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META-ANALYSIS

Same-day single-dose *vs* large-volume split-dose regimens of polyethylene glycol for bowel preparation: A systematic review and meta-analysis

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Abstract

BACKGROUND

Split-dose regimens (SpDs) of 4 L of polyethylene glycol (PEG) have been established as the "gold standard" for bowel preparation; however, its use is limited by the large volumes of fluids required and sleep disturbance associated with night doses. Meanwhile, the same-day single-dose regimens (SSDs) of PEG has been recommended as an alternative; however, its superiority compared to other regimens is a matter of debate.

AIM

To compare the efficacy and tolerability between SSDs and large-volume SpDs PEG for bowel preparation.

METHODS

We searched MEDLINE/PubMed, the Cochrane Library, RCA, EMBASE and Science Citation Index Expanded for randomized trials comparing (2 L/4 L) SSDs to large-volume (4 L/3 L) SpDs PEG-based regimens, regardless of adjuvant laxative use. The pooled analysis of relative risk ratio and mean difference was calculated for bowel cleanliness, sleep disturbance, willingness to repeat the procedure using the same preparation and adverse effects. A random effects model or fixed-effects model was chosen based on heterogeneity analysis among studies.

RESULTS

A total of 18 studies were included. There was no statistically significant difference of adequate bowel preparation (relative risk = 0.97; 95%CI: 0.92-1.02) (14 trials), right colon Boston Bowel Preparation Scale (mean difference = 0.00; 95%CI: -0.04, 0.03) (9 trials) and right colon Ottawa Bowel Preparation Scale (mean difference = 0.04; 95%CI: -0.27, 0.34) (5 trials) between (2 L/4 L) SSDs and large-volume (4 L/3 L) SpDs, regardless of adjuvant laxative use. The pooled analysis favored the use of SSDs with less sleep disturbance (relative risk = 0.52; 95%CI: 0.40, 0.68) and lower incidence of abdominal pain (relative risk = 0.75; 95%CI: 0.62, 0.90). During subgroup analysis, patients that received low-volume (2 L) SSDs showed more willingness to repeat the procedure using the same preparation than SpDs ($P < 0.05$). No significant difference in adverse effects, including nausea, vomiting and bloating, was found between the two arms ($P > 0.05$).

CONCLUSION

Regardless of adjuvant laxative use, the (2 L/4 L) SSD PEG-based arm was considered equal or better than the large-volume (≥ 3 L) SpDs PEG regimen in terms of bowel cleanliness and tolerability. Patients that received low-volume (2 L) SSDs showed more willingness to repeat the procedure using the same preparation due to the low-volume fluid requirement and less sleep disturbance.

Key Words: Bowel preparation; Colonoscopy; Polyethylene glycol; Same-day single-dose; Split-dose; Meta-analysis

Core Tip: Same-day single-dose polyethylene glycol-based regimens for bowel preparation seemed to be equal or better than large-volume (≥ 3 L) split-dose polyethylene glycol solution in terms of bowel cleanliness and tolerability as long as the optimal preparation-to-colonoscopy interval and diet instruction for bowel preparation were respected.

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INTRODUCTION

A colonoscopy is an important tool used for colorectal cancer screening and the management of colorectal lesions. However, the success of colonoscopy is strongly dependent on the quality of bowel preparation. Prior studies have reported that poor bowel preparation can increase the risk of missed diagnosis for smaller and/or flat lesions, especially in the right colon, and prolong cecal intubation time [1,2]. Polyethylene glycol (PEG) solutions, as efficient and safe purgative agents, offer the advantage of minimal fluid and electrolyte shifts and are reportedly the most widely used solutions for bowel preparation[1-3].

High volume (4 L) split-dose regimens (SpDs) of PEG have been recommended as the gold-standard regimen for bowel preparation[4]; however, the large volume of fluids or poor tolerability associated with SpDs have become a source of patient dissatisfaction. The same-day single-dose (SSD) PEG has been recommended as an alternative for patients scheduled for afternoon colonoscopy[5,6], exhibiting equal cleansing efficacy and fewer sleep disturbances than SpDs. Meanwhile, it was reported to be in favor of reducing the preparation volume and improving patient tolerance by using PEG solution combined with adjuvant laxative agents for those at risk of bowel preparation[7]. A previous systematic review by Enestvedt *et al*[8] revealed that 4 L split-dose PEG was better than other bowel preparation comparators including a regimen of 4 L single-dose PEG the night before the procedure and MiraLAX/Gatorade solutions, regardless of adjuvant laxative use. However, in order to evaluate bowel cleanliness of the SSD regimens of PEG and patient tolerance in terms of sleep disturbances and side effects for bowel preparation, we conducted a systematic review and meta-analysis to compare the efficacy and tolerability of SSD PEG-based arm *vs* large-volume (≥ 3 L) split-dose PEG solutions for bowel preparation before colonoscopy, regardless of adjuvant laxative use.

MATERIALS AND METHODS

Search strategy and study selection

Systemic searches were performed in June 2021 using MEDLINE/PubMed, EMBASE, Web of Science, Google Scholar and Cochrane Library by two independent reviewers. The search strategy used the Medical Subject Heading term along with the keywords "polyethylene glycol, (bowel preparation OR bowel preparation solution), (split dose OR split-dose) and randomized controlled." Only full texts published in English with one arm using single-dose PEG on the day of colonoscopy, regardless of adjuvant laxative use and the other arm consisting of a split-dose regimen of PEG for bowel preparation before and on the day of the procedure, were included. References from the reviewed articles were also searched to identify relevant articles that may have been missed.

Exclusion criteria consisted of the following: (1) Participants: pediatric patients, cases of prior colorectal resection and incomplete or complete bowel obstruction cases; (2) Non-colonoscopy studies; (3) Interventions: non-PEG-based solution (*i.e.* sodium phosphate, picosulfate, sodium picosulfate with magnesium citrate agents, *etc*); and (4) Comparisons: trials comparing evening-before *vs* split-dose, twice a same-day *vs* split-dose and low-volume (≤ 2 L) split-dose. A flowchart of the literature search is shown in Figure 1.

Data extraction and methodologic quality assessment

Two authors independently conducted the screening and extracted the data from selected trials with the intention to treat numbers preferred. Results from included studies reported as percentages were converted to absolute numbers.

The methodological quality of each study was graded by two investigators using a modified Jadad scoring system utilized for single (endoscopist) blinding trials[8]. This 5-point scale assigns a single point for each of the following: (1) The study is described as randomized; (2) The randomization method is described and appropriate; (3) The study is described as blind; (4) The blinding method is described and appropriate; and (5) There is a description of withdrawals and drop-outs. A score of 5 suggested excellent quality, and a score of 0 implied a poor-quality randomized controlled trial. Single-blinding rather than double-blinding can be executed logistically for bowel preparation studies. To ensure the adequacy of blinding, all endoscopists were blinded to the bowel preparation, and staff, nurses and patients were instructed not to discuss the bowel preparation with the endoscopist. The funnel plot was used to assess publication bias. The Grades of Recommendation, Assessment, Development and Evaluation approach was presented to rate the certainty of evidence. Points of disagreement were reconciled by a discussion with another author when required.

Outcomes

The primary outcome measure was bowel cleanliness, defined as adequate bowel preparation using validated scales [Ottawa Bowel Preparation Scale (OBPS) or Boston Bowel Preparation Scale (BBPS)]. Secondary outcomes included the willingness to repeat the procedure using the same preparation, sleep disturbance and side effects, including nausea, vomiting, bloating and abdominal pain/cramps.

The total OBPS score was based upon the sum of the right, transverse and left colonic segments (reference range of 0-4 each segment) plus an overall colonic fluid score (range 0-2)[9]. The total score ranged from 0 to 14; the lower the score, the better the preparation. The total BBPS score was the sum of the right colon, mid-colon and left colonic segmental scale. The total score ranged from 0 to 9 (0 = very poor, 9 = excellent)[10].

Statistical analysis

Statistical analysis was conducted with Review Manager (Version 5.4, Cochrane Collaboration, Oxford, GB). The categorical outcomes were analyzed using relative risk ratio (RR) and its corresponding 95% confidence interval (CI). Continuous data were analyzed using mean differences (MD) and corresponding 95%CI. Statistical heterogeneity was measured by graphic examination of forest plots and statistically through a homogeneity test based on the χ^2 test ($I^2 \geq 50\%$ suggests heterogeneity) in which $P < 0.10$ was considered significant for heterogeneity. A fixed-effects model was used unless there was significant heterogeneity, in which case a random-effects model was applied. Weighted MDs were used for outcomes measured on different scales. A RR > 1 favored the SSD arm, while a RR < 1 favored the SpDs arm for the favorable outcomes (adequate preparation and willingness to repeat) and the adverse outcomes (sleep disturbance and adverse effects). The MD represented the difference in means between SSD and SpDs (SSD – SpDs = MD); an MD > 0 favored the SSD arm, while an MD < 0 favored the SpDs arm. A higher mean BBPS score indicated better quality of bowel preparation, which was the opposite for OBPS scores. Subgroup analysis was performed to characterize heterogeneity and sensitivity.

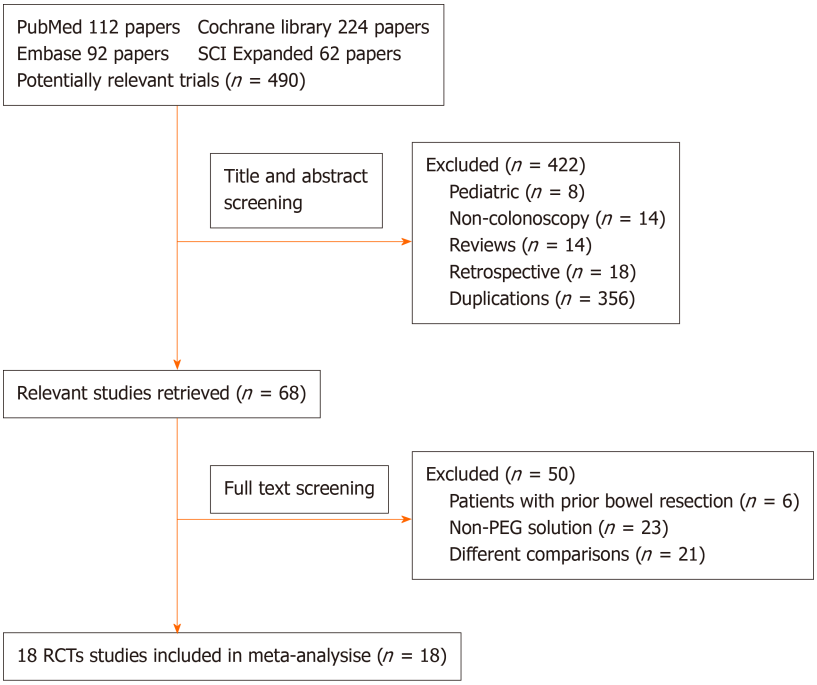

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Figure 1 Flowchart of the study selection. PEG: Polyethylene glycol; RCT: Randomized controlled trial.

RESULTS

Search results

The initial search identified 490 potentially relevant articles. A total of 422 articles were excluded based on titles and abstracts because they included patients < 18 years of age, non-colonoscopy studies, reviews, retrospective studies or duplications. Sixty-eight articles were reviewed by full text. Overall, 18 articles[11-28] comparing bowel preparation with SSDs *vs* SpDs PEG were included in this analysis. Figure 1 shows a flowchart of studies from initial results of publication searches to final inclusion or exclusion.

Table 1 summarizes the characteristics of the 18 included studies (n = 5464), which consisted of 2793 patients who received SSDs and 2671 patients who received the SpDs regimen. Nine trials evaluated low-volume (2 L) SSD PEG with adjuvant laxative use *vs* large-volume(≥ 3 L) SpDs PEG[11,12,22-28], four trials compared 4 L SSD PEG *vs* 4 L SpDs PEG[13,14,19,20], and six trials compared 2 L SSD PEG *vs* (≥ 3 L) SpDs PEG[11,15-18,21]. Interestingly, in a study by Zhang *et al*[11], patients were assigned to three groups: 2 L SSD PEG, 2 L SSD PEG with adjuvant laxative (linaclotide) and 4 L SpDs PEG.

Bowel cleanliness was evaluated either with BBPS[11,12,14,15,18,23-27] or OBPS[13,16,17,19-22,28]. An adequate bowel preparation was defined as a total BBPS score ≥ 6 with all colon segments scores ≥ 2, or a total OBPS score < 5 (including score < 7 by De Leone, score ≤ 3 by Cesaro) or all colon segment OBPS score < 2. Diet restriction was mentioned in 16 trials and consisted of low residual diet/low-fiber foods[11,14-16,20-25,27-28] or clear liquid diet[13,15,17,19,26,28] before colonoscopy. Colonoscopy was performed with optimal preparation-to-colonoscopy (PC) interval time in only 6 trials[11,12,15,16,21,24], while 9 trials did not mention the PC interval[13,14,20,22,23,25-28].

Quality of bowel cleanliness

Fourteen studies provided dichotomous information on adequate bowel preparation between the SSDs and SpDs groups, regardless of adjuvant laxative use, and significant heterogeneity was observed (P < 0.00001, I^2 = 76%) in the pooled estimate. Using a random-effects model, no statistically significant difference was found between the two groups (RR = 0.97; 95%CI: 0.92-1.02) (P = 0.19) as shown in Figure 2.

Continuous data on right colon BBPS was available in 9 trials (Figure 3). No significant heterogeneity was observed (P = 0.22, I^2 = 25%). Using a fixed-effects model, we found that there was no significant difference between the two arms (MD = 0.00; 95%CI: -0.04, 0.03).

Five studies provided continuous data on right colon OBPS (Figure 4), and significant heterogeneity was observed (P = 0.001, I^2 =78%). Using a random-effects model, no significant difference was found between the two arms (MD = 0.04; 95%CI: -0.27, 0.34) (P = 0.82).

Table 1 Characteristics of included studies

Ref.	Type of study	Participants and years of age	Bowel preparation	Patients with SSD/SpDs, *n*	Diet instruction	Colonoscopy timing	Outcomes	Interval, PC	Jadad score, modified	Use of adjuvant
Zhang *et al* [11], 2021	Single-center, single-blind, RCT	Outpatients 18-70 yr	SSD (A): 2 L PEG 6 h before procedure; SSD (B): 290 μg Lin 7 h before + 0.5 L water, 2 L PEG 6 h before colonoscopy; SpDs: 2 L PEG at 21:00 the day prior, 2 L PEG 6 h before colonoscopy	139A/141B/140	1-d LRD	Morning: 8:00-11:30; Afternoon: 13:30-17:00	BBPS	6 h	4	SSD (B): Linaclotide
Barkun *et al*[12], 2020	Multicenter, single-blind, RCT	Outpatients ≥ 18 yr	SSD: 2 L PEG 4 h before colonoscopy + 15 mg bis at 14:00 the day before; SpDs: 2 L PEG at 19:00 the day before, 2 L PEG 4-5 h before colonoscopy	583/582	Not described	10:30-16:30	BBPS	2-3 h	5	Bisacodyl
Castro *et al* [13], 2019	Single-center, single-blind, RCT	Outpatients ≥ 18 yr	SSD: 4 L PEG at 6:00; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 6 h before colonoscopy	142/158	CLD after regular breakfast the day before	13:00-16:30	OBPS	Not described	5	No
Seo *et al* [14], 2019	Single-center, single-blind, RCT	Outpatients 40–75 yr	SSD (Mor): 4 L PEG at 5:00; SSD (Aft): 2 L PEG at 7:00 + 2 L PEG at 10:00; SpDs: 2 L PEG at 21:00 the day before, 2 L PEG at 7:00 (Mor) or at 10:00 (Aft)	172/167	LFF for 2 d, soft diet dinner the day prior	Morning 10:00-12:00; Afternoon 13:30-17:00	BBPS	Not described	3	No
Kang *et al* [15], 2018	Single-center, single-blind, RCT	Patients 18-70 yr	SSD: 2 L PEG 4-6 h before colonoscopy; SpDs: 2 L PEG at 19:00-21:00 the day before, 2 L PEG 4-6 h before colonoscopy	470/470	Regular meal for lunch and CLD or LRD for dinner the day before	Morning 8:30-12:00; Afternoon 13:00-16:00	BBPS	2-4 h	5	No
Zhang *et al* [16], 2015	Multicenter, single-blind, RCT	Patients 18-75 yr	SSD: 2 L PEG 4-6 h before colonoscopy; SpDs: 1 L PEG at 21:00 the day before, 2 L PEG 4-6 h before colonoscopy	159/159	1-d LRD	Not described	OBPS	2-4 h	3	No
Shah *et al* [17], 2014	Single-center, single-blind, RCT	Patients ≥ 18 yr	SSD: 2 L PEG at 5:00-7:00; SpDs: 1 L PEG at 18:00-19:00 the day before, 1 L PEG at 6:00-7:00	103/97	1-d liquid diet and CLD after midnight	11:00-16:00	OBPS	≥ 4 h	5	No
Tellez-Avila *et al* [18], 2014	Single-center, single-blind, RCT	Inpatients ≥ 18 yr	SSD: 2 L PEG at 6:00-8:00; SpDs: 2 L PEG at 17:00-19:00 the day before, 2 L PEG at 6:00-8:00	61/67	Not described	Not described	BBPS	≥ 3 h	5	No
Kotwal *et al*[19], 2014	Single-center, single-blind, RCT	Inpatients 18-80 yr	SSD: 4 L PEG at 5:00-9:00; SpDs: 2 L PEG at 19:00-21:00 the day before, 2 L PEG at 7:00-9:00	60/60	1-d CLD	After 11:00	OBPS	≥ 2 h	5	No
Kim *et al* [20], 2014	Single-center, single-blind, RCT	Outpatients 18-75 yr	SSD: 4 L PEG 6 h before colonoscopy; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 4-6 h before colonoscopy	50/50	Avoid high-fiber foods 3 d prior	Not described	OBPS	Not described	2	No
Seo *et al* [21], 2013	Single-center, single-blind, RCT	Outpatients 18-85 yr	SSD: 2 L PEG 5 h before colonoscopy; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 5 h before colonoscopy	103/102	3-d LRD	9:00-17:00	OBPS	≥ 3 h	5	No
Cesaro *et al* [22], 2013	Single-center, single-blind,	Outpatients 18-85 yr	SSD: 2 L PEG-CS at 6:00 + bis 10-20 mg at 22:00 the day before; SpDs: 3 L PEG at 19:00 the day before, 1 L	50/51	3-d LRD	11:00-18:00	OBPS	Not described	5	Bisacodyl

	RCT		PEG at 7:00							
Kwon *et al* [23], 2016	Multicenter, single-blind, RCT	Outpatients ≥ 18 yr	SSD: 1 L PEG-ASc + 0.5 L water at 6:00, 20 mg bis + 0.5 L water at 20:00 the day before; SpDs: 1 L PEG-ASc + 0.5 L water at 20:00 the day before, 1 L PEG-ASc + 0.5 L water at 6:00	92/97	LFF for 3 d, soft meal on the day prior	Not described	BBPS	≥ 3 h	5	Bisacodyl
Kang *et al* [24], 2017	Single-center, single-blind, RCT	Outpatients 20-75 yr	SSD: 1 L PEG-ASc 4 h before colonoscopy + 1 L water, 10 mg bis at 21:00 the day before; SpDs: 1 L PEG-ASc at 20:00 the day before + 0.5 L water, 1 L PEG-ASc 4 h before colonoscopy + 0.5 L water	100/100	3-d LRD	9:00-13:00	BBPS	> 2 h	3	Bisacodyl
Choi *et al* [25], 2018	Single-center, single-blind, RCT	Outpatient 18-80 yr	SSD: 1 L PEG-ASc 5 h before colonoscopy + 0.5 L water, Pru at 19:00 the day before + 0.5 L water; SpDs: 1 L PEG-ASc at 19:00 the day before + 0.5 L water, 1 L PEG-ASc 5 h before colonoscopy + 0.5 L water	130/130	3-d LRD	9:00-13:00	BBPS	Not described	5	Prucalopride
Kim *et al* [26], 2019	Single-center, single-blind, RCT	Outpatients 20-70 yr	SSD: 1L PEG-ASc at 5:00 + 1 L water + 20 mg bis; SpDs: 1 L PEG-ASc at 21:00 the day before + 0.5 L water, 1 L PEG-ASc at 5:00 + 0.5 L water	83/85	1-d CLD	8:30-12:00	BBPS	Not described	4	Bisacodyl
Kim *et al* [27], 2020	Single-center, single-blind, RCT	Patients 18-74 yr	SSD: 1 L PEG-ASc 5 h before endoscopy + 1 L water, 10 mg bis at 21:00 the day before; SpDs: 1 L PEG-ASc at 21:00 the day before + 0.5 L water, 1 L PEG-ASc 5 h before endoscopy + 0.5 L water	99/99	3-d LRD	9:00-17:00	BBPS	Not described	4	Bisacodyl
de Leone *et al*[28], 2013	Multicenter, single-blind, RCT	Outpatients 18-85 yr	SSD: 3-4 tablets bis at bedtime, 2 L PEG-CS 5 h before endoscopy; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 5 h before endoscopy	78/79	LFF for 3 d, CLD the day before	Morning	OBPS	Not described	4	Bisacodyl

SSD: Same-day single-dose; SpDs: Split-dose; PC: Preparation-to-colonoscopy; LFF: Low-fiber foods; LRD: Low residual diet; CLD: Clear liquid diet; PEG-CS: Polyethylene glycol with citrates and simethicone; PEG-ASc: Polyethylene glycol ascorbic acid; RCT: Randomized controlled trial; PEG: Polyethylene glycol; Lin: Linaclotide; BBPS: Boston Bowel Preparation Scale; bis: Bisacodyl; OBPS: Ottawa Bowel Preparation Scale; Mor: Morning; Aft: Afternoon; Pru: Prucalopride.

Subgroup analysis

2 L SSD with adjuvant *vs* SpDs: Seven trials provided dichotomous information on adequate bowel preparation comparing the 2 L SSDs with adjuvant laxative use to the (≥ 3 L) SpDs regimen. The pooled estimates showed significant heterogeneity within the included studies (P = 0.05, I^2 = 51%). Using a random-effects model, no statistically significant difference was found between the two groups (RR = 1.00; 95%CI: 0.95, 1.05) (P = 0.99). Continuous data on the right colon BBPS was provided in 7 studies. Pooled estimate results showed no significant heterogeneity (P = 0.12, I^2 = 41%). Using a fixed-effects model, we found that there was no significant difference between the two groups. (MD = 0.00; 95%CI: -0.05, 0.05) (P = 0.93). Only 1 study reported data on right colon OBPS (Table 2).

2 L SSD without adjuvant *vs* SpDs: Five trials compared 2 L SSDs without adjuvant to ≥ 3 L SpDs regimens and provided categorical data on the adequacy of bowel preparation. The pooled estimate results showed significant heterogeneity within the included studies (P < 0.00001, I^2 = 90%). Using a random-effects model, no statistical difference was reported between the two groups (RR = 0.86; 95%CI:

Table 2 Subgroup analysis

Subgroup	Studies, *n*	SSD, *n*	SpDs, *n*	I^2, %	*P* value for heterogeneity	Pooled analysis (cat-RR/con-MD)	95%CI	*P* value
2 L SSD with adjuvant *vs* SpDs								
Adequate bowel preparation (categorical)[11,12,22,23,25,27,28]	7	1172	1177	51	0.05	1.00	(0.95, 1.05)	0.99
BBPS score for right colon (continuous)[11,12,23-27]	7	1227	1232	41	0.12	0.00	(-0.05, 0.05)	0.93
OBPS score for right colon (continuous)[22]	1	50	51					
2 L SSD without adjuvant *vs* SpDs								
Adequate bowel preparation (categorical)[11,15,16,18,21]	5	932	938	90	< 0.00001	0.86	(0.72, 1.02)	0.07
BBPS score for right colon (continuous)[11,15]	2	611	610	0	1.00	0.00	(-0.07, 0.07)	1.00
OBPS score for right colon (continuous)[16,21]	2	262	261	89	0.003	0.26	(-0.20, 0.72)	0.26
4 L SSD without adjuvant *vs* SpDs								
Adequate bowel preparation (categorical)[13,14,20]	3	364	375	0	0.66	0.99	(0.94, 1.05)	0.82
BBPS score for right colon (continuous)[14]	1	172	167					
OBPS score for right colon (continuous)[19,20]	2	110	110	0	0.71	-0.06	(-0.30, 0.18)	0.62

SSD: Same-day single-dose; SpDs: Split-dose; BBPS: Boston bowel preparation scale; OBPS: Ottawa bowel preparation scale; cat-RR/con-MD: Categorical-relative risk ratio/continuous-mean differences; CI: Confidence interval.

0.72, 1.02) (P = 0.07).

Two trials provided continuous data on right colon BBPS. The pooled estimates showed no significant heterogeneity between both studies (P = 1.00, I^2 = 0%). Using a fixed-effects model, no significant difference was found between the two groups. (MD = 0.00; 95%CI: -0.07, 0.07) (P = 1.00). Two studies provided continuous data on right colon OBPS. The pooled estimates showed significant heterogeneity (P = 0.003, I^2 = 89%). Using a random-effects model, no significant difference was found between the two groups. (MD = 0.26; 95%CI: -0.20, 0.72) (P = 0.26) (Table 2).

4 L SSD without adjuvant *vs* SpDs: Three trials compared the adequacy of bowel preparation between 4 L SSDs without adjuvant and 4 L SpDs regimens. The pooled estimates showed that no significant heterogeneity was present within these studies (P = 0.66, I^2 = 0%). Using a fixed-effects model, we found that there was no significant difference between the two groups (RR = 0.99; 95%CI: 0.94, 1.05) (P = 0.82). Only 1 study reported data on the right colon BBPS.

The right colon OBPS scores were provided in 2 studies. The pooled estimates showed no significant heterogeneity between both studies (P = 0.71, I^2 = 0%). Using a fixed-effects model, no significant difference was found between the two groups. (MD = -0.06; 95%CI: -0.30, 0.18) (P = 0.62) (Table 2).

Secondary outcomes

Fifteen studies provided dichotomous information on sleep disturbance between the SSD and SpDs PEG groups (Table 3). During the pooled estimates, significant heterogeneity was observed (P < 0.00001, I^2 = 74%). Using a random-effects model, a significant difference was found between the two groups (RR = 0.52; 95%CI: 0.40, 0.68) (P < 0.00001). During subgroup analysis, 7 trials comparing 2 L SSD with adjuvant *vs* SpDs showed no significant difference in sleep disturbance between the two groups (RR = 0.69; 95%CI: 0.43, 1.10) (P = 0.12).

Ten trials provided dichotomous information on patient willingness to repeat the procedure using the same preparation between the SSD and SpDs PEG groups (Table 3). During the pooled estimates, significant heterogeneity was observed (P < 0.00001, I^2 = 90%). Using a random-effects model, a significant difference was found between the two groups (RR=1.15; 95%CI: 1.03, 1.29) (P = 0.01). Two trials in subgroup analysis of 4 L SSD without adjuvant *vs* SpDs found no significant difference between the two groups (RR = 0.89; 95%CI: 0.71, 1.13) (P = 0.34).

Table 3 Secondary outcome

Secondary outcome	Studies (*n*)	SSD (*n*)	SpDs (*n*)	I^2 (%)	*P* value for heterogeneity	Pooled analysis (cat-RR/con-MD)	95%CI	*P* value
Sleep disturbance	15	2591	2463	74	< 0.00001	0.52	(0.40, 0.68)	< 0.00001
2 L SSD with adjuvant *vs* SpDs	7	1214	1215	69	0.003	0.69	(0.43, 1.10)	0.12
2 L SSD without adjuvant *vs* SpDs	6	1014	1013	80	0.0002	0.45	(0.30, 0.67)	< 0.0001
4 L SSD without adjuvant *vs* SpDs	3	363	375	67	0.05	0.47	(0.28, 0.78)	0.004
Willingness to repeat	10	1996	1855	90	< 0.00001	1.15	(1.03, 1.29)	0.01
2 L SSD with adjuvant *vs* SpDs	6	1073	1078	89	< 0.00001	1.24	(1.06, 1.45)	0.008
2 L SSD without adjuvant *vs* SpDs	3	691	690	82	0.004	1.14	(1.01, 1.29)	0.03
4 L SSD without adjuvant *vs* SpDs	2	232	227	54	0.14	0.89	(0.71, 1.13)	0.34
Side effects								
Nausea	17	2715	2592	68	< 0.0001	0.95	(0.78, 1.16)	0.63
Vomiting	16	2644	2521	64	0.0002	0.96	(0.66, 1.38)	0.81
Abdominal pain	17	2715	2592	38	0.06	0.75	(0,62, 0.90)	0.002
Bloating	15	2205	2077	67	0.0001	0.80	(0.63, 1.01)	0.06

SSD: Same-day single-dose; SpDs: Split-dose; cat-RR/con-MD: Categorical-relative risk ratio/continuous-mean differences; CI: Confidence interval.

The incidence of adverse effects, including nausea, vomiting, abdominal pain and bloating, was reported in 17, 16, 17 and 15 trials, respectively (Table 3). No significant difference in nausea (RR = 0.95; 95%CI: 0.78, 1.16), vomiting (RR = 0.96; 95%CI: 0.66, 1.38) and bloating (RR = 0.80; 95%CI: 0.63, 1.01) was found between the two groups. However, there was a significant difference in abdominal pain between the two arms, favoring the SSD group (RR = 0.75; 95%CI: 0.62, 0.90).

Publication bias

For the publication bias, in our meta-analysis a better symmetry was present with the use of funnel plots (Figure 5). The Grades of Recommendation, Assessment, Development and Evaluation as one systematic approach rated the certainty of evidence for moderate level in this systematic review and meta-analysis (Table 4).

DISCUSSION

This updated meta-analysis reviewed 18 trials comparing the efficacy and tolerability of bowel preparation between SSD PEG-based and large-volume SpDs PEG regimens. In recent years, the split dose of 4 L PEG has been adopted as a standard regimen for bowel preparation. However, patients often complain of the large-volume regimen and sleep disturbance due to frequent bowel movements and abdominal discomfort. To enhance patient compliance with the preparation, several studies have suggested adding other laxatives, such as bisacodyl, linaclotide or prucalopride, to a low-volume PEG bowel preparation to reduce the solution volume[11,12,25]. In the present study, according to the volume of PEG ingested and combination with adjuvant laxative, SSD PEG-based regimens were separated into three subgroups: low-volume (2 L) SSD PEG combined with an adjuvant agent, low-volume (2 L) SSD PEG without adjuvant laxative and large-volume (4 L) SSD PEG without adjuvant laxative. In a pooled analysis, we have shown that SSD PEG was as effective as SpDs PEG-based regimens in terms of bowel cleanliness, regardless of adjuvant laxative use and dosage.

Table 4 Grades of Recommendation, Assessment, Development and Evaluation rated the certainty of evidence

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSD	SpDs	RR (95%CI)	Effect/Absolute	Quality	Importance
Adequate bowel cleanliness												
14	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	2002/2468 (81.1%)	1973/2350 (84.0%) 85.5%	RR 0.97 (0.92 to 1.02)	25 fewer per 1000 (from 67 fewer to 17 more) 26 fewer per 1000 (from 68 fewer to 17 more)	(+++) moderate	Critical
Right colon BBPS												
9	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1869	1869	-	Md 0 higher (0.04 lower to 0.03 higher)	(++++) high	Critical
Right colon OBPS												
5	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	422	422	-	Md 0.04 higher (0.27 lower to 0.34 higher)	(+++) moderate	Critical
Sleep disturbance												
15	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	348/2591 (13.4%)	651/2463 (26.4%) 32.0%	RR 0.52 (0.40 to 0.68)	127 fewer per 1000 (from 85 fewer to 159 fewer) 154 fewer per 1000 (from 102 fewer to 192 fewer)	(+++) moderate	Critical
Willingness to repeat												
10	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	1624/1996 (81.4%)	1269/1855 (68.4%) 65.2%	RR 1.15 (1.03 to 1.29)	103 more per 1000 (from 21 more to 198 more) 98 more per 1000 (from 20 more to 189 more)	(+++) moderate	Critical
Nausea												
17	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	516/2715 (19.0%)	559/2592 (21.6%) 20.0%	RR 0.95 (0.78 to 1.16)	11 fewer per 1000 (from 47 fewer to 35 more) 10 fewer per 1000 (from 44 fewer to 32 more)	(+++) moderate	Critical
Vomiting												
16	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	191/2644 (7.2%)	202/2521 (8.0%) 7.2%	RR 0.96 (0.66 to 1.38)	3 fewer per 1000 (from 27 fewer to 30 more) 3 fewer per 1000 (from 24 fewer to 27 more)	(+++) moderate	Critical

Abdominal pain												
17	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	168/2715 (6.2%)	221/2592 (8.5%) 8.2%	RR 0.75 (0.62 to 0.9)	21 fewer per 1000 (from 9 fewer to 32 fewer) 20 fewer per 1000 (from 8 fewer to 31 fewer)	(+++) moderate	Critical
Bloating												
15	Randomized trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	322/2205 (14.6%)	415/2077 (20.0%) 18.4%	RR 0.8 (0.63 to 1.01)	40 fewer per 1000 (from 74 fewer to 2 more) 37 fewer per 1000 (from 68 fewer to 2 more)	(+++) moderate	Critical

[1]Only a few different studies have shown conflicting results. SSD: Same-day single-dose; SpDs: Split-dose; CI: Confidence interval; RR: Relative risk; BBPS; Boston Bowel Preparation Scale; Md: Moderate; OBPS: Ottawa Bowel Preparation Scale.

Previous meta-analyses by Cheng *et al*[29] and Avalos *et al*[30] showed a trend to the equivalent efficacy for bowel preparation in terms of bowel cleanliness and adenoma detection rate when compared to same-day (one or two doses) with split-dose bowel preparation regimens regardless of purgative type. Patients with a history of pelvic surgery and colorectal surgery as high-risks of poor bowel preparation were not excluded by the forementioned studies[29,30]. Other identified patient-related risk factors for inadequate bowel preparation include diabetes and constipation[31]. In the present study, patients with a history of constipation and diabetes mellitus were included, and analysis results obtained were consistent with previous studies. We considered that the SSD PEG-based arm had the same efficacy in bowel cleanliness as the SpDs arm for patients at high-risk of poor bowel preparation by complying with the optimal PC interval and diet instruction before colonoscopy.

In a study by Seo *et al*[3], multivariate analysis showed that the PC interval, the amount of PEG ingested and compliance with diet instructions were significant contributors to satisfactory bowel preparation, regardless of when the procedure was performed during the day. Colonoscopies performed with a PC interval of 3 to 5 h had the best bowel-cleansing quality throughout the colon, while a PC interval of 3 to 7 h was an acceptable scale for bowel preparation. It has been reported that after the optimal time window, small-bowel contents of bubbles and viscous bile-stained mucous are evacuated into the colon and restrict the visibility of the colonic mucosa, especially in the right colon. Small flat lesions that are difficult to identify in the right colon can easily be missed by the endoscopist if concealed by opaque small bowel effluent. Accordingly, same-day preparation with split-doses and full-doses improves bowel cleansing and increases the detection rate of small adenomas[28].

Compliance with dietary instructions has been documented as another factor affecting the quality of bowel preparation. A meta-analysis by Chen *et al*[32] that analyzed factors of inadequate bowel preparation found no significant difference between a low residual diet and a clear liquid diet the day before colonoscopy. In our meta-analysis, in all included trials, patients in both arms followed a low residual diet or clear liquid diet, and no heterogeneity was found for dietary restriction before colonoscopy.

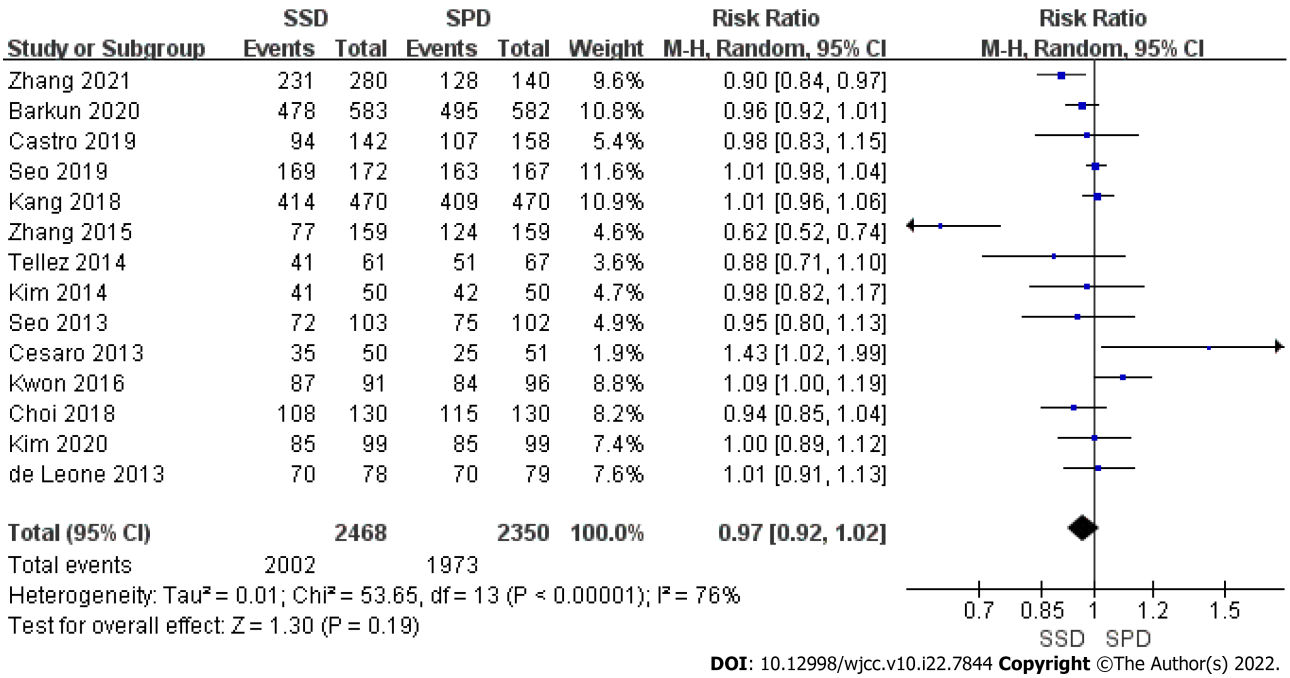

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Figure 2 Forest plot of adequate bowel cleanliness. SSD: Same-day single-dose regimen; SPD: Split-dose regimen; CI: Confidence interval.

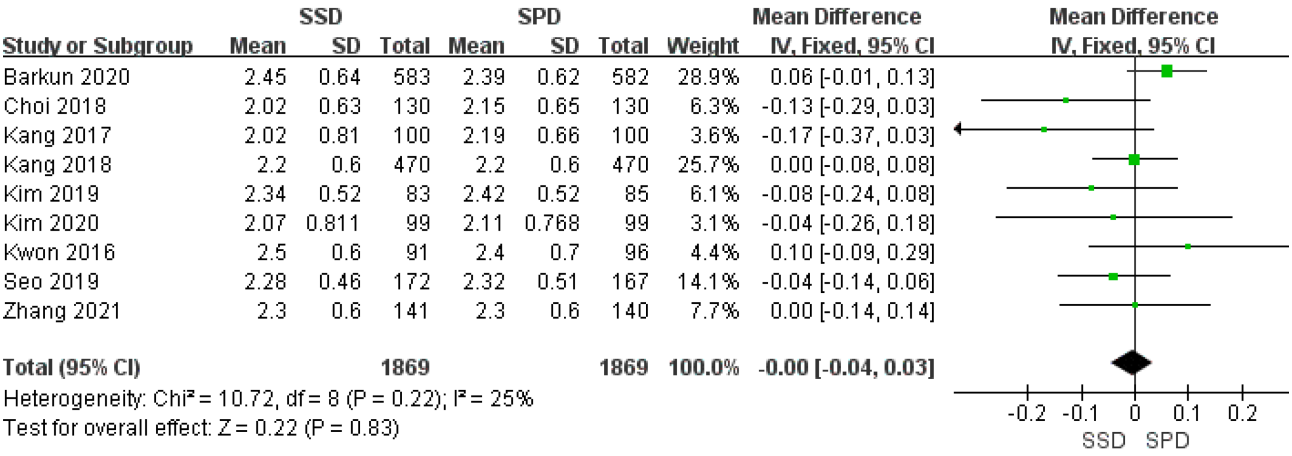

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Figure 3 Forest plot of right colon Boston Bowel Preparation Scale. SSD: Same-day single-dose regimen; SPD: Split-dose regimen; CI: Confidence interval.

Consistent with a study by Avalos *et al*[30] we found that significantly less sleep disturbance was associated with the SSD PEG-based regimens without adjuvant laxatives than the SpDs PEG. However, the incidence of sleep disturbance in combination regimens of low-volume (2 L) SSD with an adjuvant laxative (bisacodyl, linaclotide or prucalopride) was comparable with SpDs regimens. It was noted that bowel movements induced by bisacodyl taken on the night before colonoscopy occurred after waking up. De Leone *et al*[28] suggested that sleeping difficulties were more likely to be attributed to the anxiety for the day-after procedure rather than nocturnal awakenings for defecation or abdominal pain in patients who took the combination regimen consisting of low-volume PEG with bisacodyl. Based on these findings, we conclude that the split-dose regimen taken the night before colonoscopy and anxiety for the procedure play an important role in the sleep quality of patients.

Patient tolerance of bowel preparation regimens mainly depends on sleep disruptions and adverse effects such as nausea, vomiting, abdominal pain/cramping and bloating. Significantly less nocturnal awakenings for defecation were reported in the SSD PEG-based arm than other SpDs PEG regimens, and no significant difference in other adverse effects was found. Given the low incidence of sleep disturbance and abdominal pain, patients were more tolerant to the SSD PEG-based arm for bowel preparation.

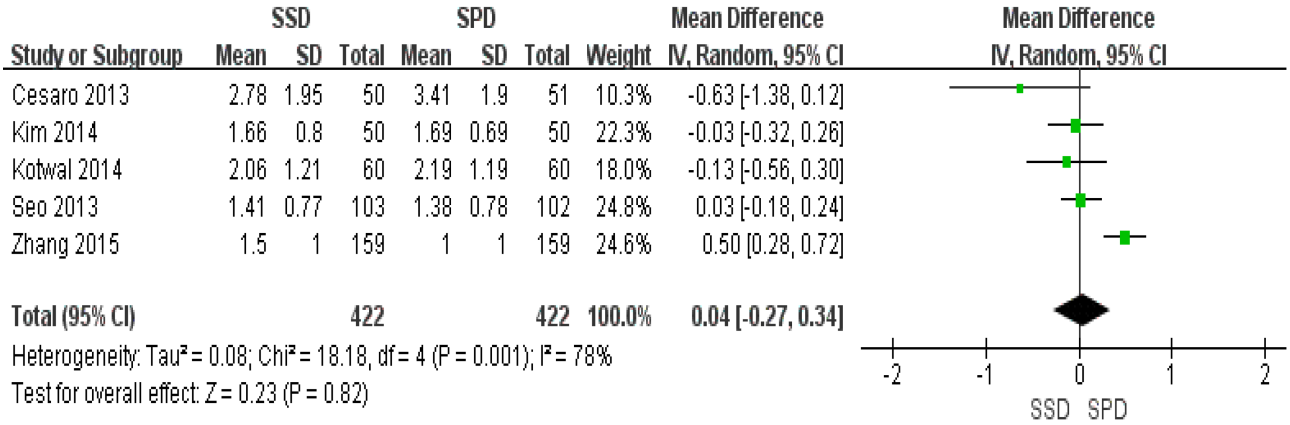

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Figure 4 Forest plot of right colon Ottawa Bowel Preparation Scale. SSD: Same-day single-dose regimen; SPD: Split-dose regimen; CI: Confidence interval.

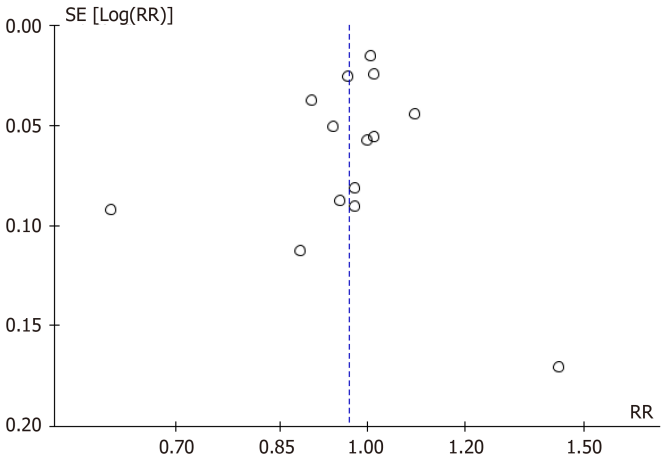

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Figure 5 Funnel plots. RR: Relative risk.

Moreover, patients who received the low-volume (2 L) SSD PEG regimens exhibited increased willingness to repeat the procedure using the same preparation. However, the large-volume (4 L) SSD PEG arm was not superior to the SpDs regimens in terms of willingness to repeat the procedure using the same preparation. This finding suggested that patient intolerance to ingestion of large volumes over a short period was a significant factor contributing to non-compliance and decreased willingness to repeat the procedure with the same regimen.

There are several advantages to this meta-analysis. We performed the extensive retrieval strategy and included only randomized controlled trials. Other advantages were related to the quality of the included studies and to the publication bias. The methodological quality assessment of the included studies was moderate to high according to the Cochrane risk of bias tool and modified Jadad score. For the publication bias, in our meta-analysis a rough symmetry was present with the use of funnel plots and the Grades of Recommendation, Assessment, Development and Evaluation approach.

This meta-analysis has several limitations. First, we enrolled only adult patients and excluded those who had undergone colorectal surgery and/or bowel obstruction; accordingly, the findings of our meta-analysis cannot be generalized for all patients that undergo colonoscopy. Moreover, it is widely acknowledged that constipation is a high-risk factor for poor preparation; however, there was a certain level of inconsistency on the proportion and severity of constipation within the included studies. Furthermore, adenoma detection rate was not evaluated as a secondary outcome. Indeed, adenoma detection rate is a quality indicator for colonoscopy and can be influenced by the endoscopist's level of expertise and the quality of the bowel preparation[33].

CONCLUSION

We found that the SSD regimens of PEG were non-inferior to large-volume (≥ 3 L) SpDs PEG in terms of bowel cleanliness. Better tolerance to SSD PEG was accounted for by less sleep disturbance and abdominal pain than with the SpDs regimens. Given its efficacy and tolerability, the low-volume (2 L) SSD PEG regimen has huge prospects as a superior alternative to SpDs regimens as long as the optimal PC interval and dietary instructions for bowel preparation are respected.

ARTICLE HIGHLIGHTS

Research background

High volume (4 L) split-dose regimens (SpDs) of polyethylene glycol (PEG) have been recommended as the gold-standard regimen for bowel preparation, but its large volume of fluids and poor tolerability have become sources of patient dissatisfaction.

Research motivation

The same-day single-dose (SSD) PEG has been recommended as an alternative for bowel preparation. However, its superiority compared to other regimens is a matter of debate.

Research objectives

To seek one PEG-based regimen for bowel preparation with characteristics of equal cleansing efficacy, reducing the preparation volume and improving patient tolerance.

Research methods

We conducted a systematic review and meta-analysis to compare the efficacy and tolerability of SSD PEG-based arm *vs* large-volume (≥ 3 L) SpDs PEG solutions for bowel preparation before colonoscopy, regardless of adjuvant laxative use.

Research results

A total of 18 studies were included. There was no statistically significant difference of adequate bowel preparation, right colon Boston Bowel Preparation Scale and right colon Ottawa Bowel Preparation Scale between (2 L/4 L) SSDs and large-volume (4 L/3 L) SpDs, regardless of adjuvant laxative use. The use of SSDs had advantages of less sleep disturbance and lower incidence of abdominal pain. Patients that received low-volume (2 L) SSDs showed more willingness to repeat the procedure than patients receiving SpDs ($P < 0.05$).

Research conclusions

Regardless of adjuvant laxative use, the (2 L/4 L) SSDs PEG-based arm was considered equal or better than the large-volume (≥ 3 L) SpDs PEG regimen in terms of bowel cleanliness and tolerability.

Research perspectives

Given its efficacy and tolerability, the low-volume (2 L) SSD PEG regimen has huge prospects as a superior alternative to SpDs regimens as long as the optimal preparation-to-colonoscopy interval and dietary instructions for bowel preparation are respected.

FOOTNOTES

Author contributions: Pan H, Fang CY, Chen JS and Wang C contributed to data curation and writing the original draft; Zheng XL and Pan H contributed to the methodology; Zheng XL, Pan H and Fang CY contributed to the project administration; Chen YD, Huang JM and Zhou YS contributed to the supervision; Zheng XL and He LP contributed to the writing, reviewing and editing; all authors have read and approved the final manuscript.

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