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Comparative efficacy of low volume versus traditional standard volume PEG on bowel preparation before colonoscopy
Protocol for an updated meta-analysis with trial sequential analysis

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Abstract

Introduction: Polyethylene glycol (PEG) has been considered as the first recommendation for bowel preparation prior to colonoscopy. A previous meta-analysis suggested that low volume PEG may improve the acceptability of ingesting bowel preparation solution. However, several limitations impaired the power of findings from this published meta-analysis, such as the variation in study design of included trials and adjuvant prescriptions. Moreover, some studies related to this topic have been published recently. And thus, the aim of this updated meta-analysis is to further assess the comparative efficacy of low volume versus standard volume of PEG on bowel preparation before colonoscopy with trial sequential analysis (TSA).

Methods and analysis: Systematic searches will be performed to capture any potential randomized controlled trials (RCTs) investigated the comparative efficacy of low volume versus traditional standard volume PEG on bowel preparation prior to colonoscopy in PubMed, EMBASE, and Cochrane Central Register of Controlled Trials. Moreover, we will also manually check the bibliographies of related studies and reviews so as to get additional studies. Two reviewers will independently screen the citation records, extract essential information, and appraise the risk of bias of each RCT in sequence. Finally, we will used the STATA software version 12.0 and TSA software version beta 0.9 to statistically analyze all data and test the robust of each pooled result, respectively.

Results: We will submit the full-text of systematic review to a peer-review journal for publication.

Conclusion: This updated systematic review and meta-analysis with TSA will further assess the comparative efficacy and safety of low-volume versus traditional standard volume PEG for bowel preparation prior to colonoscopy. And then, a more comprehensive evidence body on low-volume compared to standard volume PEG in bowel preparation will be constructed.

Abbreviations: Asc = ascorbic acid, PEG = polyethylene glycol, RCT = randomized controlled trial.

Keywords: bowel preparation, colonoscopy, meta-analysis, polyethylene glycol, trial sequential analysis

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Strengths and limitations of this study

- The systematic review and meta-analysis addresses a critical question whether low volume PEG plus ascorbic acid compared to traditional standard volume should be recommended as a preferred option for the bowel preparation before colonoscopy.
- The systematic review and meta-analysis has a clearly defined aim and a strict inclusion criterion. Meanwhile, it describes how to screen citation records, extract data, assessment of the risk of bias, quantitative synthesis, and trial sequential analysis.
- The present systematic review and meta-analysis will design a table to comprehensively document all results from the published and the present meta-analyses.
- A series of established methods will be designed to improve the reliability of the pooled results through rationally addressing heterogeneity and the risk of bias.
- Limitations include the variation in directions (eg, split or single, morning, or afternoon colonoscopy) and tools of assessing bowel preparation efficacy, which may affect the comparison results.

1. Introduction

Colonoscopy has been deemed to be the critical method of early diagnosing lesions in digestive tract, screening colorectal cancer as well as invasive treatment.[1,2] Nevertheless, it must be noted that the efficacy and safety of colonoscopy are mainly dependent upon adequate bowel preparation and patient attendance.[3–5] In practice, large volume of preparation solutions will be administered to patients who are assigned to receive colonoscopy. However, it is estimated that approximately 25% to 33% patients failed to achieve the adequate bowel preparations, because the patients are intolerant to volume-related discomfort.[6,7] Published evidences suggested that inadequate bowel preparation are associated with lower rates of cecal intubation,[8] higher operational difficulty,[9] lower adenoma detection rates, and greater financial costs.[10–12]

Polyethylene glycol (PEG) remains the first recommended regimen for bowel cleansing prior to colonoscopy.[13,14] However, in order to obtain adequate bowel cleaning, patients will be instructed to digest 4 L PEG, and thus the acceptance and compliance with this given regime will be weakened.[15,16] In addition, these limitations also decreased the courage of patients to participate in the regular colonoscopy surveillance.[17,18] Considering the limitations of traditional high volume PEG regime, researchers and practitioners turned attention to modified options, and several studies have found that low volume PEG combined with ascorbic acid (Asc) may have the potential of addressing the issues faced by traditional PEG regime.[19–21] Asc is helpful because it can allow halving the volume of the lavage solution without the loss of efficacy and disgusting taste.[22,23] Several randomized controlled trials (RCTs)[24–26] have consistently shown that low volume PEG plus Asc regime achieved similar efficacy compared to standard volume one. Similarly, the findings from a previous meta-analysis[27] is in accordance with aforementioned studies. However, this meta-analysis considered a quasi-randomized trial[28] and ignored the variation in adjuvants (Bisacodyl and Simethicone),[29,30] which potentially damaged the power of summary results.
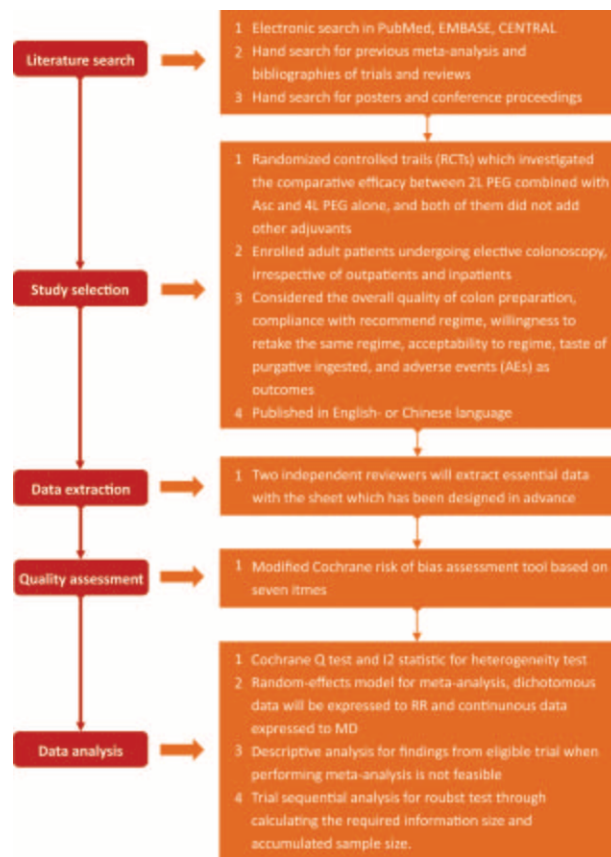
Figure 1. Flow chart of this updated systematic review and meta-analysis. AE = adverse event, Asc = ascorbic acid, CENTRAL = Cochrane Central Register of Controlled Trials, MD = mean difference, PEG = polyethylene glycol, RCT = randomized controlled trial, RR = relative risk, TSA = trial sequential analysis.

Considering the above information, we designed this updated meta-analysis to comprehensively investigate the comparative efficacy of low volume PEG plus Asc related to traditional volume PEG alone for bowel preparation before colonoscopy. In order to test whether a conclusive conclusion for a specific outcome can be drawn, we will also perform trial sequential analysis to calculate the accumulated sample size and required information size associated with all outcomes in our study. We designed this systematic review on January 20, 2018, and we expected to complete this study on May 20, 2018.

2. Methods and design

We designed and finished this protocol for a meta-analysis in line with the Preferred Reporting Items for Systematic Reviews and meta-analysis protocols 2015: elaboration and explanation.[31] This protocol has been registered in International Prospective Register of Systematic Reviews and a register number of CRD42018089827 was approved. We will carry out the full systematic review and meta-analysis in consistent with the recommendations proposed by Cochrane Collaboration.[32] What is more, all results will be reported according to the Preferred Reporting Items for Systematic Reviews and meta-analysis statement.[31] The written informed consent will not be needed, because all analyses will be completed based on published data. The Fig. 1 shows the flow chat of this ipdated systematic review and meta-analysis.

2.1. Selection criteria

We prespecified the inclusion criteria. Study will be considered if the following criteria are met: all adult patients undergoing elective colonoscopy, irrespective of outpatients, and inpatients; RCTs which investigated the comparative efficacy between 2L PEG combined with Asc and 4L PEG alone were considered, and both of them did not add other adjuvants; the overall quality of colon preparation was regarded as primary outcome, and the secondary outcomes included compliance with recommend regime, willingness to retake the same regime, acceptability to regime, taste of purgative ingested, and adverse events; and only studies published in English and Chinese will be permitted.

Article will be excluded if it met at least one of the following criteria: essential information which cannot be extracted and obtained from authors; duplicates (derive from the same research group) with poor methodology and insufficient data.

2.2. Definition of outcomes

The overall quality of colon preparation was predefined as successful bowel cleansing in our study. For the purposes of the analysis, the successful preparation was reached when conformed to one of following conditions: an Ottawa score of <5; a Boston Bowel Preparation Scale score of ≥ 2 for all segments; a grade of either excellent or good on the Aronchik scale; grades A and B according to the Harefield Cleansing Scale; and other nonvalidated 3-, 4-, or 5-point scales (excellent, good, fair, poor, and very poor).

Compliance to the regimen was assessed by asking the patients how much the dosing regimen they have ingested. We predefined good compliance as consumption of $\geq 75\%$ of the regime and excellent compliance as consumption of 100% of the regime. In terms of subjective indexes, willingness to retake the same regime, acceptability to regime, and taste of purgative ingested were measured by using an unofficial questionnaire in each suitable study (ie, produced by individual study). All adverse events related to bowel preparation were monitored and recorded during colonoscopy.

2.3. Identification of citations

An electronic search will be performed to collect any potential RCTs investigating the comparative efficacy of 2 target PEG-based regimes in PubMed, EMBASE, and Cochrane Central Register of Controlled Trials from January 2000 to April 2018. Search results will be updated weekly in order to timely capture any recent studies. "Colonoscopy," "polyethylene glycols," and "random" will be used to construct search strings based on medical subject heading and free word which are embedded in specific files involving title, keywords, and abstract. All search algorithms have been designed for targeted databases, and we have documented these algorithms in Supplemental Table 1, http://links.lww.com/MD/C225.

In addition, we will also replenish the potential studies through manually checking the bibliographies of eligible studies and relevant reviews. Two reviewers will independently and critically examine citations by reading the titles, abstracts, and full-texts in turn.

2.4. Data extraction

A predesigned data extraction form was designed by the review authors. All acquired citations will be imported into EndNote software. Whereafter, 2 reviewers will independently extract the essential information, in which involves first author, publication year, risk of bias, age of participants, sample size (male/female), bowel preparation scale, the description of intervention (study group/control group), dietary instruction, and outcomes of interest. We will contact the leading authors of relevant articles in case extractive data are not available. All information will be rechecked mutually. We will calculate the Kappa value to assess the interinvestigator reliability. We will also organize the consensus principles which serve as the means of resolving divergences among reviewers.

2.5. Quality assessment

Two reviewers will independently adopt the modified tool based on Cochrane tool to appraise the risk of bias[32,33] of each included study. The risk of bias will be assessed from 8 domains severally, including randomization sequence generation, allocation concealment, blinding of participants, blinding of study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias. Besides, the evaluation results will be cross-checked. The risk of each domain will be rated as "high risk of bias," "unclear risk of bias," and "low risk of bias" according to the match level between extractive information and evaluation criteria. Any disagreements will be resolved by discussing with a 3rd senior reviewer.

2.6. Statistical analysis

We will input all extracted data to STATA software version 12.0 (Stata Corp, College Station, TX) for statistical analyses. The estimates of dichotomous data will be expressed as relative risk and 95% confidence intervals. The estimates of continuous data will be expressed as mean differences or standard mean differences with 95% confidence intervals. Heterogeneity in included studies will be qualitatively evaluated using the Cochrane Q, and the proportion of overall variation that is attributable to between-study heterogeneity will be quantitatively evaluated by I^2 statistic.[34,35]

We will analyze the clinical diversity and methodological comparability of every suitable study firstly according to the characteristics of the participants, research design and method, intervention regimes, and measurement and statistical analysis of outcomes. If the clinical characteristic and methodology are considered heterogeneity, qualitative analysis will be used. If not, we will use the Cochrane Q to qualitatively evaluate the heterogeneity in studies in terms of each outcome.[36] Moreover, the level of heterogeneity will be quantified by the I^2 statistic. If I^2 is <50%, the suitable studies will be considered to be homogeneous; in contrast, the pooled results will be affected by substantial heterogeneity. We adopted random-effect model based on Mantel–Haenszel or inverse variance approach to perform all analyses. As to the compliance with recommend regime, subgroup analyses will be planned according to the total consumption of the regime. If the number of studies analyzed in single outcome is more than 10, publication bias will be detected by using Egger test.[37,38] If study with multiple-arm design is included, we will extract the data from intervention groups which are up to the inclusion criteria according to the recommendations proposed by Cochrane Collaboration.[32]

3. Discussion

Subjects' participation and adequate bowel cleansing are the essential requirements for a high-quality colonoscopy.[3,28,39] Therefore, the ideal colon cleansing should be capable of

emptying the colon of all fecal material without damaging its mucosa, causing no discomfort, and minimizing fluids and electrolyte imbalance.[40,41] Traditional 4 L PEG regime has been used worldwide for its high efficacy, lower price, and superior safety.[42,43] But volume-related discomfort and unpleasant taste may deter the acceptability with colonoscopy. It is closely linked to subject' s attendance.[44] Poor acceptability will impair the willingness to take the examination in the future.[17,18] Recently, low-volume PEG regime shows a better toleration under the condition that its cleanliness is equivalent to that of traditional 4 L PEG regimen.[19,24,25,45] Excessive Asc that remains in the bowel exerts an osmotic effect,[22,23] thereby, it reduces the quantity of PEG.[44]

Although a previous meta-analysis has reported that the efficacy of low-volume PEG plus Asc is comparable with that of traditional 4 L PEG regime, several limitations (such as the diversity in study designs and adjuvant prescriptions) deterred the reliability of pooled results. Moreover, some potential RCTs have been published recently. In order to further determine the comparative role between low volume PEG regime and traditional large volume one in bowel preparation prior to colonoscopy, we designed this updated systematic review and meta-analysis for the purpose of facilitating the decision making. Meanwhile, we also plan to use trial sequential analysis technique to calculate the accumulated sample size of each outcome in order to determine the robust of findings.

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