

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Bowel preparation for elective procedures in Children: A Systematic Review and meta-analysis
AUTHORS	Gordon, Morris; Karlsen, Fiona; Isaji, Sahira; Ong, Teck Guan

VERSION 1 - REVIEW

REVIEWER	Davila-Perez, Roberto Hospital Infantil de Mexico Federico Gomez CD. de Mexico, Mexico Competing interests: Pediatric Colorectal Surgery, Prehepatic Portal Hypertension Surgery, Pediatric Liver and Kidney Transplant Surgery, Neonatal Surgery
REVIEW RETURNED	20-Jun-2017

GENERAL COMMENTS	<p>It is a very interesting and difficult study, it is very heterogeneous because of in pediatric practice the bowel preparation is very heterogeneous.</p> <p>Authors do not consider the elective colonic surgery without preparation, that is a confirmed practice in pediatric colorectal departments in developed countries (USA and UK) and I think that it is important to be consider in discussion.</p> <p>Authors include a lot of bowel preparation protocols (heterogenous) and they have unclear results (evidence). I think that it could be better understood if they report the results about PEG vs others in one paper and another for the other preparation protocols if they want.</p> <p>I think it is important to consider the age of the patients treated in each study, because I am sure that the PEG studies include younger patients because of the statistic significance difference about the need to use NGT in this group of patients vs other. And it is well known that patients less than 6 years old need the NGT to the PEG preparation and it is not mentioned in the paper. I don't know if there were statistical difference between the compared groups about age.</p> <p>It is a very good systematic review, that you a lot for considering me to review the paper</p>
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REVIEWER	Saxena, Romit Great Ormond Street Hospital for Children, London, United Kingdom Competing interests: none
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	<p>Rationale :Good</p> <p>Methods:</p> <p>1.Its good that authors have mentioned that they had a predefined protocol, which will minimize outcome reporting bias. It would help if they could elaborate a bit more on the content of their protocol.</p>
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	<p>2. Was there any exclusion criterion for the study .</p> <p>3. Adequate bowel preparation: authors have mentioned that primary outcome was as defined by primary studies. It is great that they have acknowledged shortcomings on the prevalent literature and study . It would help if they could elaborate on the prevalent definition or scoring system was used by majority of the studies (at least the major ones, taking into account publication bias) to define a successful bowel preparation . Also, if they could advise what were the major points , it could help the future researchers about to embark on similar studies, who might face the same problems the authors faced.</p> <p>4. Similar problems with tolerability , though authors have acknowledged the limitations, with regards to the acceptable standards. Since clearly , the tolerance of a 1 year old and that of a 16 year old, will have different markers. It would help if authors could consider including, what were the most common or predominant scoring systems (age wise) that they had used. It will help in giving direction to future researchers.</p> <p>5 . In "Search methods for identification of studies": Well collaborated with PRISMA flow diagram , but please advise with regards to the following</p> <p>a. Please advise the readers, what were the dates of coverage, in each database. It is specified in appendix for EMBASE. It would help if it could be included in methods section.</p> <p>b. Please also mention, when the data was last searched in the databases.</p> <p>c. The research from literature from references of included trials, though it is not the primary mode of analysis, could be prone to citation or publication bias.</p> <p>6. It would help if the authors could advise what was the level of inter-rater agreement. And in what percentage of the trials, a 3rd expert's opinion had to be sought.</p>
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REVIEWER	<p>Nevitt, Sarah University of Liverpool United Kingdom Competing interests: I have no competing interests</p>
REVIEW RETURNED	11-Jul-2017

GENERAL COMMENTS	<p>I have performed a statistical review of the manuscript 'Bowel preparation for elective procedures in Children: A Systematic Review.'</p> <p>The authors present a synthesis to address a clinical question which seems to be well researched in adults and less well researched in children. I have made some comments on the content of this manuscript, as well as a few minor comments on the wording.</p> <p>1) I would suggest editing the title to 'A systematic review and meta-analysis' to better reflect the content</p> <p>2) Out of interest, as the authors have used Cochrane methodology to perform this review, did you consider registering this as a Cochrane Review?</p> <p>3) Outcomes: you define secondary outcomes of tolerability and occurrence of any adverse events. Often tolerability and adverse events are interchangeable terms so it would be helpful to add some further definition in this context – i.e. I assume here that tolerability means the child has tolerated the preparation and the</p>
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	<p>procedure has been able to go ahead rather than they have 'tolerated' the preparation with the meaning that they have had no adverse events?</p> <p>4) Primary outcome: it is stated that the primary outcome will be measured by mean difference yet risk ratios are presented in the results (and the definition of this outcome seems to be a dichotomous, adequate bowel preparation - yes or no)</p> <p>5) Primary outcome: 'Adequate' is defined by the studies, is there any validated method, guidelines etc. in this field for defining adequate or could this vary across studies? If there is variation then this is another source of clinical heterogeneity which makes any synthesis or comparison of the evidence difficult. This could be another point for the discussion</p> <p>6) Methods: Please add how I-squared is interpreted. For example is a certain cut off value used to identify whether important heterogeneity is present in analysis?</p> <p>7) Methods, page 6, line 34-35: 'A random-effects model was used, with a sensitivity analysis with the fixed-effects model, to identify differences in results that would suggest heterogeneity.' I do not recommend this type of sensitivity analysis as a method of identifying heterogeneity. If there is even a tiny amount of heterogeneity, results will be different but this does not mean that the heterogeneity is important. I would recommend comparison of study characteristics to identify clinical heterogeneity (the authors have done this) and also visual inspection of forest plots for study specific results clear going in different directions and guidance from the I-squared statistic to judge whether heterogeneity is present and whether it is important.</p> <p>8) There is a lot of heterogeneity present in Figure 2 (PEG vs Sennasoids) and Figure 6 (PEG vs Sodium Phosphate). I appreciate that the authors have used random-effects but this does not take away the heterogeneity. Please note in the results sections of the main paper and the abstract that there is a lot of statistical heterogeneity present in some results. I would also recommending thinking about why that might be – e.g. any variations in the characteristics or the populations of the pooled studies, perhaps variation in the definition of 'adequate'?</p> <p>9) Other studies: Although no meta-analysis was possible, for completeness, please present the results of these studies in an additional table. For example, the numbers in each treatment group with adequate bowel preparations, adverse events etc.</p> <p>Minor wording comments:</p> <p>Background, line 43-46: '...despite it being normal practice for paediatric gastroenterologists over several years to adult services.' I don't think this sentence makes sense, something is missing here.</p> <p>Methods, line 8: 'local stakeholders...' Please clarify who you mean by 'stakeholders,' paediatric gastroenterologists?</p> <p>Search methods, line 34-35: MEDLINE is in here twice</p> <p>Results, Description of studies: Perhaps have a separate heading for the excluded studies and then summarise the included studies. Otherwise this section is a bit confusing</p> <p>Results, Description of studies, line 30: 'two diet kits with sodium phosphate,' what is the comparison here? One diet kit versus the</p>
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	other?
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

It is a very interesting and difficult study, it is very heterogeneous because of in pediatric practice the bowel preparation is very heterogeneous.

- Indeed this is a key finding.

Authors do not consider the elective colonic surgery without preparation, that is a confirmed practice in pediatric colorectal departments in developed countries (USA and UK) and I think that it is important to be consider in discussion.

- This is an interesting point and a citation has been added mentioning this point.

Authors include a lot of bowel preparation protocols (heterogenous) and they have unclear results (evidence). I think that it could be better understood if they report the results about PEG vs others in one paper and another for the other preparation protocols if they want.

- This is also an interesting point, but I don't think is the right way to go. There seems to be an assumption or presumption in this statement that PEG is the gold standard or current default and from the studies or international guidance statements, I don't think that is the case and as such to separate in this way would introduce a bias. Rather, the point the reviewer first made regarding the heterogeneity of the evidence is key and would be lost in such a divide so we would propose to not action this point.

I think it is important to consider the age of the patients treated in each study, because I am sure that the PEG studies include younger patients because of the statistic significance difference about the need to use NGT in this group of patients vs other. And it is well known that patients less than 6 years old need the NGT to the PEG preparation and it is not mentioned in the paper. I don't know if there were statistical difference between the compared groups about age.

- This is an interesting point and why the age data is presented in table 1. Unfortunately, the primary papers do not include such subgroup analysis data and as such we cannot complete such an analysis, but have now mentioned this point in the discussion.

It is a very good systematic review, that you a lot for considering me to review the paper.

-Thank you

Reviewer: 2

Rationale :Good

Methods:

1.Its good that authors have mentioned that they had a predefined protocol, which will minimize outcome reporting bias. It would help if they could elaborate a bit more on the content of their protocol.

-This has been done

2. Was there any exclusion criterion for the study .

- Yes, this has been clarified in the methods

3. Adequate bowel preparation: authors have mentioned that primary outcome was as defined by primary studies. It is great that they have acknowledged shortcomings on the prevalent literature and study . It would help if they could elaborate on the prevalent definition or scoring system was used by majority of the studies(atleast the major ones, taking into account publication bias) to define a successful bowel preparation . Also, if they could advise what were the major points , it could help the future researchers about to embark on similar studies, who might face the same problems the authors faced.

- This is a very fair point and part of the problem. No single scoring system was used for all, but the Ottawa system the most reported. This has been mentioned in the discussion

4. Similar problems with tolerability , though authors have acknowledged the limitations, with regards to the acceptable standards. Since clearly , the tolerance of a 1 year old and that of a 16 year old, will have different markers. It would help if authors could consider including, what were the most common or predominant scoring systems(age wise) that they had used. It will help in giving direction to future researchers.

- As per the previous reviewer, limitations of primary study data means we can't comment much on this, but it is a key issue and a weakness of the literature we have now commented on.

5 . In "Search methods for identification of studies": Well collaborated with PRISMA flow diagram , but please advise with regards to the following a. Please advise the readers, what were the dates of coverage, in each database. It is specified in appendix for EMBASE. It would help if it could be included in methods section.

-As this was from inception of each database, we have not individually commented. If there was a limitation included, we would state this, but as this is not the case we haven't added this to the text and simply stated from inception, with the end date clearly stated. We hope this is acceptable.

b. Please also mention, when the data was last searched in the databases.

- This is the methods as 15th July 2016.

c. The research from literature from references of included trials, though it is not the primary mode of analysis, could be prone to citation or publication bias.

- Agreed, but as this is a standard inclusion on all Cochrane protocols we have followed this method.

6. It would help if the authors could advise what was the level of inter-rater agreement. And in what percentage of the trials, a 3rd expert's opinion had to be sought.

- This has been added.

Reviewer: 3

Comments to the Author

I have performed a statistical review of the manuscript 'Bowel preparation for elective procedures in Children: A Systematic Review.'

The authors present a synthesis to address a clinical question which seems to be well researched in adults and less well researched in children. I have made some comments on the content of this manuscript, as well as a few minor comments on the wording.

- 1) I would suggest editing the title to 'A systematic review and meta-analysis' to better reflect the content.
-Agreed and done
- 2) Out of interest, as the authors have used Cochrane methodology to perform this review, did you consider registering this as a Cochrane Review?

- Yes, but given the complexity of the results and the relatively low quality of the evidence this was not taken further. In the future when more studies are published, we would intend to complete this under the Cochrane IBD group for which I edit.
- 3) Outcomes: you define secondary outcomes of tolerability and occurrence of any adverse events. Often tolerability and adverse events are interchangeable terms so it would be helpful to add some further definition in this context – i.e. I assume here that tolerability means the child has tolerated the preparation and the procedure has been able to go ahead rather than they have 'tolerated' the preparation with the meaning that they have had no adverse events?

- Agreed and clarified, as this is a key issue in this review.
- 4) Primary outcome: it is stated that the primary outcome will be measured by mean difference yet risk ratios are presented in the results (and the definition of this outcome seems to be a dichotomous, adequate bowel preparation - yes or no)

- This was a typo and had been corrected
- 5) Primary outcome: 'Adequate' is defined by the studies, is there any validated method, guidelines etc. in this field for defining adequate or could this vary across studies? If there is variation then this is another source of clinical heterogeneity which makes any synthesis or comparison of the evidence difficult. This could be another point for the discussion

- This links to the previous reviewer and the mention of many scoring systems and we have now cited the Ottawa system used by some of the papers.
- 6) Methods: Please add how I-squared is interpreted. For example is a certain cut off value used to identify whether important heterogeneity is present in analysis?

- This has been added.
- 7) Methods, page 6, line 34-35: 'A random-effects model was used, with a sensitivity analysis with the fixed-effects model, to identify differences in results that would suggest heterogeneity.' I do not recommend this type of sensitivity analysis as a method of identifying heterogeneity. If there is even a tiny amount of heterogeneity, results will be different but this does not mean that the heterogeneity is important. I would recommend comparison of study characteristics to identify clinical heterogeneity (the authors have done this) and also visual inspection of forest plots for study specific results clear going in different directions and guidance from the I-squared statistic to judge whether heterogeneity is present and whether it is important.

- This is an interesting point, as in a recent publication in the archives of diseases in childhood (racecadotril for acute diarrhoea in children) which I authored, we had done just as the reviewer suggested and peer review suggested we do the opposite and use the random and fixed model in this

was, as we have done. It is also what the Cochrane IBD group now propose, although these are not necessarily mutually exclusive methods and as the reviewer states, we have considered clinical. Given this, can I propose we leave as it is and if the editor wishes us to revise after considering our response, please let us know.

8) There is a lot of heterogeneity present in Figure 2 (PEG vs Sennasoids) and Figure 6 (PEG vs Sodium Phosphate). I appreciate that the authors have used random-effects but this does not take away the heterogeneity. Please note in the results sections of the main paper and the abstract that there is a lot of statistical heterogeneity present in some results. I would also recommending thinking about why that might be – e.g. any variations in the characteristics or the populations of the pooled studies, perhaps variation in the definition of ‘adequate’?

- This is a fair point, but I think in the discussion, particularly with the addition of several of the responses to the reviewers, this has been addressed and the limitations of the data highlighted. This has also now been made more specifically clear in the discussion.

9) Other studies: Although no meta-analysis was possible, for completeness, please present the results of these studies in an additional table. For example, the numbers in each treatment group with adequate bowel preparations, adverse events etc.

- This is a major weakness of the primary studies. This data is simply not been presented In most studies in any meaningful way that can be presented. Whilst in the context of a Cochrane review with no word count guidance, we would add in detail, we feel in this journal article such data, when of such low quality to the reader, will not add much. Again, if the editor feels this is not the case please let us know.

Minor wording comments:

Background, line 43-46: ‘...despite it being normal practice for paediatric gastroenterologists over several years to adult services.’ I don’t think this sentence makes sense, something is missing here.

- This has been clarified as it was regarding transition to adults and was a typo.

Methods, line 8: ‘local stakeholders...’ Please clarify who you mean by ‘stakeholders,’ paediatric gastroenterologists?

- This has been clarified as tertiary centres

Search methods, line 34-35: MEDLINE is in here twice

- This has been removed.

Results, Description of studies: Perhaps have a separate heading for the excluded studies and then summarise the included studies. Otherwise this section is a bit confusing

This has been done

Results, Description of studies, line 30: ‘two diet kits with sodium phosphate,’ what is the comparison here? One diet kit versus the other?

Yes