

## Peer Review File

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### Reviewer A

Accurate bowel cleansing and patient acceptability of bowel preparation are the two pillars of quality for colonoscopy. The ideal preparation for colonoscopy should clean the colon, with no alteration of colonic mucosa and without causing patient discomfort or shifts in fluids, as well as electrolytes.

High quality bowel cleansing is obtained using high-volume (4 L) solutions of Polyethylene Glycol (PEG). However, some patients do not complete the bowel preparation with this solution because of its large volume. Therefore, low-volume (2 L) PEG solutions have been formulated to provide a more tolerable bowel preparation with similar efficacy.

In the current meta-analysis the authors evaluated both safety and efficacy of the high volume PEG solution in comparison to low-volume PEG mixed solutions used for bowel preparation before colonoscopy. Their results showed that high volume PEG solution appears to be superior to low volume PEG solutions in terms of bowel cleanliness, but is less tolerated by the patients, even if it is administered with the split regimen.

These results confirm those of two previously published meta-analyses (Martel M, Barkun AN, Menard C et al. Split-dose preparations are superior to day-before bowel cleansing regimens: a meta-analysis. *Gastroenterology* 2015; 149: 79 – 88; Enestvedt BK, Tofani C, Laine LA et al. 4-Liter split-dose polyethylene glycol is superior to other bowel preparations, based on systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2012; 10: 1225 – 1231)

### COMMENTS

- A recent RCT compared one-liter PEG ASC solution with 4L-PEG solution showing non-inferiority of the very low volume solution in achieving adequate colon cleansing with better patient compliance (Repici A, Spada C, Cannizzaro R, et al. Novel 1-L polyethylene glycol + ascorbate versus high-volume polyethylene glycol regimen for colonoscopy cleansing: a multicenter, randomized, phase IV study. *Gastrointest Endosc* 2021;94(4):823–31 Octe9Epub 2021 Apr 30. PMID: 33940043. doi: 10.1016/j. gie.2021.04.020). This RCT has not been included in the meta-analysis: why?

Reply: Thank you for your comment. This Clinical Trial article did not obtain the original text, and we have tried other methods, but still did not obtain the necessary data.

Changes in the text: None

- In the discussion, the authors state that “previous studies have found that there were no difference in the bowel cleansing pass rates between the two groups [i.e. low-volume (2 L) PEG

mixed solution group and the high-volume (4 L) PEG group] (8, 14). This statement requires further comments and perhaps the above mentioned meta-analyses should be cited and discussed.

Reply: Thank you for your comment. Further comments and the above mentioned meta-analyses has been added and cited.

Changes in the text: Paragraph 2/Discussion

- At the end of the discussion, a clear conclusion is missing.

Reply: Thank you for your comment. The conclusion has been added.

Changes in the text: Paragraph 1/ conclusion

- In table 1, the information in the "Split dose low volume" column should be better clarified (i.e. it is difficult to understand if some of the solutions have been administered in a split dose).

Reply: Thank you for your comment. To avoid misunderstandings, we have changed 'Split dose low volume' to 'low volume'.

Changes in the text: table 1

## **Reviewer B**

This is important topic, but this MA seems to have lots of issues. I am listing the major issues for example:

- "The meta-analysis showed that the high-volume PEG group had a higher intestinal cleanliness score than 4 the low-volume PEG mixed solution group (MD = 0.19, 95% CI [-0.31, 0.70], P < 0.01), and the difference was statistically significant" 95% CI crosses 0 difference. How could this be significant? Same issue with other CIs, which are significant, but p values are not. Please see the forest plots which cross 0 or 1

Reply: Thank you for your comment. Sorry for this mistake. All figures have been re reviewed and modified.

Changes in the text: Paragraph 3-9 / Results.

- How were Ottawa and Boston score results combined? They are opposite of each other i.e. Higher Boston means better cleansing. Higher Ottawa score means worse cleansing.

Reply: Thank you for your comment. We reanalyzed these data and converted both Ottawa and Boston scoring systems into standardized scores. The magnitude of this score represents the degree of deviation from the overall average, while the direction represents the quality of cleanliness.

Changes in the text: Paragraph 4/ Methods

- What is the value of difference in score of 8 or 9 on Boston scale? Using cut-off of adequate or inadequate is much more relevant.

Reply: Thank you for your comment. We reanalyzed these data and converted both Ottawa and Boston scoring systems into standardized scores. The magnitude of this score represents the

degree of deviation from the overall average, while the direction represents the quality of cleanliness.

Changes in the text: Paragraph 4/ Methods

- 3 + 1 of 4 liters is inadequate splitting and should not be included. Similarly, Simethicone is not a cleansing agent.

Reply: Thank you for your comment. The focus of this article is not on the splitting method, but on the high-volume method using a total dose of 4L. We believe that the splitting method does not affect the distinction between high and low volume, and regarding Simethicone as not a cleaning agent, we have also reviewed the original text, which should be 2L PEG+Asc. This is a writing error and has been corrected.

Changes in the text: Paragraph 4/ table 1

- It is not clear if only split low volume were used and how low volume was administered split.

Reply: Thank you for your comment. The high and low volume we focus on are only differences in the medication regimen for fractional administration, and are not the final measurement differences.

Changes in the text: None

### **Reviewer C**

The authors present a meta analysis on different bowel preparations for colonoscopy comparing their tolerance and effectiveness overall. They conducted a thorough literature review overall and scanned through more than 2000 studies. This must be commended.

However, the data presented are not novel, and have been published before in multiple meta analysis as well as in individual reviews and randomized trials. The conclusions also, are established norms with poor tolerance of large volume PEG solutions in comparison to low volume solutions. Suggestions to improve would include adding tablet based solutions and miralax gatorade based solutions and also stratify based on patient population ( normal population vs patients at high likelihood of inadequate bowel preparation).

Reply: Thank you for your detailed review and feedback. We agree with your viewpoint that similar data and conclusions have indeed been published in multiple meta-analyses, personal reviews, and randomized trials. Our research objective is mainly to further validate and consolidate existing research conclusions. In future research, we will consider exploring and incorporating these new treatment methods, and attempt to conduct more detailed stratification based on the patient population.

Changes in the text: None

### **Reviewer D**

- 1) First, the title needs to directly indicate the comparison between high- and low-volume PEG.

Reply: Thank you for your comment. We have revised the title according to your suggestion.

Changes in the text: Title

- 2) Second, the abstract is not standardized and needs further revisions. The background did not describe the controversy regarding the cleanliness between high- and low-volume PEG and did not analyze why a meta-analysis is suitable to address this controversy. In the methods, the authors need to describe the inclusion criteria of eligible studies, data extraction, and the specific tool for assessing the risk of bias of included studies. The results need to first summarize the total sample and risk of bias of include studies. The conclusion needs to have comments for the clinical implications of the findings, not to repeating them again.

Reply: Thank you for your comment. We have revised the abstract according to your suggestion.

Changes in the text: Paragraph1-4/ Abstract

- 3) Third, the introduction of the main text is bad. The authors did not describe the controversy regarding the efficacy of high- and low-volume PEG for cleanliness by using detailed examples, did not analyze the potential reasons underlying the controversy, and did not explain why a meta-analysis is suitable to address this controversy.

Reply: Thank you for your comment. We have revised the introduction according to your suggestion.

Changes in the text: Paragraph1/introduction

- 4) Fourth, in the methodology of the main text, searching literature within the three databases is not adequate. The authors also need to update the literature search when submitting the revised version. The authors need to reconsider whether it is appropriate to limit the studies to be included as “high-quality” studies and what the corresponding criteria for “high-quality” are. The tool for assessing the risk of bias is not the Cochrane manual, the authors need to describe the specific tool and describe the details of high and low risk of bias. In statistics, please describe P value for statistical significance, test of sources of heterogeneity, and test of publication bias.

Reply: Thank you for your comment. We searched some other databases, such as OVID, web of science, and gallery library, but did not find any more literature to include. The description of risk bias evaluation tools and statistical descriptions have been added.

Changes in the text: Paragraph 4,5/ Methods

Finally, some potentially interesting and related papers need to be cited for this manuscript:

1. Agrawal R, Majeed M, Attar BM, Flores E, Haque Z, Ba Aqeel S, Wang Y, Omar YA, Parajuli P, Demetria M, Gandhi S. Predictors of poor bowel preparations and colonoscopy cancellations in inpatient colonoscopies, a single center retrospective study. *Transl Gastroenterol Hepatol* 2022;7:4. 2. Yu H, Xu L, Yin S, Hong C, Yang S, Chen J, Li J, Wu W, Zhang C. A Chinese survey of current practice patterns of preoperative bowel preparation

in colorectal surgery. Dig Med Res 2022;5:22.

Reply: Thank you for your comment. Relevant literature has been added and cited.

Changes in the text: Paragraph1/introduction; Paragraph 1/Discussion

## Reviewer E

1. According to Item 1 in PRISMA checklist, you should indicate “systematic review” in the manuscript title, therefore please revise your title to “*The safety and effects of high- and low-volume PEG bowel preparation methods before colonoscopy on bowel cleanliness: a **systematic review and meta-analysis***”.

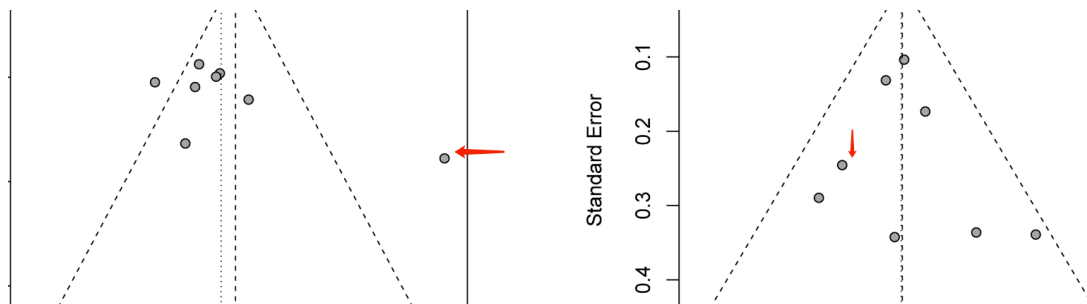
Reply: We have added it. Thanks.

2. Please provide the academic degree (use abbreviation) for the corresponding author.

Correspondence to: Xiaojuan Fang. Digestive Department, Zhejiang Hospital, No. 12 Lingyin Road, Hangzhou 310013, China. Email: 631301120335@mails.cqjtu.edu.cn. ↵

Reply: We have added it. Thanks.

3. Figure 10: Please define those grey circles either inside the figure or in figure legends.



Reply: We have added it. Thanks.