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Meta-analysis: the relative efficacy of oral bowel preparations for colonoscopy 1985–2010

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SUMMARY

Background

Previous reviews of bowel preparation for colonoscopy have given contradictory answers.

Aim

To provide a definitive insight, using PRISMA-compliant methodology.

Methods

A comprehensive literature review identified randomised controlled trials comparing bowel preparation regimens. Data for quality of bowel preparation were pooled in multiple meta-analyses exploring a range of inclusion criteria.

Results

A total of 104 qualifying studies were identified, the majority of which involved comparisons of sodium phosphate (NaP) or polyethylene glycol (PEG). There was no significant difference demonstrated between NaP and PEG overall (OR = 0.82; 95% CI = 0.56–1.21; $P = 0.36$). Cumulative meta-analysis demonstrated that this conclusion has been qualitatively similar since the mid 1990s, with little quantitative change for the past 10 years. Amongst studies with previous day dosing in both study arms there was a significant advantage in favour of PEG (OR = 1.78; 95% CI = 1.13–2.81; $P = 0.006$). Studies focussing on results in the proximal colon also favoured PEG (OR = 2.36; 95% CI = 1.16–4.77; $P = 0.012$). PEG was also significantly more effective than non-NaP bowel preparation regimens (OR = 2.02; 95% CI = 1.08–3.78; $P = 0.03$). Other comparisons showed no significant difference between regimens.

Conclusions

Although there is no compelling evidence favouring either of the two most commonly used bowel preparation regimens, this may reflect shortcomings in study design. Where studies have ensured comparable dosage, or the clinically relevant outcome of proximal bowel clearance is considered, PEG-based regimens offer the most effective option.

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INTRODUCTION

Rationale

The central role of adequate bowel preparation in ensuring adequacy of visualisation in colonoscopy is well established from both a clinical^{1, 2} and a financial standpoint,³ although there is still a lack of consensus regarding which treatment regimen offers the most effective bowel clearance.

The most commonly used regimens are based on polyethylene glycol (PEG) or sodium phosphates (NaP), with sodium picosulphate-based regimens also being popular in some areas. Although all of these have been widely used for many years, recent concerns regarding the renal safety of NaP⁴ have resulted in changes in patterns of use. Modifications to dosage recommendations and a re-emphasis of the patient groups in whom NaP is considered unsuitable⁵ have led to a re-evaluation of its position in bowel preparation. Given the requirement to balance benefit with risk, it is therefore of considerable importance that the relative effectiveness of bowel preparation options is objectively assessed.

A large number of clinical trials published over the past 20 years have set out to identify which of these treatments offers the most effective bowel clearance. However, systematic reviews of this literature have arrived at differing conclusions, with one recently published analysis suggesting that NaP is the more effective option,⁶ whereas another showed no significant difference between regimens.⁷ Although, in theory, two meta-analyses of the same general evidence base should yield consistent results, in practice the criteria used to select studies for inclusion in a review can create biased datasets and therefore generate apparently contradictory conclusions.

In consequence, our objective in this systematic review is to provide a comprehensive review of the literature following a PRISMA-compliant methodology.⁸ Analyses will be based on both inclusive and exclusive criteria, to identify unequivocally whether any single treatment offers an advantage over the others and also to clarify which elements of study design may influence the conclusions of published comparisons.

METHODS

A comprehensive research protocol was agreed by all authors prior to undertaking the literature review.

Eligibility

Studies were to be included if they met all of the following criteria:

- (i) Prospective randomised controlled trial.
- (ii) Fully published in a peer-reviewed journal.
- (iii) Patients undergoing diagnostic, screening or therapeutic colonoscopy.
- (iii) Two or more treatment arms, using different bowel preparation regimens.
- (iv) Treatment efficacy reported using an explicit categorical measure.

The intention was to undertake an inclusive primary review and then to use secondary subgroup analyses to explore the impact of various aspects of treatment or study design. Consequently, exclusion criteria were few and were generally implicit in the inclusion criteria. Important exclusions included:

- (i) Case series or retrospective analyses.
- (ii) Mixed treatment regimens including rectally administered agents.
- (iii) Insufficiently defined or reported outcome measures.

Specifically there were no primary exclusions based on language or year of publication.

Information sources

Searches were carried out on three electronic databases: MEDLINE, EMBASE and Cochrane CENTRAL, covering all entries up to the end of July 2010. Each database required an individual search strategy, reflecting their own key word dictionary. As an example, the strategy for MEDLINE was:

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Laxatives [MeSH] OR Cathartics [MeSH] OR Bowel
Preparation [TW]
AND
Colonoscopy [MeSH] OR Colonoscopy [TW]
AND
Randomised Controlled Trial [PT] OR Randomized
[TW] OR Randomised [TW]
NOT
Constipation [MeSH]
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Where: MeSH = Medical Subject Heading, TW = Text Word, PT = Publication Type.

A similarly worded search was also carried out to identify any previously published systematic reviews and/or meta-analyses.

All abstracts were examined: where this indicated that a study was likely to fulfil the inclusion criteria, the full text of the article was retrieved. Reference lists of these full texts (and all identified review articles) were further scrutinised to identify studies that had not been picked up in the primary searches.

Where the primary searches identified four or more potentially includable studies in any given journal, further hand searches were carried out on the indices for these journals. Consequently, hand searches of past 20 years' editions of the following journals were carried out: (i) *Alimentary Pharmacology and Therapeutics*, (ii) *American Journal of Gastroenterology*, (iii) *Diseases of Colon and Rectum*, (iv) *Endoscopy*, (v) *Gastroenterology*, (vi) *Gastrointestinal Endoscopy*.

Once the inclusion and exclusion criteria had been applied, and prior to data extraction, all studies were quality appraised using the Cochrane Collaboration Risk of Bias Tool. This uses a semi-quantitative approach to assess the quality of study design, with each of the following criteria being scored as 'satisfactory', 'unsatisfactory' or 'unclear':

- (i) Randomisation sequence generation
- (ii) Allocation concealment
- (iii) Blinding of participants and outcome assessors
- (iv) Completeness of outcome data
- (v) Selective outcome reporting
- (vi) Other sources of bias

All articles were assessed by two authors. In the event of disagreement on any criterion, the views of a third reviewer were used to decide the score. Although no study exclusions were planned on the basis of quality appraisal, in the event that there were differences in study quality detected, the scoring results were to be used to inform a sensitivity analysis.

Data

Studies included in the analysis were grouped according to the investigation and treatment comparisons. Groups used were:

- (i) PEG vs. NaP solution
- (ii) PEG vs. PEG (different doses or \pm prokinetics)
- (iii) NaP vs. NaP (different doses or \pm prokinetics)
- (iv) PEG vs. other regimens
- (v) NaP vs. other regimens
- (vi) Other comparisons

For primary analyses of studies using NaP solution, only studies that complied with current dosage recommendations were included (maximum 90 mL in two doses separated by at least 10 h). Sensitivity analysis was carried out to explore the effect of this exclusion (see below).

For each study, data were extracted from description of the endoscopist's categorical assessment of the adequacy of preparation. Where there were only two categories (satisfactory/unsatisfactory) the proportion of

patients achieving a 'satisfactory' rating in each treatment arm was extracted. Where multiple categories were used, the proportions achieving an 'excellent' or 'good' rating were recorded.

Where results were only presented graphically, these were enlarged and scale measurement used to estimate the numerical values represented in the graphs.

Statistical analysis

Results within groups were statistically pooled using a DerSimonian Laird random effects model,⁹ where study design and treatment regimens were sufficiently similar, to arrive at an estimate of relative treatment benefit. Between-studies heterogeneity was assessed using Q statistic testing in combination with the I^2 index. In view of the overall high treatment success rate (typically 70–95%), results were expressed as odds ratios, to avoid the problem of constraint associated with risk ratios in this circumstance. All analyses were carried out using a bespoke MS EXCEL application, with Forest plots generated using MetaAnalyst Beta 3.13 (Tufts Medical Center).

Where studies were not deemed sufficiently similar to allow meta-analysis, an account of these dissimilarities was given and a narrative review was carried out.

Sub-analyses

In addition to the global comparisons described above, an *a priori* intention to explore the following sub-analyses was stated, where the relevant data was available and sufficiently robust.

Several of these sub-analyses related to studies comparing PEG vs. NaP, as this is the area which has yielded contradictory results from different systematic reviews.

(i) Extend comparison to include those studies which used NaP at greater than the currently recommended dosage (90 mL) or where the gap between doses was less than 10 h.

(ii) Limit comparison to studies where the timing of treatment was identical between arms (i.e. both doses given the day before or both split overnight) and compare this result with studies where differing regimens were used.

(iii) Carry out a cumulative meta-analysis to explore any temporal trends in study results.

(iv) Compare the relative effects of the two treatments on proximal and distal colon.

In the other treatment groups the following analyses were planned

(i) Compare high volume PEG with low volume PEG + ascorbate.

- (ii) Limit ‘PEG vs. others’ and ‘NaP vs. others’ to studies involving sodium picosulphate.
- (iii) Explore the impact of baseline bowel activity, body mass index and dietary modification on treatment efficacy.

RESULTS

The search strategy identified 292 potentially relevant studies, 154 of which were examined in detail and 104 of which were included in the final analysis.¹⁰⁻¹¹³ (see Figure 1). Of the 138 studies excluded at the initial screening, the majority of these were inappropriate for further consideration either because they were not randomised controlled trials (71/138), or because they used rectal forms of bowel preparation in addition to oral treatment (44/138). The breakdown of finally included studies by treatment group is summarised in Table 1. One study¹⁶ was included in two comparison groups.

Study quality

Few studies were of high quality.

- (i) In general there was little indication of the methods by which randomisation and sequence generation had been achieved.
- (ii) In general, no information was given regarding allocation concealment.
- (iii) Differences in appearance, taste or volume of bowel preparation meant that blinding of patients and

Table 1 | Included studies broken down by comparison group

Regimen	Trials (n)	References
PEG vs. NaP	31	[10-40]
PEG vs. PEG	29	[16, 41-68]
NaP vs. NaP	11	[69-79]
PEG vs. Others	12	[80-91]
NaP vs. Others	9	[92-100]
Other comparisons	13	[101-113]

PEG, polyethylene glycol; NaP, sodium phosphates.

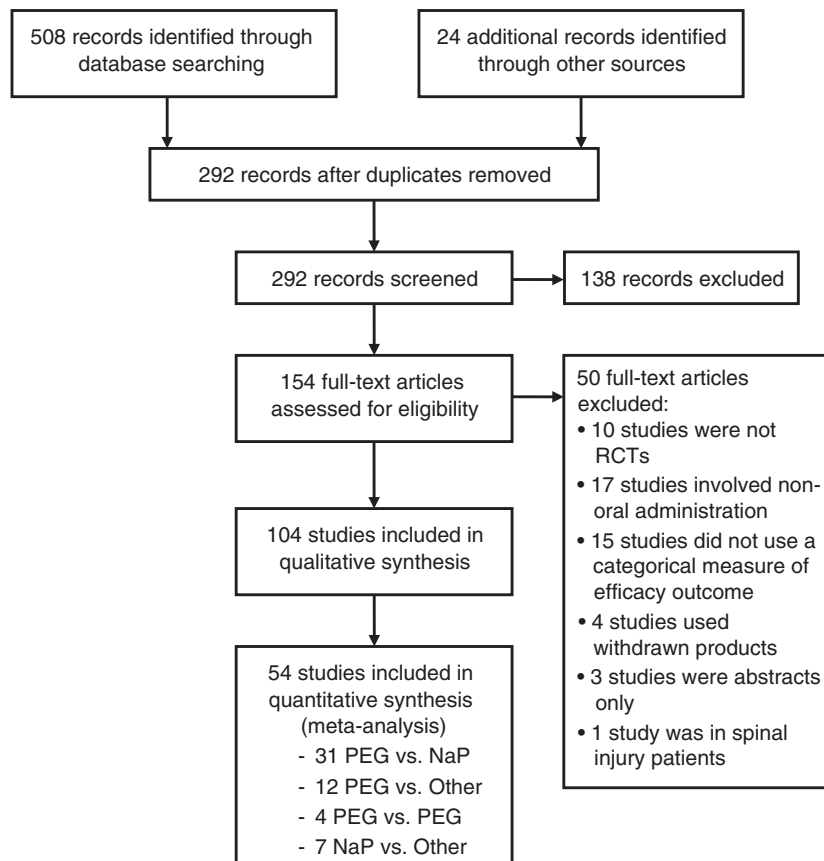


Figure 1 | PRISMA flow chart showing literature review results.

those involved in pre-operative care was rarely possible. However, the majority of studies were explicit that endoscopists were blinded to treatment group.

(iv) There were good data regarding withdrawals and dropouts, which were generally few, thanks to the short duration of treatment and follow-up. Sufficient information were given to allow intention-to-treat results to be used for the meta-analyses.

(v) Those studies that did not report the outcome of interest to this analysis were excluded by virtue of the inclusion criteria. Selective outcome reporting was therefore not an issue here.

Despite the low overall quality, no study was considered to be sufficiently poor to warrant exclusion from the review. The results presented therefore reflect the totality of the literature search results, except where explicitly stated in the relevant sections below.

Group 1: PEG vs. sodium phosphate. There were 31 qualifying studies involving 4450 patients in which bowel preparation using PEG was compared with NaP solution.⁷⁻³⁷ Of these, 21 studies involving 2,920 patients in 22 treatment comparisons⁷⁻²⁷ used doses of NaP that were in accordance with current safety recommendations.

When taken as a whole, there was no significant difference between NaP and PEG in the dose compliant dataset (OR = 0.82; 95% CI = 0.56-1.21; $P = 0.36$), where an OR >1 favours PEG and an OR <1 favours NaP (Figure 2).

However, there was significant heterogeneity between the studies ($Q = 114.6$; $I^2 = 81.7\%$; $P < 0.0001$) suggesting that, despite apparently similar trial protocols, there were significant differences either in the way in which bowel preparations were administered, or the way study results were recorded. An additional potential source of bias is dose timing: in earlier trials the advantage of using a nocturnal pause during administration of the bowel preparations was not realised.

Analysis of older vs. newer studies, suggested that studies published prior to 2000 were more likely to show a benefit for NaP than those published in the past 10 years, although in neither case were the observed differences statistically significant. The chosen threshold of 2000 was arbitrary, based on the observed clustering of publication dates. However, exploration of other date thresholds (1998, 2002, 2004) did not yield different results.

For studies published before 2000:

Effect: OR = 0.59; 95% CI = 0.26-1.32; $P = 0.19$

Heterogeneity: $Q = 45.6$; $I^2 = 84.6\%$; $P < 0.0001$

For studies published after 2000:

Effect: OR = 1.23; 95% CI = 0.75-2.04; $P = 0.41$

Heterogeneity: $Q = 53.1$; $I^2 = 76.0\%$; $P < 0.0001$

In most studies identified in the review, PEG was administered as a single treatment the day before colonoscopy, whereas the two doses of NaP were given the night before and on the morning of the procedure. This appears to be a potent cause of heterogeneity. If the meta-analysis is restricted to dose-compliant studies where identical dosage regimens were used, the heterogeneity is removed.

For studies where both treatments were given the preceding evening, there was a significant advantage demonstrated for PEG:

Effect: OR = 1.78; 95% CI = 1.13-2.81; $P = 0.006$

Heterogeneity: $Q = 4.7$; $I^2 = 14.1\%$; $P = 0.46$

For studies where both treatments were given as split doses overnight, there was no significant difference between treatments:

Effect: OR = 0.93; 95% CI = 0.64-1.35; $P = 0.72$

Heterogeneity: $Q = 2.1$; $I^2 = 0\%$; $P = 0.71$ (Figure 3).

Cumulative meta-analysis was carried out for the complete dataset, including studies that examined dose regimens of NaP that are no longer recommended (Figure 4). Between 1990 and 2009, 33 comparisons were carried out in 31 studies. The qualitative results of the analysis were apparent by the mid 1990s, with little appreciable movement in the quantitative results (either the point estimate of odds ratio or the confidence intervals) for the past 10 years.

Four studies reported results broken down by multiple colonic sites. Looking at the results for the ascending colon alone, there was a significant benefit for PEG vs. NaP:

Effect: OR = 2.36; 95% CI = 1.16-4.77; $P = 0.012$

Heterogeneity: $Q = 18.4$; $I^2 = 78.3\%$; $P = 0.001$

The results for the descending colon showed no significant difference:

Effect: OR = 1.18; 95% CI = 0.63-2.20; $P = 0.56$

Heterogeneity: $Q = 12.6$; $I^2 = 68.2\%$; $P = 0.014$

Group 2 - PEG vs. PEG. This group included a disparate range of studies that do not lend themselves readily to meta-analysis, thanks to significant differences in treatment regimens. The following is a narrative summary of the studies in this group.

Six studies (seven treatment arms) compared the use of differing volumes of PEG, variously 4 L vs. 3 L^{13, 46, 47, 63} 4 L vs. 2 L^{46, 50} and 3 L vs. 1.5 L.⁶⁵ In five

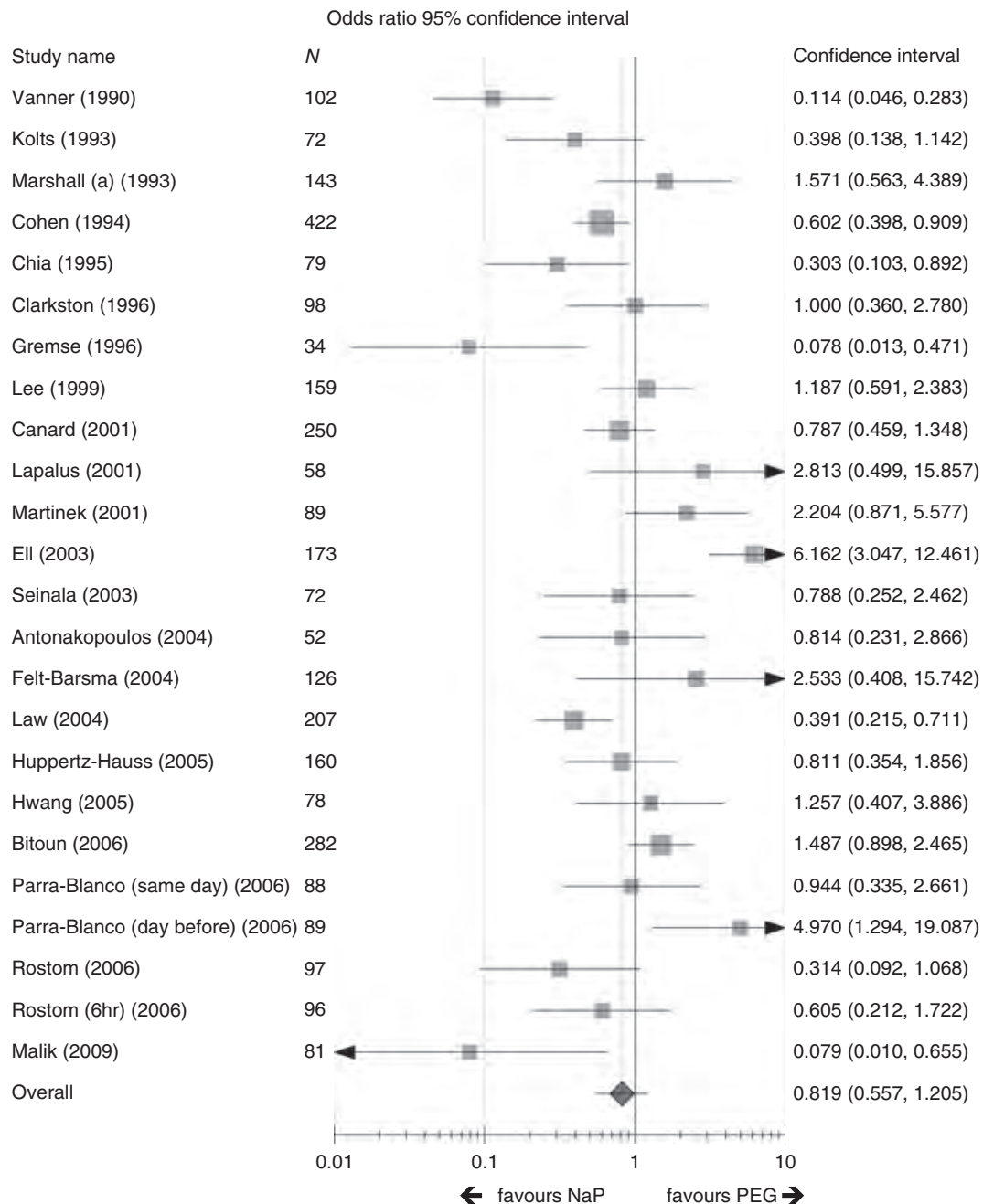


Figure 2 | Random effects pooling of efficacy assessments for PEG vs. NaP (excellent/good vs. all other outcomes). All NaP dose-compliant studies. PEG, polyethylene glycol; NaP, sodium phosphates.

studies,^{46, 47, 50, 63, 65} there was no significant difference between treatment groups. In the sixth study,¹³ 4 L PEG was shown to be significantly more effective than 3 L PEG.

Seven studies (nine treatment arms) compared the use of 4 L PEG with a reduced volume of PEG (1.5 L or 2 L) given with an additional laxative (ascorbate components,⁵³ magnesium hydroxide,³⁸ magnesium citrate,⁶¹

bisacodyl^{39, 48, 54, 61} sennosides⁵¹ or olive oil³⁸). There was no difference in efficacy demonstrated between 4 L PEG and 1.5–2 L PEG with either ascorbate components, magnesium citrate, bisacodyl or olive oil. A limited meta-analysis carried out on the four bisacodyl study confirmed this finding (OR = 1.11; 95% CI = 0.77–1.60; *P* = 0.59). A volume of 4 L PEG was shown to be significantly better than 2 L PEG given with either magnesium

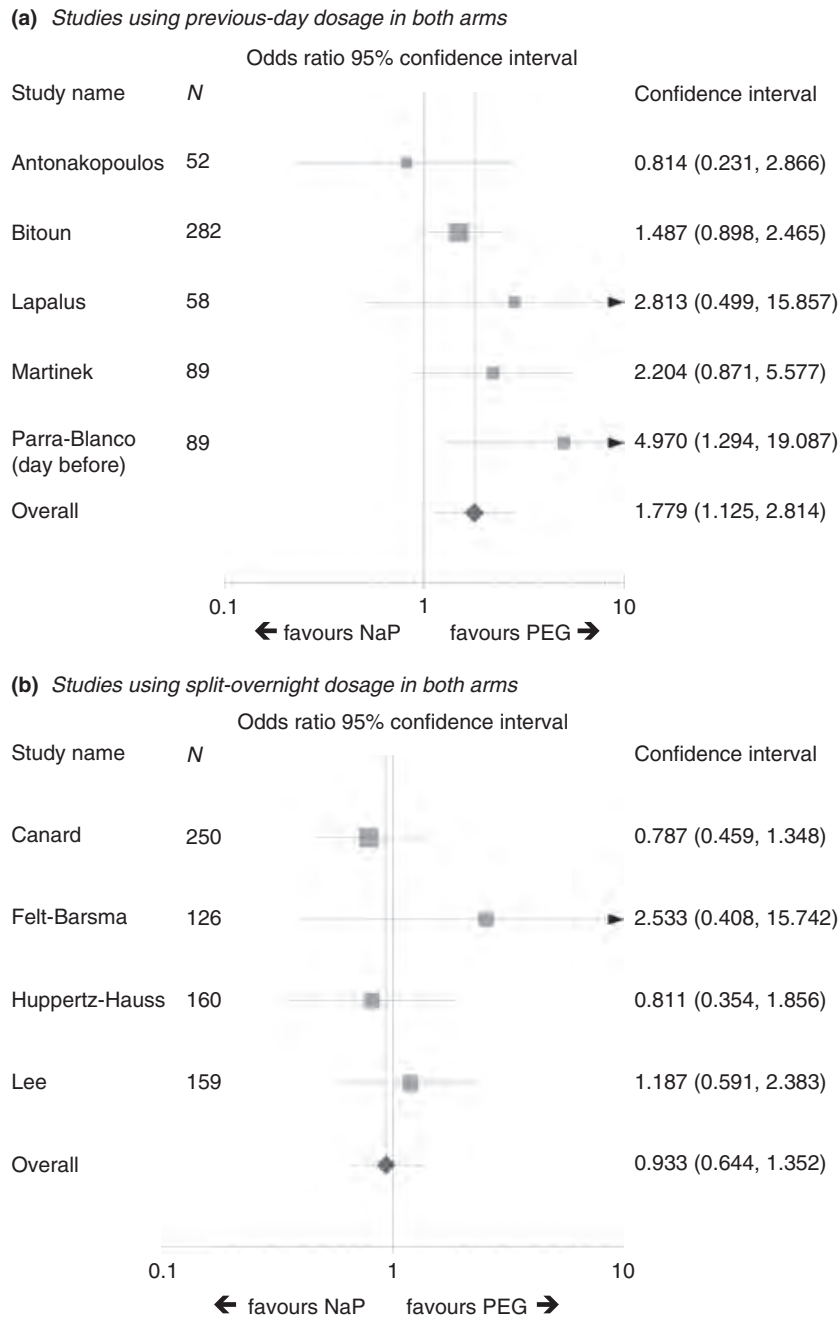


Figure 3 | Random effects pooling of efficacy assessments for PEG vs. NaP (excellent/good vs. all other outcomes). (a) Studies using previous-day dosage in both arms. (b) Studies using split-overnight dosage in both arms. PEG, polyethylene glycol; NaP, sodium phosphates.

hydroxide or sennosides, however, the one available article comparing 4 L PEG to a 2 L PEG and ascorbate component product showed no difference in efficacy.

Seven studies^{42, 43, 45, 52, 60, 62, 64} examined the impact of adding supplementary agents (metoclopramide, bisacodyl, simethicone, lubiprostone or senna) to standard volume PEG. None demonstrated any significant impact on bowel-clearing efficacy.

Three studies investigated the impact of varying dose timing. One study showed that full volume PEG given the day before the procedure was less effective than giving it the same day.⁴⁴ A second study demonstrated that a similar benefit was observed if the PEG dosage was split overnight before colonoscopy.⁵⁶ A similar, but much smaller study failed to show a difference between single and split-dose PEG.⁵⁸

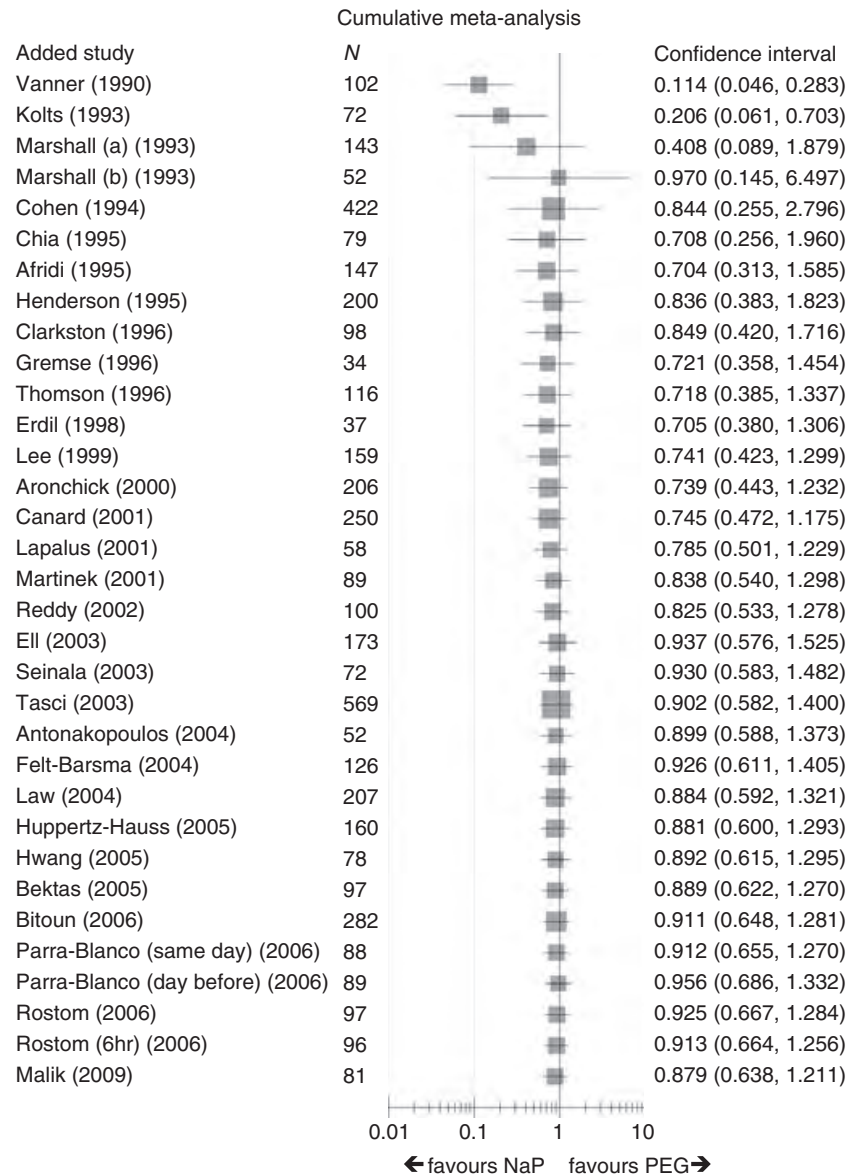


Figure 4 | Cumulative meta-analysis of PEG vs. NaP studies: 1990–2009; all NaP dose regimens. Random effects pooling of efficacy assessments (excellent/good vs. all other outcomes). PEG, polyethylene glycol; NaP, sodium phosphates.

Finally, three studies examined the impact of dietary and dose manipulation on the effectiveness of PEG. One study⁴⁰ compared 4 L PEG + liquid diet with split dose PEG (2 L + 2 L) with a normal diet. The second group demonstrated significantly better visibility, although it remains unclear to what extent this reflects the dose splitting or the dietary difference. A second study⁴⁹ compared 3 L PEG + liquid diet with split dose PEG (2 L + 1 L) with a normal diet and bisacodyl 10 mg. Quality of cleansing was significantly better in the second group, but once again it was unclear which element of the treatment difference might account for this. Finally, a

third study⁵⁷ compared 4 L PEG + liquid diet with 4 L PEG + a proprietary low-residue diet. No difference was seen in cleansing adequacy.

Group 3 - Sodium phosphate vs. sodium phosphate. Eleven studies were identified comparing different NaP-based regimens, although as was seen for the PEG vs. PEG studies, differences in study design precluded meaningful meta-analytical combination of the results.

Seven of these studies compared different doses/formulations of liquid,^{67, 68, 70} tablet^{71, 72, 76} or both⁶⁶

preparations of NaP. NaP tablet doses ranging 28–40 tablets were found to be equivalent in terms of efficacy, with no evidence of a difference between standard and microcrystalline cellulose-free formulations.^{71, 72, 76} A single study,⁶⁶ however, suggested that the liquid formulation was superior to the tablets. Increasing the dose of liquid above 90 mL was found to improve efficacy,⁶⁷ but adopting this strategy would contravene current dose-safety recommendations. Giving NaP on the morning of the procedure rather than the night before did not influence efficacy outcomes.⁷⁰ The use of an aspartame-based diluents did not alter the efficacy result compared with sucrose-based solutions.⁶⁸

The addition of various antiemetics,⁶⁹ carbohydrate/electrolyte solution,⁷⁴ or simethicone⁷⁵ to liquid NaP did not alter bowel wall visibility, although the use of both antiemetics and the electrolyte solution improved patient tolerability. The use of a low residue, rather than liquid diet alongside the NaP also did not influence outcomes.⁷³

Group 4 - PEG vs. other comparators. A mixed group of 12 studies compared the use of other regimens with PEG. Comparators included mannitol,⁸⁰ senna (\pm magnesium citrate),^{81, 85} mixed oral sulphates,⁸³ bisacodyl (\pm magnesium citrate or NaP)^{84, 86, 90} and sodium picosulphate/magnesium citrate (\pm mannitol).^{82, 87–89, 91}

If the results of all these studies are pooled, there is a significant benefit demonstrated in favour of PEG vs. the comparators (see Figure 5):

Effect: OR = 2.02; 95% CI = 1.08–3.78; $P = 0.03$

Heterogeneity: $Q = 64.4$; $I^2 = 79.8\%$; $P < 0.0001$

If the analysis is limited purely to those studies carried out vs. sodium picosulphate containing regimens, the trend remains the same, although the result is no longer statistically significant (Figure 6).

Effect: OR = 2.29; 95% CI = 0.78–6.73; $P = 0.12$

Heterogeneity: $Q = 18.1$; $I^2 = 77.9\%$; $P = 0.001$

Group 5 - NaP vs. other comparators. A mixed group of nine studies compared the use of other regimens with NaP. Comparators included mannitol,⁹⁴ senna,⁹⁹ bisacodyl,⁹² magnesium citrate,⁹¹ sodium picosulphate/magnesium citrate^{95–98} and a low dose combination of sodium picosulphate, senna and PEG.⁹³ The mannitol study⁹⁴ used double the standard dose of NaP, whereas one of the picosulphate studies⁹⁵ only left 5 h between NaP doses. As this goes against safe-dosage guidance, they have not been included in the quantitative meta-analysis.

If the remaining studies are pooled, there is no significant difference demonstrated between comparators.

Effect: OR = 1.24; 95% CI = 0.36–4.24; $P = 0.73$

Heterogeneity: $Q = 89.7$; $I^2 = 93.3\%$; $P < 0.0001$

If the analysis is limited purely to those studies carried out vs. full dose sodium picosulphate containing regimens, the trend remains the same, with no significant difference demonstrated.

Effect: OR = 1.12; 95% CI = 0.34–3.74; $P = 0.77$

Heterogeneity: $Q = 8.8$; $I^2 = 77.2\%$; $P = 0.01$

Group 6 - other comparators. The remaining studies identified by the literature search^{100–112} compared a wide range of differing bowel preparation regimes – generally using bespoke combinations of PEG, NaP, senna, sodium picosulphate or prokinetic agents. Variations in study design and the lack of a constant comparator would make it unhelpful to list the results of these studies, none of which demonstrated any unexpected benefit for one treatment strategy over another.

Additional analyses

The protocol proposed analyses to assess the impact of dietary restriction, baseline body mass index and baseline constipation status on the relative performance of different bowel cleansing regimens.

Assessment of the evidence base on completion of the literature search showed that there was insufficient information presented in the identified studies to allow meaningful answers to these questions. These analyses were therefore omitted.

DISCUSSION

There is an extensive evidence base relating to bowel preparation for colonoscopy, particularly in regard to comparisons between PEG-based and NaP-based regimens. Although the quality of the studies is not high, they are not so flawed as to preclude drawing broad conclusions. Of the studies identified in the current review, 54 also appeared in our previously published systematic review,⁷ which covered publications up to January 2006. Of the 50 new studies included in this analysis, 31 had been published since January 2006, with the remainder reflecting more comprehensive inclusion criteria. Interestingly, despite these differences between these datasets, and the more robust PRISMA methodology adopted in the current review, the overall results of the two are consistent with each other.

This is particularly notable for the PEG vs. NaP comparison in which, as previously, we have confirmed that no overall significant difference between the two regimens can be demonstrated on the basis of published

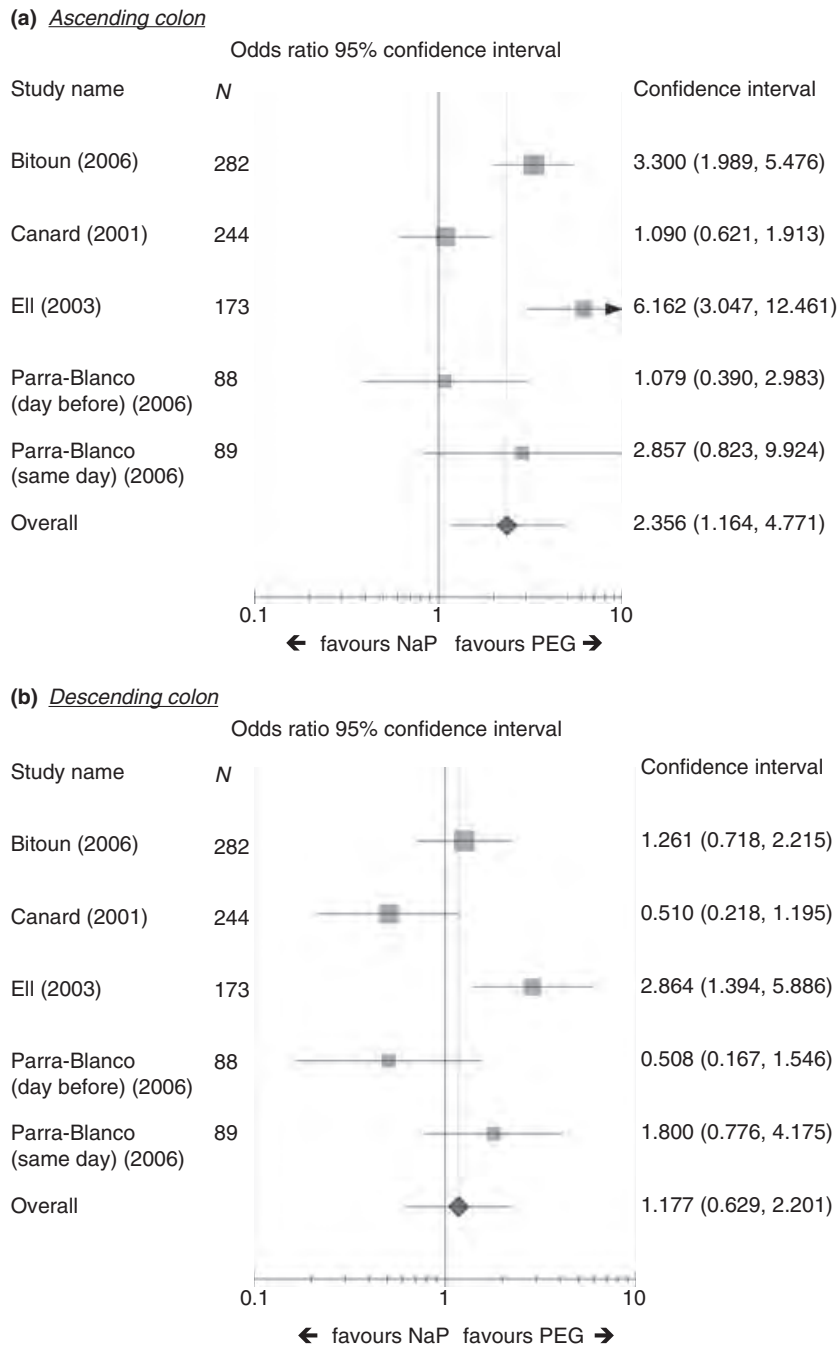


Figure 5 | Random effects pooling of efficacy assessments for PEG vs. NaP (excellent/good vs. all other outcomes). (a) Ascending colon. (b) Descending colon. PEG, polyethylene glycol; NaP, sodium phosphates.

reports. The finding of an odds ratio of 0.82 (0.56–1.21) for dose compliant studies and 0.88 (0.64–1.21) for all published studies being consistent with our previous result of 0.94 (0.64–1.39). The cumulative meta-analysis that we have carried out demonstrates that the large number studies published since 2006 yield results that are entirely consistent with the earlier studies.

However, a significant problem with this data set is that, in these studies, treatment regimens have not been well-matched, with split doses of NaP and single doses of PEG commonly being compared. This, combined with the lack of blinding in most studies, means that the overall conclusion is likely to be subject to bias. Indeed, when the analysis is restricted to those studies where similar

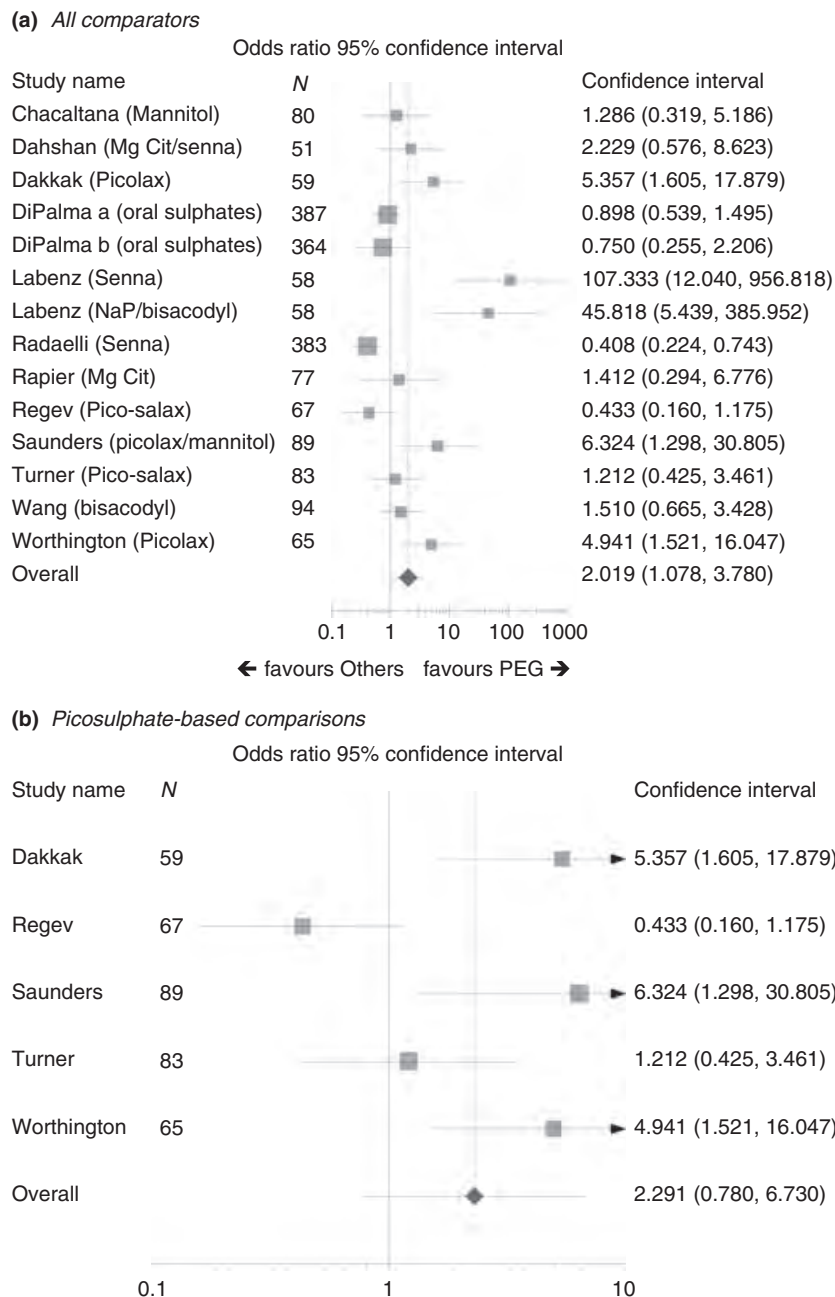


Figure 6 | Random effects pooling of efficacy assessments for polyethylene glycol (PEG) vs. other agents (excellent/good vs. all other outcomes). (a) All comparators. (b) Picosulphate-based comparisons.

dosage schemes were used, PEG is shown to be significantly more effective than NaP when day-before dosing was used for both treatments, but not for the split dosing with nocturnal pause regimen. In addition, when the analysis is restricted to studies where segmental cleansing was assessed, regardless of intake regimen, PEG is found to be superior to NaP in the proximal colon.

With regard to other comparisons, PEG was significantly more effective than all other non-NaP bowel

cleansing regimens. Similar assessment of NaP vs. other comparators showed no significant difference. Given the differences in comparators and the relatively poor study quality, the quantitative results of this group of comparisons should be treated with caution.

An apparent benefit of PEG vs. sodium picosulphate does not reach statistical significance due to insufficient patient numbers; as a result no clear conclusions can be drawn from this comparison. Similarly, there was no

significant benefit demonstrated for NaP vs. sodium picosulphate.

Studies comparing different regimens with the same base-laxative were inconclusive, owing to major differences in study design and treatment types preventing meaningful meta-analysis. Thus, we are unable to give a clear answer as to whether there is a difference in effect between different volumes of PEG, or different formulations of NaP. Equally, we could not determine whether the co-prescription prokinetic agents offered any advantages over PEG or NaP prescribed alone.

STUDY LIMITATIONS

The limitations of this review essentially relate to the limitations of the component studies themselves.

Studies are generally small and have almost exclusively been carried out in single centres. Most are explicitly unblinded to all participants except the endoscopist and few give any details to allow appraisal of the potential for bias in the randomisation process. Assessment of outcome was inevitably subjective and only a few studies used independent third parties to evaluate treatment efficacy.^{11, 53}

Only a minority of studies used validated tools to determine the quality of bowel preparation. The latter point is a potentially serious concern with regard to the outcomes and will not be immediately apparent in the normal assessment of heterogeneity. As an example in the comparison of PEG and NaP, at one extreme one study showed satisfactory efficacy for 25% of NaP patients vs. 67% of PEG patients¹⁶ whilst another showed 94% vs. 97% respectively.¹⁷ It seems unlikely that the patient populations varied sufficiently to justify these differences – it is far more likely that between-assessor differences underlie these conclusions.

FUTURE RESEARCH RECOMMENDATIONS

Generic single-centre studies comparing one regimen with another are unlikely to further our understanding of this clinical area. Future studies should be targeted at answering specific questions, such as the impact of dose-volume on the efficacy of PEG, the role of patient clinical characteristics on treatment outcome, or the benefit of differing levels of dietary restriction. The latter point has been little investigated, although a study published after this review had been completed suggested that the quality of bowel prep is directly related to dietary residue in the pre-preparatory phase.¹¹⁴

Attention is also merited to the appropriateness of the outcome measure used. In future trials, new study end-

points such as the caecal intubation rate or the polyp detection rate should be taken into consideration, as these may more adequately mirror the quality of colonoscopy, rather than subjective endoscopist assessment.

Finally, specific attention also should be given to improving the quality of studies in the field, including attention to randomisation and blinding methods, ensuring the equivalence of treatment protocols, use of validated assessment tools and third-party validation of results.

CONCLUSIONS

Overall with reference to efficacy outcome measures, there is no compelling evidence to suggest that either of the most commonly used bowel preparation regimens are significantly more effective than the other, although there is evidence that PEG is better than non-NaP alternatives and in some administration regimens better than NaP. However, of greater importance for bowel cancer screening programmes is the finding that when segmental cleansing assessments have been undertaken, PEG has been found to give superior cleansing to NaP in the proximal colon. In addition, in determining the optimal choice for patients, assessment of the risk-benefit balance will tend to hinge more on safety issues than any perceived difference in treatment efficacy. Several studies^{4, 115, 116} have now drawn attention to the risk of occurrence of significant adverse events with NaP, even in otherwise healthy patients, which whilst the symptoms may not present immediately, do raise questions for the future health of patients which have already resulted in some regulators taking actions to limit⁵ or prohibit¹¹⁷ their use as bowel cleansing agents.

In conclusion, whilst limitations in study design mean that statistically robust studies are relatively few, the overall risk benefit balance suggest that PEG-based regimens offer the optimum choice for bowel preparation, with lower volume PEG regimens potentially offering better patient acceptability.

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