rated as unclear risk of bias for allocation concealment as the methods were not clearly described in the manuscripts. One described the allocated researcher as performing colonoscopies and was rated as high risk.

Ten studies were blinded and were judged to be at low risk of bias for blinding of personnel (performance bias) for such an intervention. Four studies described themselves as blinded, but gave no further details so was rated as unclear risk of bias. One study was open-label and judged to be at high risk of bias for blinding.

Eight studies reported full and appropriate data and satisfactorily documented withdrawals and dropouts and were therefore judged to be at low risk of bias for incomplete outcome data (attrition bias) and nine were judged as low risk for selective reporting (reporting bias). Two studies did not record full data for all patients and were judged high risk of bias for attrition bias. Four studies did not offer outcome data regarding side effects and tolerability so were judged at high risk for reporting bias.

All studies were judged to be at low risk for other sources of bias. However, the small sample sized of many of these studies is concerning, suggesting they were pilot or similarly underpowered studies, raising a further concern regarding bias. Details are summarised in Table 1.

The 15 studies present significant clinical and methodological heterogeneity (Table 1) and this severely limits the scope for synthesis.

PEG vs Sennasoids

Meta-analysis of 3 studies (n = 241)[6,7,8] found no difference between polyethylene glycol (PEG) and Sennasoids in adequate bowel preparation (RR 0.73 [95% CI, 0.31-1.76], Figure 2). High statistical heterogeneity was noted. Data regarding tolerability and safety was not presented to allow synthesis.

Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS)

Within these two studies versus PEG-ELS[9,10], equivocal adequacy of bowel preparation was seen (RR 0.99 [95% CI, 0.89-1.11], Figure 3). PEG's acceptability was reportedly poorer than sodium picosulphate in both studies. Meta-analysis of two PEG-ELS studies using the random effects model found a significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS group (45 of 117) than the sodium picosulphate group (2 of 121), (RR 0.04 [95% CI, 0.01-0.18], Figure 4).

One patient in the PEG-ELS group and one in the sodium picosulphate group in the two studies were assessed as dehydrated and required intravenous (IV) fluids. For the PEG-ELS patient, a 10-year-old girl is reported who required intravenous fluid for 6 hours because of lethargy and dehydration (dryness of the oral mucosa and orthostatic hypotension) with serum electrolyte and glucose serum levels within the normal range. For the child in the sodium picosulphate group, a 12-year-old girl is reported that required intravenous fluids for 2 hours due to mild lethargy post procedure and was discharged well thereafter. Her vital signs were always within normal limits, but her serum osmolality was 316 mosm/L; she had drunk only two glasses of apple juice during the entire duration of the bowel cleanout. No other serious adverse events were noted.

PEG vs Normal Saline

Meta-analysis of 2 studies (n = 125) comparing PEG with normal saline[11,12] found no difference in rate of adequate bowel preparation (RR 0.95 [95% CI, 0.87-1.04], Figure 5). Adverse events were not reported homogenously to allow analysis, but occurred in both groups, including abdominal pain and vomiting.

PEG vs Sodium phosphate

There were two studies concerning 63 participants.[4,13] Meta-analysis of 2 studies using the random-effect model found no difference in the adequacy of bowel preparation (RR 1.27 [95% CI, 0.66-2.45], Figure 6). Again, high statistical heterogeneity was noted. One of the studies needed to insert a nasogastric tube in all patients receiving PEG, while in the remaining study, 53% of participants in the PEG group were unable to finish taking the solution whilst all the patients in the sodium phosphate

group could complete the medication. As these were reported differently, no meta-analysis was performed. No serious adverse events were reported.

Other studies

Within the remaining studies[1, 14-18] no meta-analysis was possible. However, no individual study found any different in adequacy of bowel preparation or adverse events. Tolerability was not well reported across studies. Whilst secondary outcome analysis for further items were planned, data was not presented to allow this to take place.

Discussion:

Despite the common requirement for bowel preparation in young people, the results of this review have highlighted a very poor evidence base. A mixture of clinical heterogeneity related to multiple agent regimens and methodological heterogeneity limiting the ability for meta-analysis has significantly limited synthesis. In multiple small analyses, PEG-ELS, Senna, Normal Saline, Sodium phosphate and Sodium picosulphate / Magnesium citrate found no difference in adequacy of bowel preparation. This was similar across the remaining individual studies. As such, despite the significant weaknesses of the evidence base, it is worth noting that no difference in adequacy of bowel preparation has been reported in any included study. This was also the case with adverse events, although it must be noted these were reported in an extremely heterogeneous fashion, with individual minor, major and patient overall recording of events across studies.

Of note, there was a significant difference in favour of sodium pico-sulphate and magnesium citrate regarding tolerability, specifically the need for a nasogastric tube to complete the bowel preparation. This is a particularly interesting finding, as the primary studies highlighted that whilst tolerability of PEG was extremely poor, smaller volumes than planned appeared to have little impact on efficacy. This raises the question of the need for the nasogastric tube at all and so this may need further investigation in the future. Sodium pico-sulphate was also compared to bisacodyl and a phosphate enema in a single study with equivocal preparation, tolerability and safety reported.

PEG appeared to be the least tolerable agent across all studies - with a number of the patients requiring a nasogastric tube insertion, but this is from qualitative synthesis of individual studies, with this outcome reported in heterogeneous fashion so meta-analysis was not possible. Additionally, as the age ranges of included participants varied greatly, it is hard to make firm conclusions on this finding as the need for nasogastric tubes is likely to be very age dependent. Oral sodium phosphate was well tolerated in individual studies. Despite the satisfactory tolerability and safety profile of sodium phosphate, it should be noted that care must be taken when using this agent as it can cause significant electrolyte imbalances. As such, it should not be used in patients with deranged baseline electrolytes, suboptimal renal and hepatic function, as it poses a risk of acute kidney injury and phosphate nephropathy.[19]

With all the agents studied the occurrence of minor adverse events such as abdominal pain, bloating, faecal incontinence, nausea, vomiting, headaches and anal irritation was comparable. No serious adverse events were reported in any of the studies. It should also be noted that in the context of elective surgery, there is growing recognition of the role for proceeding without bowel preparation. [20]

The evidence base for this review covers a large number of trials with a reasonable number of patients, but is severely limited due to clinical and methodological heterogeneity, as well as concerns with risk of bias. As such, the findings of this review should be interpreted with extreme caution as it is difficult to draw firm conclusions for any of the investigated agents. it must also be noted that for the primary outcome, successful bowel preparation was 'as defined' by primary studies, with several different scoring systems and criteria used. This also limits the appropriateness of meta-analysis in this context, although those wishing to complete future studies should note the Ottawa scoring system[21] was the only such scoring method reported in multiple studies. This is also true of adverse events, which were reported in a sporadic and inconsistent manner that prevented comment on even simple complaints, such as nausea or vomiting.

Considering the small sample sizes, the high degree of heterogeneity and a wide variation in the regimen of each cleansing agent; the findings of this review cannot be reliably used to inform clinical practise, but most usefully should inform future research. In particular, as the question of adequacy of bowel preparation has been established as essentially equivocal amongst all study agents, a shift of focus for future studies is needed. Given the unique needs of a paediatric population, considering the issue of tolerability as a primary outcome is vital and looking at the lower volume options presented as enteral agents could offer potential practical advantages and need a high quality study to investigate them.

Conclusions:

The publishing evidence base investigating this issue is large, but is clinically heterogeneous and at risk of bias. All regimens appear equivocal for adequacy of bowel preparation. However, when compared with sodium pico-sulphate, sodium pico-sulphate is better tolerated. Future research should seek to consider safety and tolerability, as well as efficacy, given the key importance of these issues in a childhood population.

Figure legend

Fig 1: Patient flow diagram

Fig 2: Forest plot for PEG vs Senna, adequacy of bowel preparation

Fig 3: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), adequacy of bowel preparation

Fig 4: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), Tolerability of agent

Fig 5: Forest plot for PEG vs Normal Saline, adequacy of bowel preparation

Fig 6: Forest plot for PEG vs Sodium Phosphate, adequacy of bowel preparation

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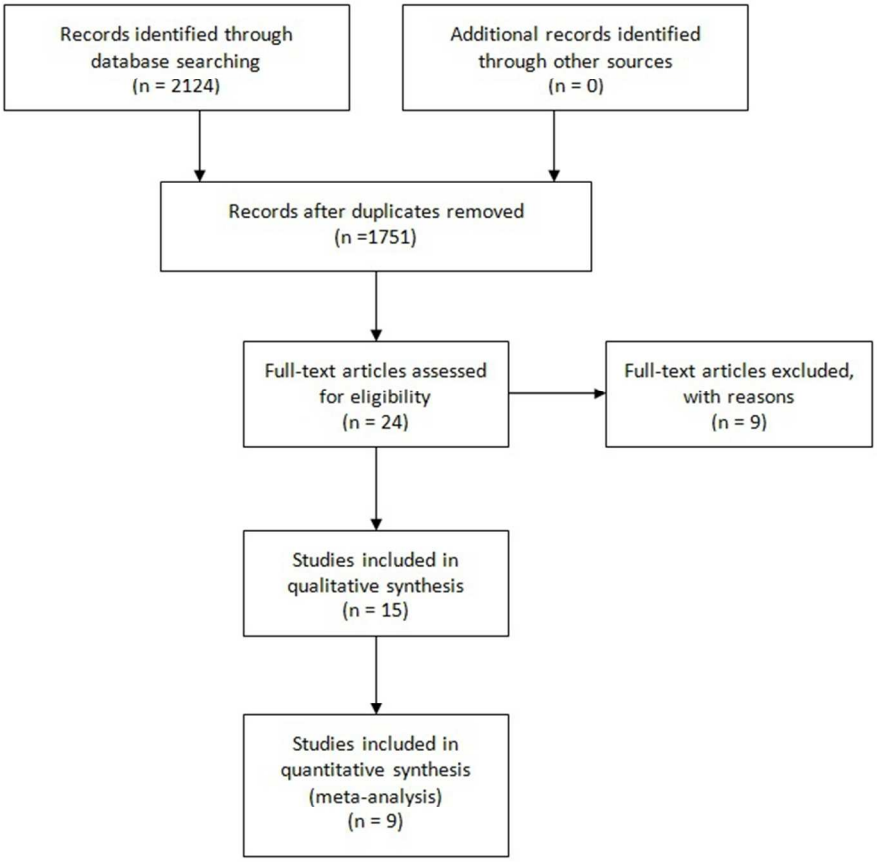

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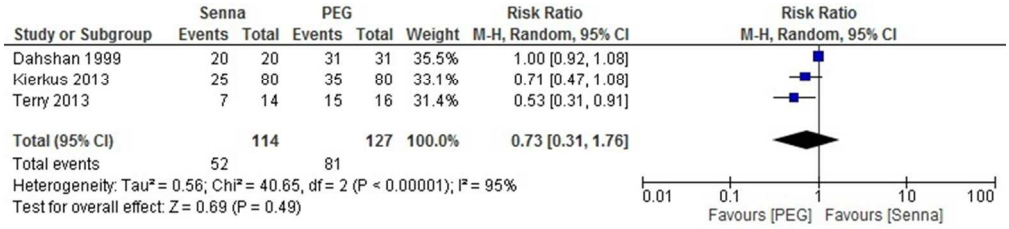

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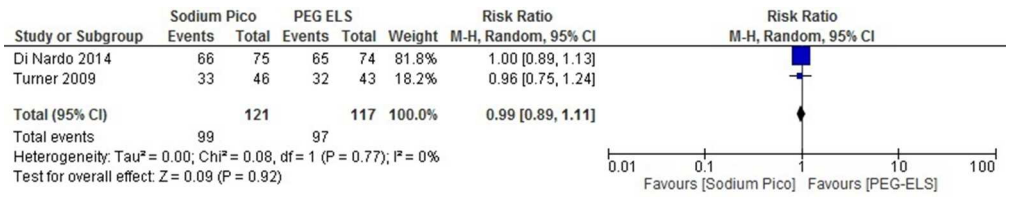

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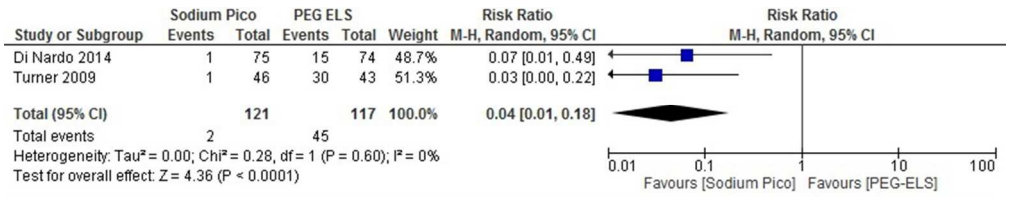

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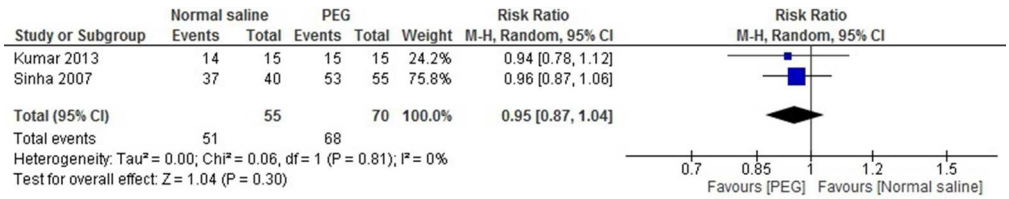

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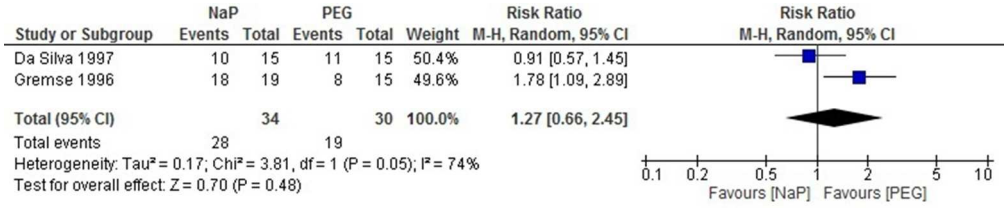

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Appendix 1 - Search strategy

vid EMBASE 1974 to 16 July 2016

1. exp colonoscopy/ OR colonoscop*.mp.
2. Surgery OR procedure
3. 1 or 2
4. infant/
5. child/
6. school child/
7. adolescent/
8. (infant* or child* or pediatric* or paediatric* or adolescent* or neonat* or toddler or young).mp.
9. 4 or 5 or 6 or 7 or 8
10. colon lavage/
11. intestine preparation/
12. exp laxative/
13. exp macrogol derivative/
14. exp phosphate/
15. exp citric acid/
16. exp magnesium oxide/
17. exp bisacodyl/
18. exp organometallic compound/
19. exp sulfate/
20. exp anthraquinone derivative/
21. exp enema/
22. (cathartic* or polyethylene glycol* or laxative* or phosphate* or citrate* or magnesium oxide* or bisacodyl or organometallic compound* or sulfat* or anthraquinone* or enema or bowel preparation or bowel cleansing or PEG-ELS or macrogol* or senna or docusate sodium or Sodium picosulphate or Cascara or casanthranol or Buckthorn or senokot or Aloe Vera or aloin Phenolphthalein or Dulcolax or stimulant or osmotic).mp.
23. (Miralax or Transipeg or Movicol or Forlax or Idrolax or GoLytely or PMF-100 or Golitely or Nulitely or Fortans or TriLyte or Colyte or lactulose or disaccharide or Apo-Lactulose or Chronulac or lactitol or sorbitol or Generlac or Cephulac or Cholac or Constilac or Enulose or Cilac or Heptalac or Actilax or Duphalac or Kristalose or Citroma or Osmoprep or Visicol).mp.
24. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 3 and 9 and 24
26. CROSSOVER PROCEDURE.sh.
27. DOUBLE-BLIND PROCEDURE.sh.
28. SINGLE-BLIND PROCEDURE.sh.
29. (crossover* or cross over*).ti,ab.
30. placebo*.ti,ab.
31. (doubl* adj blind*).ti,ab.
32. allocat*.ti,ab.
33. trial.ti.
34. RANDOMIZED CONTROLLED TRIAL.sh.
35. random*.ti,ab.
36. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)

38. 36 not 37
39. 25 and 38

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Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis

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Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis

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What is known about the subject

- Bowel preparation is vital to imaging and surgery in young people, but it is key to consider tolerability as well as efficacy in these patients
- Previous systematic reviews have only considered preparation for imaging and limit the age range, despite paediatricians often caring for children till older.

What this study adds

- Despite many trials, there is much clinical heterogeneity and risk of bias concerns with the evidence base, as well as poor safety and tolerability reporting.
- There is evidence that PEG regimens are effective. However, when compared, sodium picosulphate was better tolerated than PEG
- Future research needs to address these key methodology issues and also consider safety and tolerability, as well as efficacy.

Abstract

Objective: Adequate bowel preparation is crucial for both surgery and imaging in young people. Whilst systematic reviews have considered preparation for colonoscopy, they do not consider surgical interventions and to the age of 16, despite it being normal practice for paediatric gastroenterologists to care for transitioning children till older. We carried out a systematic review investigating the optimum bowel preparation agents for all indications in children and young people.

Design: A Cochrane format systematic review of randomised controlled trials (RCTs). Data extraction and assessment of methodological quality were performed independently by two reviewers. Methodological quality was assessed using the Cochrane risk of bias tool.

Patients: Young people requiring bowel preparation for any elective procedure, as defined by the primary studies.

Interventions: RCTs comparing bowel preparation with placebo or other interventions.

Main outcome measures: Adequacy of bowel preparation, tolerability and adverse events.

Results: The search yielded 2124 results and 15 randomised controlled studies (n = 1435), but heterogeneity limited synthesis. Meta-analysis of 2 studies comparing PEG with sodium phosphate showed no difference in the quality of bowel preparation (RR 1.27 [95% CI, 0.66-2.44]). Two studies comparing sodium picosulphate / magnesium citrate with PEG found no difference in bowel preparation, but significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS (RR 0.04 [95% CI, 0.01-0.18], 45 of 117 in PEG group vs 2 of 121 in Sodium picosulphate group). Meta-analysis of 3 studies (n = 241) found no difference between PEG and Sennasoids (RR 0.73 [95% CI, 0.31-1.71]).

Conclusions: The evidence base is clinically heterogeneous and methodologically at risk of bias. There is evidence that all regimens are equally effective. However, sodium picosulphate was better tolerated than PEG. Future research is needed with all agents and should seek to consider safety and tolerability, as well as efficacy.

Background:

Bowel imaging is a crucial modality in the diagnosis and monitoring of Inflammatory Bowel Disease (IBD), as well as surgery frequently being required in such patients. Multiple studies have suggested that bowel preparations must be individually tailored according to patient age, size and clinical status.[1] However, currently there is no internationally recognised gold standard regimen for paediatric bowel preparations.[2] Several regimens have been tried with the aim of identifying the safest, efficacious and tolerable combination, with varying success.[3]

Bowel preparation regimens can be based on lavage (bowel clean out) or cathartics (agents that accelerates defecation). Examples included; large volume of polyethylene glycol-electrolyte (PEG-ELS) lavage solution, sodium phosphate (an oral, low-volume, hyperosmotic agent), sodium pico-sulphate, bisacodyl and dietary measures, such as diet packs or clear liquid diets (often in combination with other agents).

Adequate bowel preparation prior to such procedures is crucial to ensure complete visualisation of the colonic mucosa (thus successful diagnostic and therapeutic colonoscopy, endoscopy and capsule endoscopy) and to minimize the risk of possible contamination during surgery. Administration of the agents is much more problematic in children compared to adults who manage to take the agents readily. In un-cooperative children, use of a naso-gastric tube to administer the agents has been reported to be an effective method to guarantee bowel wash out.[4] Reduced tolerance can result in poor outcomes due to inadequate preparation, increased rate of complications, extended procedural time and missed lesions.[3] Additionally, side effects have previously been noted, such as hyperphosphataemia in children who receive sodium phosphate.[4]

Whilst previous reviews have considered preparation for colonoscopy[3], they do not always consider surgical interventions and often limit their populations at the age of 16, despite it being normal practice for paediatric gastroenterologists to look after such patients for a number of years before transition to adult services.[5]

We carried out an up to date systematic review using the Cochrane collaboration format to summarise the available evidence investigating the optimum bowel preparation agents for all indications in children and young people.

Methods:

The objectives of this review were to evaluate the efficacy and safety of different bowel preparation for young people for any indication. A full protocol for the study was completed by the authors prior to commencement of the study and is available on request. This set out the procedure for the search, study screening, data extraction, risk of bias evaluation and analysis.

Criteria for considering studies for this review

RCTs were included in this systematic review. Participants were aged 0 to 21 years. This age range was selected after a scoping search and discussion with local stakeholders (tertiary centres) confirmed that it can be normal practice in pediatric gastroenterology for these patient groups to have variable transition to adult services, but 21 years was agreed as an absolute cut off and reflected several studies that would otherwise be excluded. Studies with adults included that did not allow analysis of this Paediatric age range were excluded. Studies compared bowel preparation with another bowel preparation or placebo, with all forms and dosing regimens considered. The purpose of bowel clearance was for colonoscopy or elective surgery. Studies were excluded if the purpose was to treat faecal impaction or encopresis. The primary outcome measure for the studies was the number of adequate bowel preparations, as defined by the included studies. Secondary outcomes included: tolerability (the propoprtion of children who could take the given therapy without the need for support through a nasogastric tube or incomplete dosing), Duration of procedure, Missed lesions due to inadequate bowel preparation and occurrence of any adverse events.

Search methods for identification of studies

Electronic searches (search strategy not limited by language) were completed of MEDLINE, The Cochrane Central Register of Controlled Trials, EMBASE and CINAHL (Inception- 15 July 2016), Appendix 1. References of included trials were also searched. Manufacturers were contacted to identify further negative and unpublished research. Abstracts were considered for inclusion if full details to judge inclusion were offered or available from the authors after contact by the study team.

Data extraction and assessment of methodological quality of included studies were independently performed by 2 authors and disagreements solved with involvement of the third author.

Data collection and analysis

All identified abstracts and results from searches were reviewed by the authors. If the reference appeared relevant, a full copy of the study was obtained. After reading the full texts, each author independently assessed the eligibility of all trials identified based on the inclusion criteria above. Disagreement among authors was discussed and agreement reached by consensus. If the data to judge inclusion were unclear, attempts were made to contact the authors.

A data extraction form was developed and piloted to extract information on relevant features and results of all primary and secondary outcomes of included studies. The two reviewers separately extracted and recorded data on the predefined checklist, with disagreement discussed and consensus reached.

The risk of bias of selected trials was assessed independently by the authors using the Cochrane risk of bias tool with disagreement once again resolved by reaching consensus. Study authors were contacted for further information when insufficient information was offered to judge risk of bias or data were missing for primary outcomes. Analysis was completed using Revman (Review Manager 5.2, V.5.2.9, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2012).

The primary outcome—efficacy of bowel preparation agents—was assessed using the Risk Ratio (RR) with 95% CI. The secondary outcomes were assessed by calculating the risk ratio (RR) and 95% CI or the MD with 95% CI, as indicated. The authors of included studies were again contacted to supply any missing data. Heterogeneity among trial results was assessed by inspection of graphical presentations and by calculating the $\chi 2$ test of heterogeneity (a p value of 0.10 was regarded as statistically significant). We also used the I2 statistic to quantity the effect of heterogeneity.[12] A result of less than 25% was defined as low, upto 75% moderate and above 75% high heterogeneity. A random-effects model was used, with a sensitivity analysis with the fixed-effects model, to identify differences in results that would suggest heterogeneity.

Results:

The electronic database search identified 2124 studies that were screened for inclusion. Of these, 15 studies (n = 1435) were judged to be potentially relevant and subjected to full text review (Figure 1). Only 12 papers needed consideration of a third author (less than 1%) to reach consensus, with one included and 11 excluded. Experts were contacted, but no extra reports were received and no further studies were identified from drug companies.

Description of studies

Excluded studies

Nine reports were excluded for failing to meet the inclusion criteria. Five were not solely with patients under 21 years of age, three were not RCTs and one was an abstract with insufficient data to judge inclusion.

Included studies

The 15 RCTs included described various regimens and comparative agents, with nine included in quantitative analysis (Table 1) and the remaining six in qualitative analysis (Table 2). Four studies compared various different regimens and combinations of PEG, Two compared polyethylene glycol (PEG) with oral sodium phosphate, two compared PEG with Normal Saline, three compared multiple combinations of PEG, sennasoids and sodium picosluphate, two diet kits with sodium phosphate, one study compared sodium picosulphate with phosphate enemas and one sodium picospulphate with PEG.

Study	Year	No	Age	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Context	Randomisation	Allocation Concealment	Blinding	Incomplete Outcomes	Selective reporting	Other
Gremse et al	1996	34	3 years - 17 years	Sodium Phosphate	PEG	N/A	N/A	Elective Colonoscopy	Unclear - one of the authors randomised patients into groups	One of the authors assigned the patients to their groups, also perform colonoscopies	Appear Single Blind	Unclear, no ITT	High – Details of adverse events not given	None
Sinha et al	2007	126	Mean 3 years	Sodium Chloride	PEG	Ringer Lactate	N/A	Elective surgery	Unclear	Unclear	Appear Single Blind	Low risk	Unclear risk	None
Kierkus et al	2013	240	10 years – 18 years	BPEG	PEG	Sennosides	N/A	Elective colonoscopy	List Created by independent person using block	Yes	Single Blind	Low risk	Low Risk	None
Kumar et al	2013	30	1 month – 7 years	Normal Saline	PEG	N/A	N/A	Various surgical procedures	Unclear	Unclear	Unclear	Low risk	Low	None apparent
Turner et al	2009	83	4 years – 18 years	Pico-Salax	PEG-ELS	N/A	N/A	Elective colonoscopy	Computer-generated list in blocks of 6	Yes	Single Blind	Yes	Low risk	Funded by pharma but not involved in study
Di Nardo et al	2014	299	2 years – 18 years	PEG-ELS with simethicone	PEG with citrate and bisacodyl	PEG 3350 with ascorbic acid	Sodium picosulphate, Magesium oxide and citric acid	Elective colonoscopy	Computer generated list	Opaque sealed signed envelop	Unblind	Low Risk	Low risk	None apparent
Dahsan et al	1999	70	3 years – 20 years	Magnesium citrate with X-prep	Dulcolax and Fleet Enema	Golytely (PEG)	N/A	Elective Colonoscopy	No detail given	unclear	Single blind	Low Risk	Low risk	None apparent
Terry et al	2013	33	6 years – 21 years	PEG-P	Senna	N/A	N/A	Elective Colonoscopy	Randomly chosen preparation packet	A nurse administer – no further details	Single Blind	Low risk	Low Risk	None apparent
Da Silva et al	1997	30	3 years – 14 years	Sodium Phosphate	PEG	N/A	N/A	Elective Colonoscopy	Computer generated randomly assigned	Unclear Risk	Unclear Risk	Unclear	High Risk	None apparent

Table 1. Characteristics of studies included in quantitative analysis and risk of bias ratings
(BPEG: PEG combined with bisacodyl; PEG: Polyethylene glycol; PEG-ELS Polyethylene glycol –electrolyte lavage solution; PEG – P Polyethylene glycol without electrolytes)

Study	Year	No	Age	Regimen 1	Regimen 2	Main outcomes reported in the study	Context	Randomisation	Allocation Concealment	Blinding	Incomplete Outcomes	Selective reporting	Other
Trautwein et al	1996	140	5 years – 18 years	X-Pep and Sodium Phosphate	Magnesium citrate and Sodium phosphate	No significant different reported between bowel preparations for the two regimens. No safety concerns were raised, but numbers of adverse events were not described	Elective colonoscopy	Unclear	Unclear	Unclear	Unclear	Unclear Risk	None apparent
Pinfield et al	1999	63	18 months - 16 years	Picolax	Bisacodyl + Phosphate enema	Bowel preparation was good or excellent in all of the patients in the Picolax group (n=32) compared with 22 patients in the bisacodyl phosphate enema group(n=31). Abdominal discomfort was reported by 7 in the picolax group vs 18 in the bisacodyl group and vomiting by 3 in the picolax group and 0 in the bisacodyl group	Elective colonoscopy	Unclear	Sealed envelopes	Single blind	High Risk – only adverse events	High risk	None apparent
Elitsur et al	2013	93	Mean 10yrs	4-day protocol PEG 3350	2-day protocol PEG 3350 + bisacodyl	Adequate colon preparation was reached in 57.5% of regimen 1 and 73.6% of regimen 2. Side effects were reported as minimal and comparable in both groups (abdominal pain: 26%-32%, vomiting: 2%). None of the children discontinued his protocol due to side effects	Elective Colonoscopy	Computer generated random list	unclear	unclear	unclear	High risk	None apparent
Sorser et al	2014	32	2 years – 21 years	1 day PEG 3350 Max 255g	3 day PEG 3350 max 85g/day	A grading of excellent or good was given to 18/18 in regimen 1 and 13/14 in regimen 2. Regimen 1 5 reports of minor side effects were made vs 10 reports in regimen 2.	Elective Colonoscopy	No detail given	unclear	Single blind	Low risk	Low risk	None apparent
Najafi et al	2015	100	2 years – 14 years	1-day 2g/kg PEG + Bisacodyl Suppository	2-day 1.5g/kg PEG + Bisacodyl suppository	A grading of excellent or good was given to 35/50 in regimen 1 and 36/50 in regimen 2. Regimen 1 8/18 complained of nausea, 1/18 vomiting and 4/18 abdominal pain vs 3/14 nausea, 2/14 vomiting and 3/14 of abdominal pain in regimen 2.	Elective Colonoscopy	Computer generated random numbers	A technician randomly assign	Single blind	Low Risk	Low Risk	None apparent
El-Baba et al	2006	62	4 years – 18 years	Pre-packaged food kit, magnesium citrate	Sodium Phosphate	Quality of colon cleansing rated as excellent in 50% of regimen 1 and 19% of regimen 2. 30/36 in group 1 reported minor side effects vs 26/26 in group 2.	Elective colonoscopy	Computer random number generator	Unclear	Single Blind	Unclear	Low risk	None apparent

Table 2. Characteristics of studies included in qualitative analysis and risk of bias ratings
(BPEG: PEG combined with bisacodyl; PEG: Polyethylene glycol; PEG-ELS Polyethylene glycol –electrolyte lavage solution; PEG – P Polyethylene glycol without electrolytes)

Risk of bias of included studies

Seven studies were rated as low risk for random sequence generation (selection bias) because these studies employed computer-generated randomisation. The remaining studies described themselves as randomised but, with no further details given or available from authors, were rated as unclear risk of bias.

Five studies were rated as low risk of bias for allocation concealment (selection bias). Nine remaining studies were rated as unclear risk of bias for allocation concealment as the methods were not clearly described in the manuscripts. One described the allocated researcher as performing colonoscopies and was rated as high risk.

Ten studies were blinded and were judged to be at low risk of bias for blinding of personnel (performance bias) for such an intervention. Four studies described themselves as blinded, but gave no further details so was rated as unclear risk of bias. One study was open-label and judged to be at high risk of bias for blinding.

Eight studies reported full and appropriate data and satisfactorily documented withdrawals and dropouts and were therefore judged to be at low risk of bias for incomplete outcome data (attrition bias) and nine were judged as low risk for selective reporting (reporting bias). Two studies did not record full data for all patients and were judged high risk of bias for attrition bias. Four studies did not offer outcome data regarding side effects and tolerability so were judged at high risk for reporting bias.

All studies were judged to be at low risk for other sources of bias. However, the small sample sized of many of these studies is concerning, suggesting they were pilot or similarly underpowered studies, raising a further concern regarding bias. Details are summarised in Table 1.

The 15 studies present significant clinical and methodological heterogeneity (Table 1) and this severely limits the scope for synthesis.

PEG vs Sennasoids

Meta-analysis of 3 studies (n = 241)[6,7,8] found no difference between polyethylene glycol (PEG) and Sennasoids in adequate bowel preparation (RR 0.73 [95% CI, 0.31-1.76], Figure 2). High statistical heterogeneity was noted. Data regarding tolerability and safety was not presented to allow synthesis.

Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS)

Within these two studies versus PEG-ELS[9,10], equivocal adequacy of bowel preparation was seen (RR 0.99 [95% CI, 0.89-1.11], Figure 3). PEG's acceptability was reportedly poorer than sodium picosulphate in both studies. Meta-analysis of two PEG-ELS studies using the random effects model found a significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS group (45 of 117) than the sodium picosulphate group (2 of 121), (RR 0.04 [95% CI, 0.01-0.18], Figure 4).

One patient in the PEG-ELS group and one in the sodium picosulphate group in the two studies were assessed as dehydrated and required intravenous (IV) fluids. For the PEG-ELS patient, a 10-year-old girl is reported who required intravenous fluid for 6 hours because of lethargy and dehydration (dryness of the oral mucosa and orthostatic hypotension) with serum electrolyte and glucose serum levels within the normal range. For the child in the sodium picosulphate group, a 12-year-old girl is reported that required intravenous fluids for 2 hours due to mild lethargy post procedure and was discharged well thereafter. Her vital signs were always within normal limits, but her serum osmolality was 316 mosm/L; she had drunk only two glasses of apple juice during the entire duration of the bowel cleanout. No other serious adverse events were noted.

PEG vs Normal Saline

Meta-analysis of 2 studies (n = 125) comparing PEG with normal saline[11,12] found no difference in rate of adequate bowel preparation (RR 0.95 [95% CI, 0.87-1.04], Figure 5). Adverse events were not reported homogenously to allow analysis, but occurred in both groups, including abdominal pain and vomiting.

PEG vs Sodium phosphate

There were two studies concerning 63 participants.[4,13] Meta-analysis of 2 studies using the random-effect model found no difference in the adequacy of bowel preparation (RR 1.27 [95% CI, 0.66-2.45], Figure 6). Again, high statistical heterogeneity was noted. One of the studies needed to insert a nasogastric tube in all patients receiving PEG, while in the remaining study, 53% of participants in the PEG group were unable to finish taking the solution whilst all the patients in the sodium phosphate

group could complete the medication. As these were reported differently, no meta-analysis was performed. No serious adverse events were reported.

Other studies

Within the remaining studies[1, 14-18] no meta-analysis was possible. However, no individual study found any different in adequacy of bowel preparation or adverse events. Tolerability was not well reported across studies. Whilst secondary outcome analysis for further items were planned, data was not presented to allow this to take place.

Discussion:

Despite the common requirement for bowel preparation in young people, the results of this review have highlighted a very poor evidence base. A mixture of clinical heterogeneity related to multiple agent regimens and methodological heterogeneity limiting the ability for meta-analysis has significantly limited synthesis. In multiple small analyses, PEG-ELS, Senna, Normal Saline, Sodium phosphate and Sodium picosulphate / Magnesium citrate found no difference in adequacy of bowel preparation. This was similar across the remaining individual studies. As such, despite the significant weaknesses of the evidence base, it is worth noting that no difference in adequacy of bowel preparation has been reported in any included study. This was also the case with adverse events, although it must be noted these were reported in an extremely heterogeneous fashion, with individual minor, major and patient overall recording of events across studies.

Of note, there was a significant difference in favour of sodium pico-sulphate and magnesium citrate regarding tolerability, specifically the need for a nasogastric tube to complete the bowel preparation. This is a particularly interesting finding, as the primary studies highlighted that whilst tolerability of PEG was extremely poor, smaller volumes than planned appeared to have little impact on efficacy. This raises the question of the need for the nasogastric tube at all and so this may need further investigation in the future. Sodium pico-sulphate was also compared to bisacodyl and a phosphate enema in a single study with equivocal preparation, tolerability and safety reported.

PEG appeared to be the least tolerable agent across all studies - with a number of the patients requiring a nasogastric tube insertion, but this is from qualitative synthesis of individual studies, with this outcome reported in heterogeneous fashion so meta-analysis was not possible. Additionally, as the age ranges of included participants varied greatly, it is hard to make firm conclusions on this finding as the need for nasogastric tubes is likely to be very age dependent. Oral sodium phosphate was well tolerated in individual studies. Despite the satisfactory tolerability and safety profile of sodium phosphate, it should be noted that care must be taken when using this agent as it can cause significant electrolyte imbalances. As such, it should not be used in patients with deranged baseline electrolytes, suboptimal renal and hepatic function, as it poses a risk of acute kidney injury and phosphate nephropathy.[19]

With all the agents studied the occurrence of minor adverse events such as abdominal pain, bloating, faecal incontinence, nausea, vomiting, headaches and anal irritation was comparable. No serious adverse events were reported in any of the studies. It should also be noted that in the context of elective surgery, there is growing recognition of the role for proceeding without bowel preparation. [20]

The evidence base for this review covers a large number of trials with a reasonable number of patients, but is severely limited due to clinical and methodological heterogeneity, as well as concerns with risk of bias. As such, the findings of this review should be interpreted with extreme caution as it is difficult to draw firm conclusions for any of the investigated agents. it must also be noted that for the primary outcome, successful bowel preparation was 'as defined' by primary studies, with several different scoring systems and criteria used. This also limits the appropriateness of meta-analysis in this context, although those wishing to complete future studies should note the Ottawa scoring system[21] was the only such scoring method reported in multiple studies. This is also true of adverse events, which were reported in a sporadic and inconsistent manner that prevented comment on even simple complaints, such as nausea or vomiting.

Considering the small sample sizes, the high degree of heterogeneity and a wide variation in the regimen of each cleansing agent; the findings of this review cannot be reliably used to inform clinical practise, but most usefully should inform future research. In particular, as the question of adequacy of bowel preparation has been established as essentially equivocal amongst all study agents, a shift of focus for future studies is needed. Given the unique needs of a paediatric population, considering the issue of tolerability as a primary outcome is vital and looking at the lower volume options presented as enteral agents could offer potential practical advantages and need a high quality study to investigate them.

Conclusions:

The publishing evidence base investigating this issue is large, but is clinically heterogeneous and at risk of bias. All regimens appear equivocal for adequacy of bowel preparation. However, when compared with sodium pico-sulphate, sodium pico-sulphate is better tolerated. Future research should seek to consider safety and tolerability, as well as efficacy, given the key importance of these issues in a childhood population.

Figure legend

Fig 1: Patient flow diagram

Fig 2: Forest plot for PEG vs Senna, adequacy of bowel preparation

Fig 3: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), adequacy of bowel preparation

Fig 4: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), Tolerability of agent

Fig 5: Forest plot for PEG vs Normal Saline, adequacy of bowel preparation

Fig 6: Forest plot for PEG vs Sodium Phosphate, adequacy of bowel preparation

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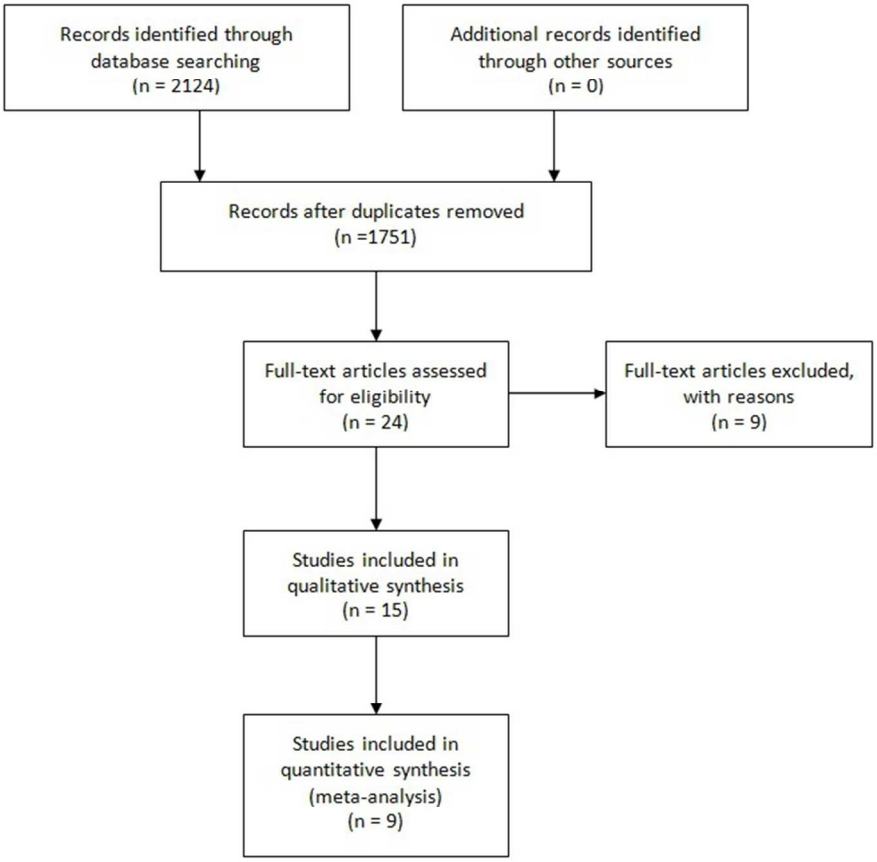
21. Rostom A, Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. Gastrointes Endosc 2004; 59: 482–486.



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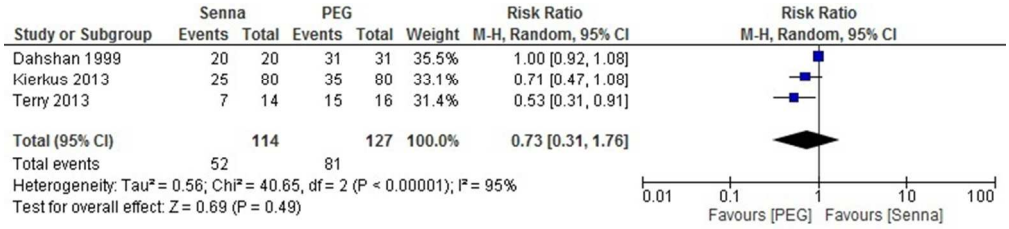

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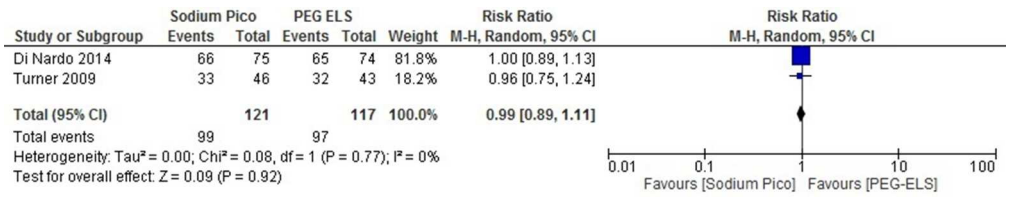

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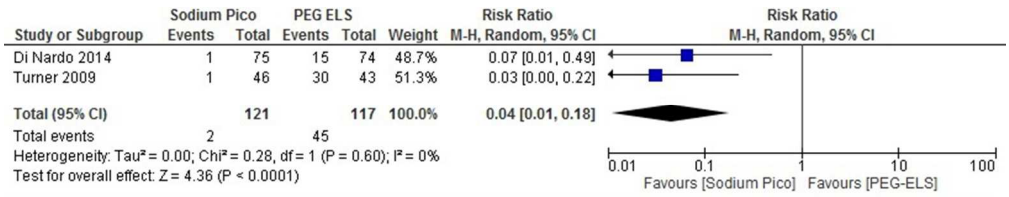

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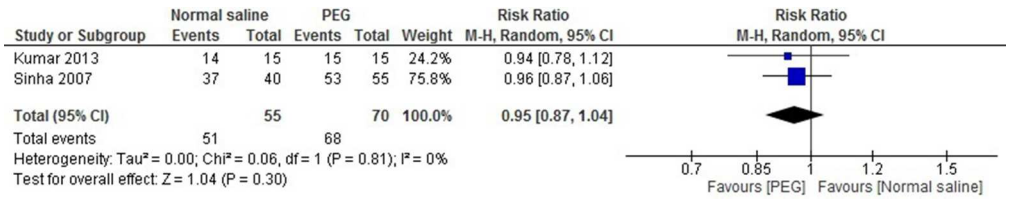

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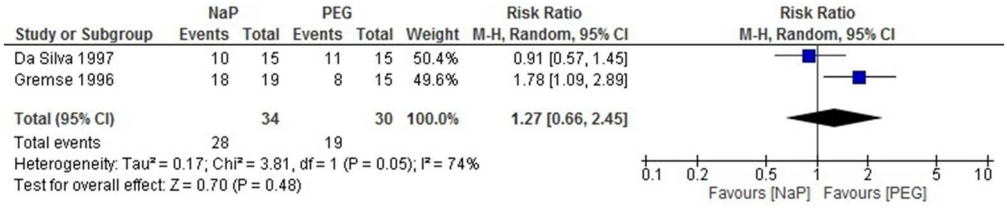

64x13mm (300 x 300 DPI)

Appendix 1 - Search strategy

vid EMBASE 1974 to 16 July 2016

1. exp colonoscopy/ OR colonoscop*.mp.
2. Surgery OR procedure
3. 1 or 2
4. infant/
5. child/
6. school child/
7. adolescent/
8. (infant* or child* or pediatric* or paediatric* or adolescent* or neonat* or toddler or young).mp.
9. 4 or 5 or 6 or 7 or 8
10. colon lavage/
11. intestine preparation/
12. exp laxative/
13. exp macrogol derivative/
14. exp phosphate/
15. exp citric acid/
16. exp magnesium oxide/
17. exp bisacodyl/
18. exp organometallic compound/
19. exp sulfate/
20. exp anthraquinone derivative/
21. exp enema/
22. (cathartic* or polyethylene glycol* or laxative* or phosphate* or citrate* or magnesium oxide* or bisacodyl or organometallic compound* or sulfat* or anthraquinone* or enema or bowel preparation or bowel cleansing or PEG-ELS or macrogol* or senna or docusate sodium or Sodium picosulphate or Cascara or casanthranol or Buckthorn or senokot or Aloe Vera or aloin Phenolphthalein or Dulcolax or stimulant or osmotic).mp.
23. (Miralax or Transipeg or Movicol or Forlax or Idrolax or GoLytely or PMF-100 or Golitely or Nulitely or Fortans or TriLyte or Colyte or lactulose or disaccharide or Apo-Lactulose or Chronulac or lactitol or sorbitol or Generlac or Cephulac or Cholac or Constilac or Enulose or Cilac or Heptalac or Actilax or Duphalac or Kristalose or Citroma or Osmoprep or Visicol).mp.
24. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 3 and 9 and 24
26. CROSSOVER PROCEDURE.sh.
27. DOUBLE-BLIND PROCEDURE.sh.
28. SINGLE-BLIND PROCEDURE.sh.
29. (crossover* or cross over*).ti,ab.
30. placebo*.ti,ab.
31. (doubl* adj blind*).ti,ab.
32. allocat*.ti,ab.
33. trial.ti.
34. RANDOMIZED CONTROLLED TRIAL.sh.
35. random*.ti,ab.
36. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)

38. 36 not 37
39. 25 and 38

BMJ Paediatrics Open

Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis

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Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis

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What is known about the subject

- Bowel preparation is vital to imaging and surgery in young people, but it is key to consider tolerability as well as efficacy in these patients
- Previous systematic reviews have only considered preparation for imaging and limit the age range, despite paediatricians often caring for children till older.

What this study adds

- Despite many trials, there is much clinical heterogeneity and risk of bias concerns with the evidence base, as well as poor safety and tolerability reporting.
- There is evidence that PEG regimens are effective. However, when compared, sodium picosulphate was better tolerated than PEG
- Future research needs to address these key methodology issues and also consider safety and tolerability, as well as efficacy.

Abstract

Objective: Adequate bowel preparation is crucial for both surgery and imaging in young people. Whilst systematic reviews have considered preparation for colonoscopy, they do not consider surgical interventions and to the age of 16, despite it being normal practice for paediatric gastroenterologists to care for transitioning children till older. We carried out a systematic review investigating the optimum bowel preparation agents for all indications in children and young people.

Design: A Cochrane format systematic review of randomised controlled trials (RCTs). Data extraction and assessment of methodological quality were performed independently by two reviewers. Methodological quality was assessed using the Cochrane risk of bias tool.

Patients: Young people requiring bowel preparation for any elective procedure, as defined by the primary studies.

Interventions: RCTs comparing bowel preparation with placebo or other interventions.

Main outcome measures: Adequacy of bowel preparation, tolerability and adverse events.

Results: The search yielded 2124 results and 15 randomised controlled studies (n = 1435), but heterogeneity limited synthesis. Meta-analysis of 2 studies comparing PEG with sodium phosphate showed no difference in the quality of bowel preparation (RR 1.27 [95% CI, 0.66-2.44]). Two studies comparing sodium picosulphate / magnesium citrate with PEG found no difference in bowel preparation, but significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS (RR 0.04 [95% CI, 0.01-0.18], 45 of 117 in PEG group vs 2 of 121 in Sodium picosulphate group). Meta-analysis of 3 studies (n = 241) found no difference between PEG and Sennasoids (RR 0.73 [95% CI, 0.31-1.71]).

Conclusions: The evidence base is clinically heterogeneous and methodologically at risk of bias. There is evidence that all regimens are equally effective. However, sodium picosulphate was better tolerated than PEG. Future research is needed with all agents and should seek to consider safety and tolerability, as well as efficacy.

Background:

Bowel imaging is a crucial modality in the diagnosis and monitoring of Inflammatory Bowel Disease (IBD), as well as surgery frequently being required in such patients. Multiple studies have suggested that bowel preparations must be individually tailored according to patient age, size and clinical status.[1] However, currently there is no internationally recognised gold standard regimen for paediatric bowel preparations.[2] Several regimens have been tried with the aim of identifying the safest, efficacious and tolerable combination, with varying success.[3]

Bowel preparation regimens can be based on lavage (bowel clean out) or cathartics (agents that accelerates defecation). Examples included; large volume of polyethylene glycol-electrolyte (PEG-ELS) lavage solution, sodium phosphate (an oral, low-volume, hyperosmotic agent), sodium pico-sulphate, bisacodyl and dietary measures, such as diet packs or clear liquid diets (often in combination with other agents).

Adequate bowel preparation prior to such procedures is crucial to ensure complete visualisation of the colonic mucosa (thus successful diagnostic and therapeutic colonoscopy, endoscopy and capsule endoscopy) and to minimize the risk of possible contamination during surgery. Administration of the agents is much more problematic in children compared to adults who manage to take the agents readily. In un-cooperative children, use of a naso-gastric tube to administer the agents has been reported to be an effective method to guarantee bowel wash out.[4] Reduced tolerance can result in poor outcomes due to inadequate preparation, increased rate of complications, extended procedural time and missed lesions.[3] Additionally, side effects have previously been noted, such as hyperphosphataemia in children who receive sodium phosphate.[4]

Whilst previous reviews have considered preparation for colonoscopy[3], they do not always consider surgical interventions and often limit their populations at the age of 16, despite it being normal practice for paediatric gastroenterologists to look after such patients for a number of years before transition to adult services.[5]

We carried out an up to date systematic review using the Cochrane collaboration format to summarise the available evidence investigating the optimum bowel preparation agents for all indications in children and young people.

Methods:

The objectives of this review were to evaluate the efficacy and safety of different bowel preparation for young people for any indication. A full protocol for the study was completed by the authors prior to commencement of the study and is available on request. This set out the procedure for the search, study screening, data extraction, risk of bias evaluation and analysis.

Criteria for considering studies for this review

RCTs were included in this systematic review. Participants were aged 0 to 21 years. This age range was selected after a scoping search and discussion with local stakeholders (tertiary centres) confirmed that it can be normal practice in pediatric gastroenterology for these patient groups to have variable transition to adult services, but 21 years was agreed as an absolute cut off and reflected several studies that would otherwise be excluded. Studies with adults included that did not allow analysis of this Paediatric age range were excluded. Studies compared bowel preparation with another bowel preparation or placebo, with all forms and dosing regimens considered. The purpose of bowel clearance was for colonoscopy or elective surgery. Studies were excluded if the purpose was to treat faecal impaction or encopresis. The primary outcome measure for the studies was the number of adequate bowel preparations, as defined by the included studies. Secondary outcomes included: tolerability (the propoprtion of children who could take the given therapy without the need for support through a nasogastric tube or incomplete dosing), Duration of procedure, Missed lesions due to inadequate bowel preparation and occurrence of any adverse events.

Search methods for identification of studies

Electronic searches (search strategy not limited by language) were completed of MEDLINE, The Cochrane Central Register of Controlled Trials, EMBASE and CINAHL (Inception- 15 July 2016), Appendix 1. References of included trials were also searched. Manufacturers were contacted to identify further negative and unpublished research. Abstracts were considered for inclusion if full details to judge inclusion were offered or available from the authors after contact by the study team.

Data extraction and assessment of methodological quality of included studies were independently performed by 2 authors and disagreements solved with involvement of the third author.

Data collection and analysis

All identified abstracts and results from searches were reviewed by the authors. If the reference appeared relevant, a full copy of the study was obtained. After reading the full texts, each author independently assessed the eligibility of all trials identified based on the inclusion criteria above. Disagreement among authors was discussed and agreement reached by consensus. If the data to judge inclusion were unclear, attempts were made to contact the authors.

A data extraction form was developed and piloted to extract information on relevant features and results of all primary and secondary outcomes of included studies. The two reviewers separately extracted and recorded data on the predefined checklist, with disagreement discussed and consensus reached.

The risk of bias of selected trials was assessed independently by the authors using the Cochrane risk of bias tool with disagreement once again resolved by reaching consensus. Study authors were contacted for further information when insufficient information was offered to judge risk of bias or data were missing for primary outcomes. Analysis was completed using Revman (Review Manager 5.2, V.5.2.9, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2012).

The primary outcome—efficacy of bowel preparation agents—was assessed using the Risk Ratio (RR) with 95% CI. The secondary outcomes were assessed by calculating the risk ratio (RR) and 95% CI or the MD with 95% CI, as indicated. The authors of included studies were again contacted to supply any missing data. Heterogeneity among trial results was assessed by inspection of graphical presentations and by calculating the $\chi 2$ test of heterogeneity (a p value of 0.10 was regarded as statistically significant). We also used the I2 statistic to quantity the effect of heterogeneity.[12] A result of less than 25% was defined as low, upto 75% moderate and above 75% high heterogeneity. A random-effects model was used, with a sensitivity analysis with the fixed-effects model, to identify differences in results that would suggest heterogeneity.

Results:

The electronic database search identified 2124 studies that were screened for inclusion. Of these, 15 studies (n = 1435) were judged to be potentially relevant and subjected to full text review (Figure 1). Only 12 papers needed consideration of a third author (less than 1%) to reach consensus, with one included and 11 excluded. Experts were contacted, but no extra reports were received and no further studies were identified from drug companies.

Description of studies

Excluded studies

Nine reports were excluded for failing to meet the inclusion criteria. Five were not solely with patients under 21 years of age, three were not RCTs and one was an abstract with insufficient data to judge inclusion.

Included studies

The 15 RCTs included described various regimens and comparative agents, with nine included in quantitative analysis (Table 1) and the remaining six in qualitative analysis (Table 2). Four studies compared various different regimens and combinations of PEG, Two compared polyethylene glycol (PEG) with oral sodium phosphate, two compared PEG with Normal Saline, three compared multiple combinations of PEG, sennasoids and sodium picosluphate, two diet kits with sodium phosphate, one study compared sodium picosulphate with phosphate enemas and one sodium picospulphate with PEG.

Study	Year	No	Age	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Main outcomes reported in the study	Context	Randomisation	Allocation Concealment	Blinding	Incomplete Outcomes	Selective reporting	Other
Gremse et al	1996	34	3 years - 17 years	Sodium Phosphate	PEG	N/A	N/A	The bowel preparation was excellent or good in 18/19 patients in sodium phosphate Group & 6/15 in PEG group. The incidence of vomiting was similar in both groups, but abdominal pain occurred more in PEG group.	Elective Colonoscopy	Unclear - one of the authors randomised patients into groups	One of the authors assigned the patients to their groups, also perform colonoscopies	Appear Single Blind	Unclear, no ITT	High – Details of adverse events not given	None
Sinha et al	2007	126	Mean 3 years	Sodium Chloride	PEG	Ringer Lactate	N/A	Bowel preparation was good in 35/40 in Nacl group, 49/55 in PEG group and 29/31 of lactate group. All three were similar in safety	Elective surgery	Unclear	Unclear	Appear Single Blind	Low risk	Unclear risk	None
Kierkus et al	2013	240	10 years – 18 years	BPEG	PEG	Sennosides	N/A	There were no significant differences found for the proportions of participants with excellent/good (PEG: 35/79, BPEG: 26/79, sennosides 25/76) bowel preparation	Elective colonoscopy	List Created by independent person using block	Yes	Single Blind	Low risk	Low Risk	None
Kumar et al	2013	30	1 month – 7 years	Normal Saline	PEG	N/A	N/A	Bowel preparation was rated as good/very good in 14/15 in the PEG group and 15/15 in the NS group. More symptomatic complications were noted in the NS group (7) then PEG grouo (1).	Various surgical procedures	Unclear	Unclear	Unclear	Low risk	Low	None apparent
Turner et al	2009	83	4 years – 18 years	Pico-Salax	PEG-ELS	N/A	N/A	Bowel preparation was judged as good/excellent in 33/43 of picosalax group and 32/40 PEG-ELS group. No significant difference in safety was found between the groups	Elective colonoscopy	Computer-generated list in blocks of 6	Yes	Single Blind	Yes	Low risk	Funded by pharma but not involved in study
Di Nardo et al	2014	299	2 years – 18 years	PEG-ELS with simethicone	PEG with citrate and bisacodyl	PEG 3350 with ascorbic acid	Sodium picosulphate, Magesium oxide + citric acid	No statistical difference was found between any group using the Boston scoring system (P = .910).No serious adverse events occurred in any group.	Elective colonoscopy	Computer generated list	Opaque sealed signed envelop	Unblind	Low Risk	Low risk	None apparent

Dahsan et al	1999	70	3 years – 20 years	Magnesium citrate with X-prep	Dulcolax and Fleet Enema	Golytely (PEG)	N/A	Bowel preparation was rated as excellent in 6/20 of X-prep group, 2/19 dulcolax and 15/31 of PEG group. Statistically more side effects were reported in the PEG group.	Elective Colonoscopy	No detail given	unclear	Single blind	Low Risk	Low risk	None apparent
Terry et al	2013	33	6 years – 21 years	PEG-P	Senna	N/A	N/A	Bowel preparation was rated as excellent/good in 14/16 of PEG-P group and 4/14 of the Senna group. Both were well-tolerated by patient-graded ease of preparation.	Elective Colonoscopy	Randomly chosen preparation packet	A nurse administer – no further details	Single Blind	Low risk	Low Risk	None apparent
Da Silva et al	1997	30	3 years – 14 years	Sodium Phosphate	PEG	N/A	N/A	Excellent-to-good colonic cleansing was achieved in 10/14 in sodium phosphate group and 11/15 of PEG group. Patients recorded less discomfort with orally administered Fleet than with high-volume balanced-lavage preparation	Elective Colonoscopy	Computer generated randomly assigned	Unclear Risk	Unclear Risk	Unclear	High Risk	None apparent

Table 1. Characteristics of studies included in quantitative analysis and risk of bias ratings
(BPEG: PEG combined with bisacodyl; PEG: Polyethylene glycol; PEG-ELS Polyethylene glycol –electrolyte lavage solution; PEG – P Polyethylene glycol without electrolytes)

Study	Year	No	Age	Regimen 1	Regimen 2	Main outcomes reported in the study	Context	Randomisation	Allocation Concealment	Blinding	Incomplete Outcomes	Selective reporting	Other
Trautwein et al	1996	140	5 years – 18 years	X-Pep and Sodium Phosphate	Magnesium citrate and Sodium phosphate	No significant different reported between bowel preparations for the two regimens. No safety concerns were raised, but numbers of adverse events were not described	Elective colonoscopy	Unclear	Unclear	Unclear	Unclear	Unclear Risk	None apparent
Pinfield et al	1999	63	18 months - 16 years	Picolax	Bisacodyl + Phosphate enema	Bowel preparation was good or excellent in all of the patients in the Picolax group (n=32) compared with 22 patients in the bisacodyl phosphate enema group(n=31). Abdominal discomfort was reported by 7 in the picolax group vs 18 in the bisacodyl group and vomiting by 3 in the picolax group and 0 in the bisacodyl group	Elective colonoscopy	Unclear	Sealed envelopes	Single blind	High Risk – only adverse events	High risk	None apparent
Elitsur et al	2013	93	Mean 10yrs	4-day protocol PEG 3350	2-day protocol PEG 3350 + bisacodyl	Adequate colon preparation was reached in 57.5% of regimen 1 and 73.6% of regimen 2. Side effects were reported as minimal and comparable in both groups (abdominal pain: 26%-32%, vomiting: 2%). None of the children discontinued his protocol due to side effects	Elective Colonoscopy	Computer generated random list	unclear	unclear	unclear	High risk	None apparent
Sorser et al	2014	32	2 years – 21 years	1 day PEG 3350 Max 255g	3 day PEG 3350 max 85g/day	A grading of excellent or good was given to 18/18 in regimen 1 and 13/14 in regimen 2. Regimen 1 5 reports of minor side effects were made vs 10 reports in regimen 2.	Elective Colonoscopy	No detail given	unclear	Single blind	Low risk	Low risk	None apparent
Najafi et al	2015	100	2 years – 14 years	1-day 2g/kg PEG + Bisacodyl Suppository	2-day 1.5g/kg PEG + Bisacodyl suppository	A grading of excellent or good was given to 35/50 in regimen 1 and 36/50 in regimen 2. Regimen 1 8/18 complained of nausea, 1/18 vomiting and 4/18 abdominal pain vs 3/14 nausea, 2/14 vomiting and 3/14 of abdominal pain in regimen 2.	Elective Colonoscopy	Computer generated random numbers	A technician randomly assign	Single blind	Low Risk	Low Risk	None apparent
El-Baba et al	2006	62	4 years – 18 years	Pre-packaged food kit, magnesium citrate	Sodium Phosphate	Quality of colon cleansing rated as excellent in 50% of regimen 1 and 19% of regimen 2. 30/36 in group 1 reported minor side effects vs 26/26 in group 2.	Elective colonoscopy	Computer random number generator	Unclear	Single Blind	Unclear	Low risk	None apparent

Table 2. Characteristics of studies included in qualitative analysis and risk of bias ratings
(BPEG: PEG combined with bisacodyl; PEG: Polyethylene glycol; PEG-ELS Polyethylene glycol –electrolyte lavage solution; PEG – P Polyethylene glycol without electrolytes)

Risk of bias of included studies

Seven studies were rated as low risk for random sequence generation (selection bias) because these studies employed computer-generated randomisation. The remaining studies described themselves as randomised but, with no further details given or available from authors, were rated as unclear risk of bias.

Five studies were rated as low risk of bias for allocation concealment (selection bias). Nine remaining studies were rated as unclear risk of bias for allocation concealment as the methods were not clearly described in the manuscripts. One described the allocated researcher as performing colonoscopies and was rated as high risk.

Ten studies were blinded and were judged to be at low risk of bias for blinding of personnel (performance bias) for such an intervention. Four studies described themselves as blinded, but gave no further details so was rated as unclear risk of bias. One study was open-label and judged to be at high risk of bias for blinding.

Eight studies reported full and appropriate data and satisfactorily documented withdrawals and dropouts and were therefore judged to be at low risk of bias for incomplete outcome data (attrition bias) and nine were judged as low risk for selective reporting (reporting bias). Two studies did not record full data for all patients and were judged high risk of bias for attrition bias. Four studies did not offer outcome data regarding side effects and tolerability so were judged at high risk for reporting bias.

All studies were judged to be at low risk for other sources of bias. However, the small sample sized of many of these studies is concerning, suggesting they were pilot or similarly underpowered studies, raising a further concern regarding bias. Details are summarised in Table 1.

The 15 studies present significant clinical and methodological heterogeneity (Table 1) and this severely limits the scope for synthesis.

PEG vs Sennasoids

Meta-analysis of 3 studies (n = 241)[6,7,8] found no difference between polyethylene glycol (PEG) and Sennasoids in adequate bowel preparation (RR 0.73 [95% CI, 0.31-1.76], Figure 2). High statistical heterogeneity was noted. Data regarding tolerability and safety was not presented to allow synthesis.

Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS)

Within these two studies versus PEG-ELS[9,10], equivocal adequacy of bowel preparation was seen (RR 0.99 [95% CI, 0.89-1.11], Figure 3). PEG's acceptability was reportedly poorer than sodium picosulphate in both studies. Meta-analysis of two PEG-ELS studies using the random effects model found a significantly higher number of patients needing nasogastric tube insertion in the PEG-ELS group (45 of 117) than the sodium picosulphate group (2 of 121), (RR 0.04 [95% CI, 0.01-0.18], Figure 4).

One patient in the PEG-ELS group and one in the sodium picosulphate group in the two studies were assessed as dehydrated and required intravenous (IV) fluids. For the PEG-ELS patient, a 10-year-old girl is reported who required intravenous fluid for 6 hours because of lethargy and dehydration (dryness of the oral mucosa and orthostatic hypotension) with serum electrolyte and glucose serum levels within the normal range. For the child in the sodium picosulphate group, a 12-year-old girl is reported that required intravenous fluids for 2 hours due to mild lethargy post procedure and was discharged well thereafter. Her vital signs were always within normal limits, but her serum osmolality was 316 mosm/L; she had drunk only two glasses of apple juice during the entire duration of the bowel cleanout. No other serious adverse events were noted.

PEG vs Normal Saline

Meta-analysis of 2 studies (n = 125) comparing PEG with normal saline[11,12] found no difference in rate of adequate bowel preparation (RR 0.95 [95% CI, 0.87-1.04], Figure 5). Adverse events were not reported homogenously to allow analysis, but occurred in both groups, including abdominal pain and vomiting.

PEG vs Sodium phosphate

There were two studies concerning 63 participants.[4,13] Meta-analysis of 2 studies using the random-effect model found no difference in the adequacy of bowel preparation (RR 1.27 [95% CI, 0.66-2.45], Figure 6). Again, high statistical heterogeneity was noted. One of the studies needed to insert a nasogastric tube in all patients receiving PEG, while in the remaining study, 53% of participants in the PEG group were unable to finish taking the solution whilst all the patients in the sodium phosphate

group could complete the medication. As these were reported differently, no meta-analysis was performed. No serious adverse events were reported.

Other studies

Within the remaining studies[1, 14-18] no meta-analysis was possible. However, no individual study found any different in adequacy of bowel preparation or adverse events. Tolerability was not well reported across studies. Whilst secondary outcome analysis for further items were planned, data was not presented to allow this to take place.

Discussion:

Despite the common requirement for bowel preparation in young people, the results of this review have highlighted a very poor evidence base. A mixture of clinical heterogeneity related to multiple agent regimens and methodological heterogeneity limiting the ability for meta-analysis has significantly limited synthesis. In multiple small analyses, PEG-ELS, Senna, Normal Saline, Sodium phosphate and Sodium picosulphate / Magnesium citrate found no difference in adequacy of bowel preparation. This was similar across the remaining individual studies. As such, despite the significant weaknesses of the evidence base, it is worth noting that no difference in adequacy of bowel preparation has been reported in any included study. This was also the case with adverse events, although it must be noted these were reported in an extremely heterogeneous fashion, with individual minor, major and patient overall recording of events across studies.

Of note, there was a significant difference in favour of sodium pico-sulphate and magnesium citrate regarding tolerability, specifically the need for a nasogastric tube to complete the bowel preparation. This is a particularly interesting finding, as the primary studies highlighted that whilst tolerability of PEG was extremely poor, smaller volumes than planned appeared to have little impact on efficacy. This raises the question of the need for the nasogastric tube at all and so this may need further investigation in the future. Sodium pico-sulphate was also compared to bisacodyl and a phosphate enema in a single study with equivocal preparation, tolerability and safety reported.

PEG appeared to be the least tolerable agent across all studies - with a number of the patients requiring a nasogastric tube insertion, but this is from qualitative synthesis of individual studies, with this outcome reported in heterogeneous fashion so meta-analysis was not possible. Additionally, as the age ranges of included participants varied greatly, it is hard to make firm conclusions on this finding as the need for nasogastric tubes is likely to be very age dependent. Oral sodium phosphate was well tolerated in individual studies. Despite the satisfactory tolerability and safety profile of sodium phosphate, it should be noted that care must be taken when using this agent as it can cause significant electrolyte imbalances. As such, it should not be used in patients with deranged baseline electrolytes, suboptimal renal and hepatic function, as it poses a risk of acute kidney injury and phosphate nephropathy.[19]

With all the agents studied the occurrence of minor adverse events such as abdominal pain, bloating, faecal incontinence, nausea, vomiting, headaches and anal irritation was comparable. No serious adverse events were reported in any of the studies. It should also be noted that in the context of elective surgery, there is growing recognition of the role for proceeding without bowel preparation. [20]

The evidence base for this review covers a large number of trials with a reasonable number of patients, but is severely limited due to clinical and methodological heterogeneity, as well as concerns with risk of bias. As such, the findings of this review should be interpreted with extreme caution as it is difficult to draw firm conclusions for any of the investigated agents. it must also be noted that for the primary outcome, successful bowel preparation was 'as defined' by primary studies, with several different scoring systems and criteria used. This also limits the appropriateness of meta-analysis in this context, although those wishing to complete future studies should note the Ottawa scoring system[21] was the only such scoring method reported in multiple studies. This is also true of adverse events, which were reported in a sporadic and inconsistent manner that prevented comment on even simple complaints, such as nausea or vomiting.

Considering the small sample sizes, the high degree of heterogeneity and a wide variation in the regimen of each cleansing agent; the findings of this review cannot be reliably used to inform clinical practise, but most usefully should inform future research. In particular, as the question of adequacy of bowel preparation has been established as essentially equivocal amongst all study agents, a shift of focus for future studies is needed. Given the unique needs of a paediatric population, considering the issue of tolerability as a primary outcome is vital and looking at the lower volume options presented as enteral agents could offer potential practical advantages and need a high quality study to investigate them.

Conclusions:

The publishing evidence base investigating this issue is large, but is clinically heterogeneous and at risk of bias. All regimens appear equivocal for adequacy of bowel preparation. However, when compared with sodium pico-sulphate, sodium pico-sulphate is better tolerated. Future research should seek to consider safety and tolerability, as well as efficacy, given the key importance of these issues in a childhood population.

Figure legend

Fig 1: Patient flow diagram

Fig 2: Forest plot for PEG vs Senna, adequacy of bowel preparation

Fig 3: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), adequacy of bowel preparation

Fig 4: Forest plot for Sodium picosulphate and magnesium citrate versus polyethylene glycol-electrolyte lavage solution (PEG-ELS), Tolerability of agent

Fig 5: Forest plot for PEG vs Normal Saline, adequacy of bowel preparation

Fig 6: Forest plot for PEG vs Sodium Phosphate, adequacy of bowel preparation

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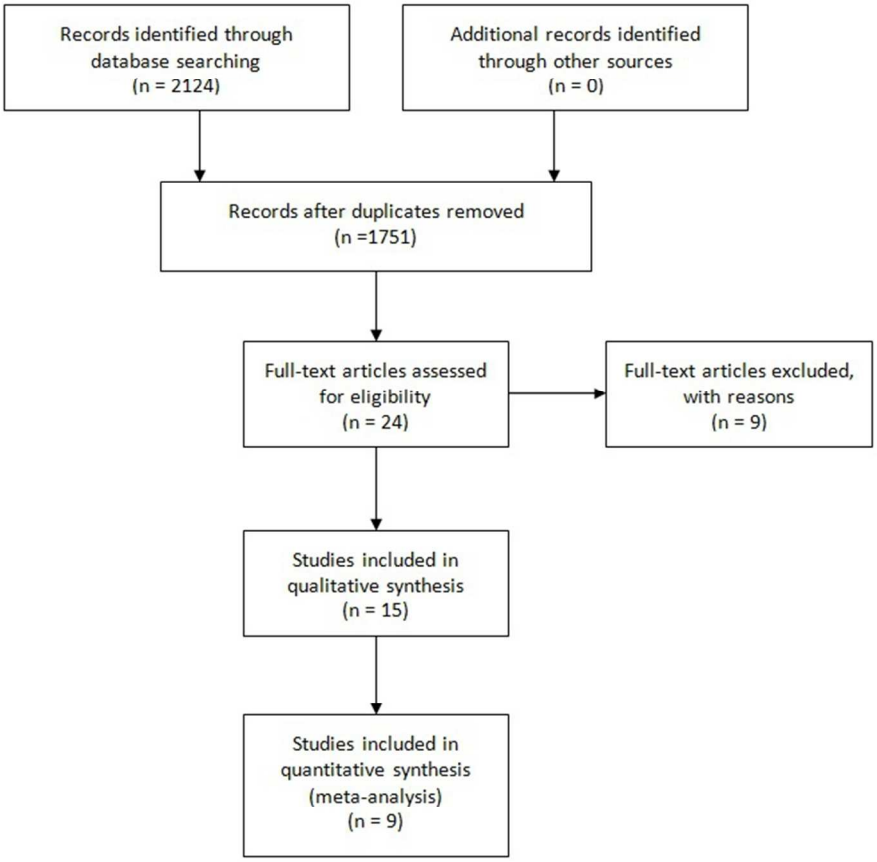

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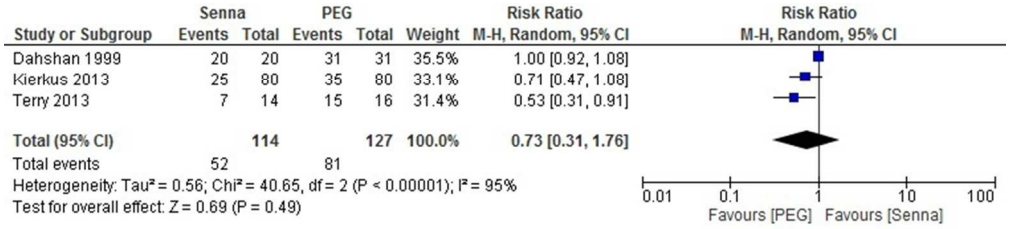

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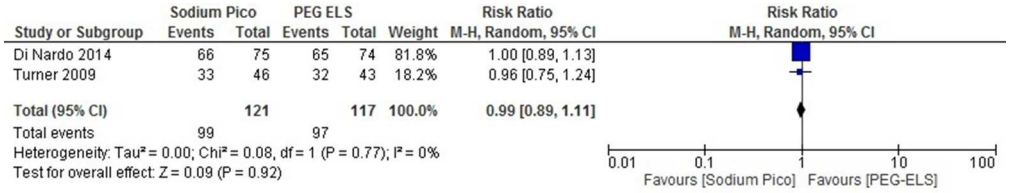

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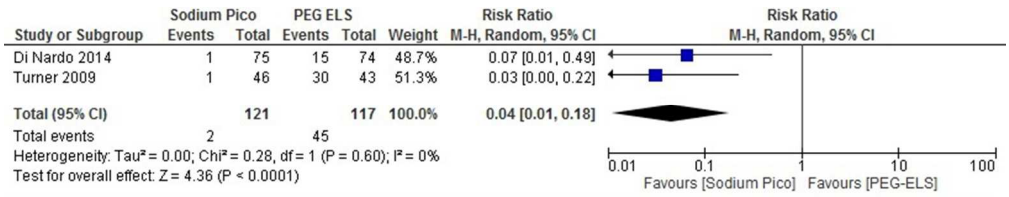

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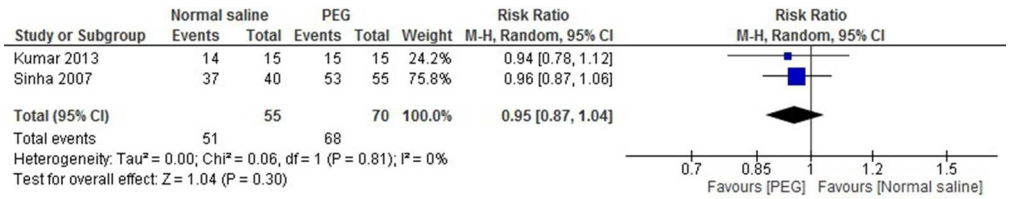

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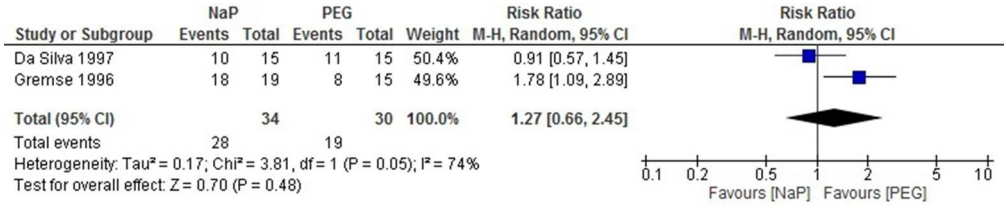

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Appendix 1 - Search strategy

vid EMBASE 1974 to 16 July 2016

1. exp colonoscopy/ OR colonoscop*.mp.
2. Surgery OR procedure
3. 1 or 2
4. infant/
5. child/
6. school child/
7. adolescent/
8. (infant* or child* or pediatric* or paediatric* or adolescent* or neonat* or toddler or young).mp.
9. 4 or 5 or 6 or 7 or 8
10. colon lavage/
11. intestine preparation/
12. exp laxative/
13. exp macrogol derivative/
14. exp phosphate/
15. exp citric acid/
16. exp magnesium oxide/
17. exp bisacodyl/
18. exp organometallic compound/
19. exp sulfate/
20. exp anthraquinone derivative/
21. exp enema/
22. (cathartic* or polyethylene glycol* or laxative* or phosphate* or citrate* or magnesium oxide* or bisacodyl or organometallic compound* or sulfat* or anthraquinone* or enema or bowel preparation or bowel cleansing or PEG-ELS or macrogol* or senna or docusate sodium or Sodium picosulphate or Cascara or casanthranol or Buckthorn or senokot or Aloe Vera or aloin Phenolphthalein or Dulcolax or stimulant or osmotic).mp.
23. (Miralax or Transipeg or Movicol or Forlax or Idrolax or GoLytely or PMF-100 or Golitely or Nulitely or Fortans or TriLyte or Colyte or lactulose or disaccharide or Apo-Lactulose or Chronulac or lactitol or sorbitol or Generlac or Cephulac or Cholac or Constilac or Enulose or Cilac or Heptalac or Actilax or Duphalac or Kristalose or Citroma or Osmoprep or Visicol).mp.
24. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 3 and 9 and 24
26. CROSSOVER PROCEDURE.sh.
27. DOUBLE-BLIND PROCEDURE.sh.
28. SINGLE-BLIND PROCEDURE.sh.
29. (crossover* or cross over*).ti,ab.
30. placebo*.ti,ab.
31. (doubl* adj blind*).ti,ab.
32. allocat*.ti,ab.
33. trial.ti.
34. RANDOMIZED CONTROLLED TRIAL.sh.
35. random*.ti,ab.
36. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)

38. 36 not 37
39. 25 and 38