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ABOUT COVER

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AIMS AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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Sodium picosulphate or polyethylene glycol before elective colonoscopy in outpatients? A systematic review and meta-analysis

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Abstract

AIM

To determine the best option for bowel preparation [sodium picosulphate or polyethylene glycol (PEG)] for elective colonoscopy in adult outpatients.

METHODS

A systematic review of the literature following the PRISMA guidelines was performed using Medline, Scopus, EMBASE, Central, Cinahl and Lilacs. No restrictions were placed for country, year of publication or language. The last search in the literature was performed on November 20th, 2017. Only randomized clinical trials with full texts published were included. The subjects included were adult outpatients who underwent bowel cleansing for elective colonoscopy. The included studies compared sodium picosulphate with magnesium citrate (SPMC) and PEG for bowel preparation. Exclusion criteria were the inclusion of inpatients or groups with specific conditions, failure to mention patient status (outpatient or inpatient) or dietary restrictions, and permission to have unrestricted diet on the day prior to the exam. Primary outcomes were bowel cleaning success and/or tolerability of colon preparation. Secondary outcomes were adverse events, polyp and adenoma detection rates. Data on intention-to-treat were extracted by two independent authors and risk of bias assessed through the Jadad scale. Funnel plots, Egger's test, Higgins' test (I^2) and sensitivity analyses were used to assess reporting bias and heterogeneity. The meta-analysis was performed by computing risk difference (RD) using Mantel-Haenszel (MH) method with fixed-effects (FE) and random-effects (RE) models. Review Manager 5 (RevMan 5) version 6.1 (The Cochrane Collaboration) was the software chosen to perform the meta-analysis.

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RESULTS
662 records were identified but only 16 trials with 6200 subjects were included for the meta-analysis. High heterogeneity among studies was found and sensitivity analysis was needed and performed to interpret data. In the pooled analysis, SPMC was better for bowel cleaning [MH FE, RD 0.03, IC (0.01, 0.05), $P = 0.003$, $I^2 = 33\%$, NNT 34], for tolerability [MH RE, RD 0.08, IC (0.03, 0.13), $P = 0.002$, $I^2 = 88\%$, NNT 13] and for adverse events [MH RE, RD 0.13, IC (0.05, 0.22), $P = 0.002$, $I^2 = 88\%$, NNT 7]. There was no difference in regard to polyp and adenoma detection rates. Additional analyses were made by subgroups (type of regimen, volume of PEG solution and dietary recommendations). SPMC demonstrated better tolerability levels when compared to PEG in the following subgroups: "day-before preparation" [MH FE, RD 0.17, IC (0.13, 0.21), $P < 0.0001$, $I^2 = 0\%$, NNT 6], "preparation in accordance with time interval for colonoscopy" [MH RE, RD 0.08, IC (0.01, 0.15), $P = 0.02$, $I^2 = 54\%$, NNT 13], when compared to "high-volume PEG solutions" [MH RE, RD 0.08, IC (0.01, 0.14), $I^2 = 89\%$, $P = 0.02$, NNT 13] and in the subgroup "liquid diet on day before" [MH RE, RD 0.14, IC (0.06, 0.22), $P = 0.0006$, $I^2 = 81\%$, NNT 8]. SPMC was also found to cause fewer adverse events than PEG in the "high-volume PEG solutions" [MH RE, RD -0.18, IC (-0.30, -0.07), $P = 0.002$, $I^2 = 79\%$, NNT 6] and PEG in the "low-residue diet" subgroup [MH RE, RD -0.17, IC (-0.27, 0.07), $P = 0.0008$, $I^2 = 86\%$, NNT 6].

CONCLUSION
SPMC seems to be better than PEG for bowel preparation, with a similar bowel cleaning success rate, better tolerability and lower prevalence of adverse events.

Key words: Sodium picosulphate; Polyethylene glycol; Bowel cleaning success; Tolerability; Colonoscopy; Randomized clinical trials; Meta-analysis

Core tip: Previous meta-analyses did not consider patient status (if inpatient or outpatient) for inclusion in the studies and grouped different types of patients. They also failed to conduct analyses by subgroups (regimen schedule, volume of polyethylene glycol solution, dietary restriction) in order to elucidate confounding factors. This is the first systematic review and meta-analysis for this specific group of patients and the first to communicate effectiveness by NNT.

INTRODUCTION

Colonoscopy is the gold-standard method for polyp and adenoma detection and can reduce both incidence and mortality for colorectal cancer[1,2]. Different devices and tools were created to improve mucosal exposure and the detection of neoplastic lesions[3] and carbon dioxide insufflation used to increase tolerance to colonoscopy[4]. Even so, bowel cleaning is still the cornerstone for optimizing colonoscopy.

Cleaning efficacy is the most important characteristic of bowel cleansers as the quality of cleaning directly impacts on evaluation, difficulty, speed, and completeness of colonoscopy[5,6]. As inadequate bowel preparation results in missing pre-cancerous lesions and increases the costs related to repetition of colonoscopy, the choice of the product should aim to achieve high-quality bowel preparation and optimize the evaluation[7,8].

Polyethylene glycol (PEG)-based solutions are the most widely used and studied bowel cleansers. PEG is an isosmotic laxative which achieves high-quality bowel preparations through the ingestion of large volumes of the solution (approximately four liters). Their poor palatability and the volume to be ingested increase the

incidence of adverse events and decrease full intake of the medication[9-11].

Among purgatives that have been recently developed to overcome these limitations is sodium picosulphate with magnesium citrate (PICO or SPMC), a low-volume dual laxative which may cause less gastrointestinal symptoms. It promotes colon cleansing by retaining fluids in the colon and by increasing the frequency and the force of peristalsis; however, due to electrolyte exchanges it can cause dehydration and biochemical impairments[12,13].

PEG solutions trials date from 1982 and have contributed to their consolidation as the most widely used solutions[14]. Although sodium picosulphate has been used for several years in the United Kingdom and Australia, large randomized clinical trials evaluating its efficacy are recent and usually compare it to PEG solution[13,15]. Other solutions that have already been compared to SPMC are oral sulfate solution and mannitol[16,17].

The highest level of evidence for medical practice is found in meta-analyses of randomized clinical trials. Among meta-analyses that compared PEG and sodium picosulphate for bowel preparation before colonoscopy[18-20], the largest one (Jin *et al*[20]) included 21 studies and showed no difference in bowel cleaning efficacy between them. Unfortunately, inclusion criteria for population did not specify patient status (their condition of inpatient or outpatient), which impaired the quality of the results obtained to be applied in medical practice as inpatient status is an independent risk factor for inadequate bowel preparation[11,21].

As most colonoscopies are performed in outpatients and there is no established evidence comparing sodium picosulphate and PEG cleaning efficacy and tolerability in this subset of patients, we therefore conducted this meta-analysis. Regimens adopted for bowel preparation were also considered for analysis since there are studies demonstrating differences in cleaning efficacy depending on the kind of the regimen adopted[22].

MATERIALS AND METHODS

Protocol and registration
Strategies for the search, selection and analysis were pre-specified as stated in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and documented in a protocol registered in International Prospective Register of Systematic Reviews (PROSPERO) database (CRD 42016050059)[23].

Eligibility criteria
Eligibility criteria were based on PICOS (population, intervention, comparison, outcomes and study design) strategy. Only randomized clinical trials with full texts published were included irrespective of language or time of publication. The subjects included were adult outpatients who underwent bowel cleaning for elective colonoscopy. The included studies compared sodium picosulphate/magnesium citrate and PEG. Exclusion criteria were inpatient status, groups with specific comorbidities, combination of different products for the preparation of the solution, association with enema or enteroclysis and the absence of dietary restrictions on the day prior to the exam. Primary outcomes evaluated were efficacy and tolerability. Secondary outcomes were prevalence of adverse events, and polyp and adenoma detection rates.

Search strategy and study selection
Two independent authors identified records in the following electronic databases: Medline, Scopus, EMBASE, Central, Cinahl and Lilacs. No limits were applied for country, year of publication or language. The last search in the literature was performed on November 20th, 2017. Search keywords were "colonoscopy", "colonosc*", "sodium picosulphate", "sodium picosulfate", "polyethylene glycol", "polyethylene glycols" and "random*". Full search strategy for each database is shown in Supplementary material (Appendix 1). Medline was the main database for the development of the search strategy, as follows: "(colonoscopy OR colonoscopies OR bowel preparation OR bowel prep* OR bowel cleansing OR bowel clean* OR colon preparation OR colon prep* OR colon cleansing OR colon clean' AND (sodium picosuffate OR sodium picosulphate OR picosulfate OR picosulphate) AND (polyethylene OR polyethylene glycol OR polyethylene glycols OR polyethylene glicol OR polyethylene glicols)".

Two independent authors performed eligibility assessment and studies selection. Duplicated references were excluded and the remaining ones were screened by title and abstract. Those that met any of the exclusion criteria were disregarded. The full

texts of the remaining records were assessed and the studies that met the eligibility criteria were included for the meta-analysis. The gray literature search was made in the references of the included studies and a third author solved disagreements between the other two.

Data collection process

Data available in texts, charts or tables were extracted by two independent authors using a previously devised form. Data presented in percentage were converted into frequency and rounded up if the number obtained was not an integer.

Data items: The following data were collected for each trial: (1) characteristics of participants; (2) type of intervention; (3) outcomes; and (4) type of outcome measurement (including definition, score adopted, bowel cleansing success, tolerability, adverse events prevalence, polyp and adenoma detection rate).

The following definitions standardizations were previously established for outcomes: (1) bowel cleaning success, defined as the number of patients with successful cleaning by either the study or by the assessment score as "excellent, adequate, good or clean"; (2) tolerability, defined as the number of patients who ingested the entire bowel cleaning preparation or the minimum established by the study as acceptable; (3) adverse events prevalence, defined as the number of patients affected by at least one adverse event; (4) polyp detection rate (PDR), defined as the number of patients with at least one polyp detected during colonoscopy; (5) adenoma detection rate (ADR), defined as the number of patients with at least one adenoma detected during colonoscopy.

Risk of bias in individual studies

As treatment effect size may differ due to selection, performance, detection and attrition bias, the methodological evaluation of the studies was performed. Two authors working independently determined the adequacy of randomization, adequacy of blinding, and the description of withdrawals and dropouts using the Jadad scale[24] for the evaluation of the randomized clinical trials.

Summary measures

Meta-analysis was preferably performed using intention-to-treat (ITT) data. Per-protocol (PP) data were only used when ITT data were not available. Outcomes evaluated were dichotomous (bowel cleansing success, tolerability, adverse events prevalence, polyp and adenoma detection rate). Risk difference (RD) with 95% confidence intervals (CI) was calculated for each outcome.

Synthesis of results

Meta-analyses were performed by computing RD for dichotomous outcomes using Mantel-Haenszel method (MH) with fixed-effects (FE) and random-effects (RE) models. Heterogeneity was assessed by Cochran's Q test (P value), which examines the null hypothesis that all studies are evaluating the same effect, and by Higgins' test (I^2), which quantifies inconsistency across studies and describes the percentage of the variability in effect estimates that is due to heterogeneity[25]. FE model was used in the presence of null or low heterogeneity ($I^2 < 50\%$) assuming the true effect size did not differ across studies. However, an I^2 value equal to or greater than 50% was considered substantial heterogeneity and RE model was preferred to FE as true effect size varied from one study to another and a more conservative approach for statistical significance was needed. The number needed to treat (NNT) for each outcome with statistical difference was also calculated. Review Manager 5 (RevMan 5) Version 6.1 (by the Cochrane Collaboration, 2015) was the software chosen to run the meta-analysis.

Risk of bias across studies

Reporting bias across studies was evaluated by a graphic diagnostic tool named funnel plot. For each trial, the treatment effect was plotted against the measure of study precision (represented by the inverse of its standard error) and the symmetry of scatter plot assessed by Egger's test[26]. Asymmetrical funnel plot suggests the presence of reporting bias (absence of low-precision studies that have negative or non-significant results), methodological bias or true heterogeneity between smaller and larger studies.

Additional analysis

In the presence of an asymmetrical funnel plot or high heterogeneity, ($I^2 \geq 50\%$) a sensitivity analysis was conducted to explore how the results of the meta-analysis change under different assumptions[27]. Heterogeneity and funnel plot before and after the removal of each study from the meta-analysis was assessed to identify the study

accounting for the inconsistency among trials (usually due to a markedly different intervention effect or an undue influence on the summary results). If heterogeneity was reduced to below 50% after the removal of the outlier, the corrected intervention effect estimate was applied and the interpretation of results made with caution. If inconsistency did not decrease, it was considered true heterogeneity.

Subgroup analyses were performed for variables that could knowingly influence the effect sizes: (1) types of regimen [(A) full intake on the day prior the exam; (B) intake split into the day prior and the same day of the exam; and (C) intake only on the same day of the exam]; (2) volume of PEG-based solution [(A) low-volume group - 2L or less; and (B) high-volume group - more than 2L]; (3) dietary restrictions on day before [(A) low fiber or low residue diet; and (B) liquid diet].

RESULTS

Search and study selection

A total of 662 records were identified through a search in the databases (57 in MEDLINE, 128 in EMBASE, 384 in Scopus, 85 in CENTRAL, 8 in CINAHL and none in LILACS) (Figure 1). After adjusting for duplicates, 457 records remained and were evaluated by title and abstract. 390 records were excluded because they met one or more exclusion criteria. Of the 67 remaining, 28 were then excluded (2 were short communications and 26 were congress abstracts). The full texts of the remaining 39 records were examined and 23 were rejected. Reasons are presented in Supplementary material (Appendix 2). At the end, 16 studies were included in the meta-analysis[9,11,23-36].

Studies characteristics

All 16 studies selected were RCTs, with full text available, published in English between 1996 and 2017. Included studies involved 6200 participants, from 18 to 86 years of age. Main patient exclusion criteria were age, renal insufficiency, congestive heart failure, recent myocardial infarction, constipation, gastrointestinal or colon disorders, and previous colorectal surgery (Table 1).

Thirteen of 16 studies were multicenter. Six studies were conducted in South Korea, two in the United States and eight in different countries. Brand names of sodium picosulphate based products were CitraFleet®, Pico®, Pico-Salax®, Picolax®, Picoprep®, Picolight powder® and Prepopik®, while polyethylene glycol-based products were Colyte®, ColonLytely®, Coolprep powder®, Endofalk®, Half-Lytely®, Kleanprep®, Moviprep®, New Meroken® and Fortrans™.

Seven studies compared split dose regimens[28-30,32,33,38,40] and 4 studies compared day-before dose[13,33,34,41]. None of the included studies compared same-day dose. Four studies compared different regimens of bowel cleaning between the two products[15,31,39,40] and three others[35-37] according to the interval time to colonoscopy.

Two different adjuvants were used in 5 studies. Four studies[13,15,36,41] used Bisacodyl with PEG and 2 studies used it with SPMC[29,41]. Magnesium citrate was also used separated from sodium picosulphate in one study[36].

Dietary restrictions on the day prior to the procedure were considered in all studies. In four studies, patients were given liquid diet[13,15,34,36] and in twelve studies a low-fiber or low-residue diet[23-26,28,30,32-36] was allowed.

Outcomes

Sixteen studies evaluated bowel cleaning success. Efficacy was measured by five different bowel preparation scales: a 4-point scale[42], Boston bowel preparation scale[29,30,32,37,38], Aronchick scale[13,15,32,33,40,41], Harefield scale[32] and Ottawa bowel preparation scale[15,35,36,39,40]. Tolerability was evaluated in 12 studies[9,11,23,24,28-30,32-36], adverse events prevalence in 13 studies[13,15,28,29,31,34,37-39,41], PDR in seven[28,31,37-41] and ADR in five studies[31,32,38,39,41].

Risk of bias within studies

The maximum Jadad score obtained was three, since patient blinding was not possible due to the different characteristics of cleaning protocols (Table 2). Eleven studies scored three points[9,11,26-28,30-34,36], four studies scored two points[28-30,34] and one study scored just one point[40]. All of them were randomized, but Kim *et al*[40] did not describe the randomization method and Regev *et al*[34] randomized patients inappropriately. Kim *et al*[40], Leitao *et al*[28], Kim *et al*[29] and Munsterman *et al*[30] also failed to describe losses.

Results of individual studies

Raw data of included studies are presented in Supplementary material (appendix 3).
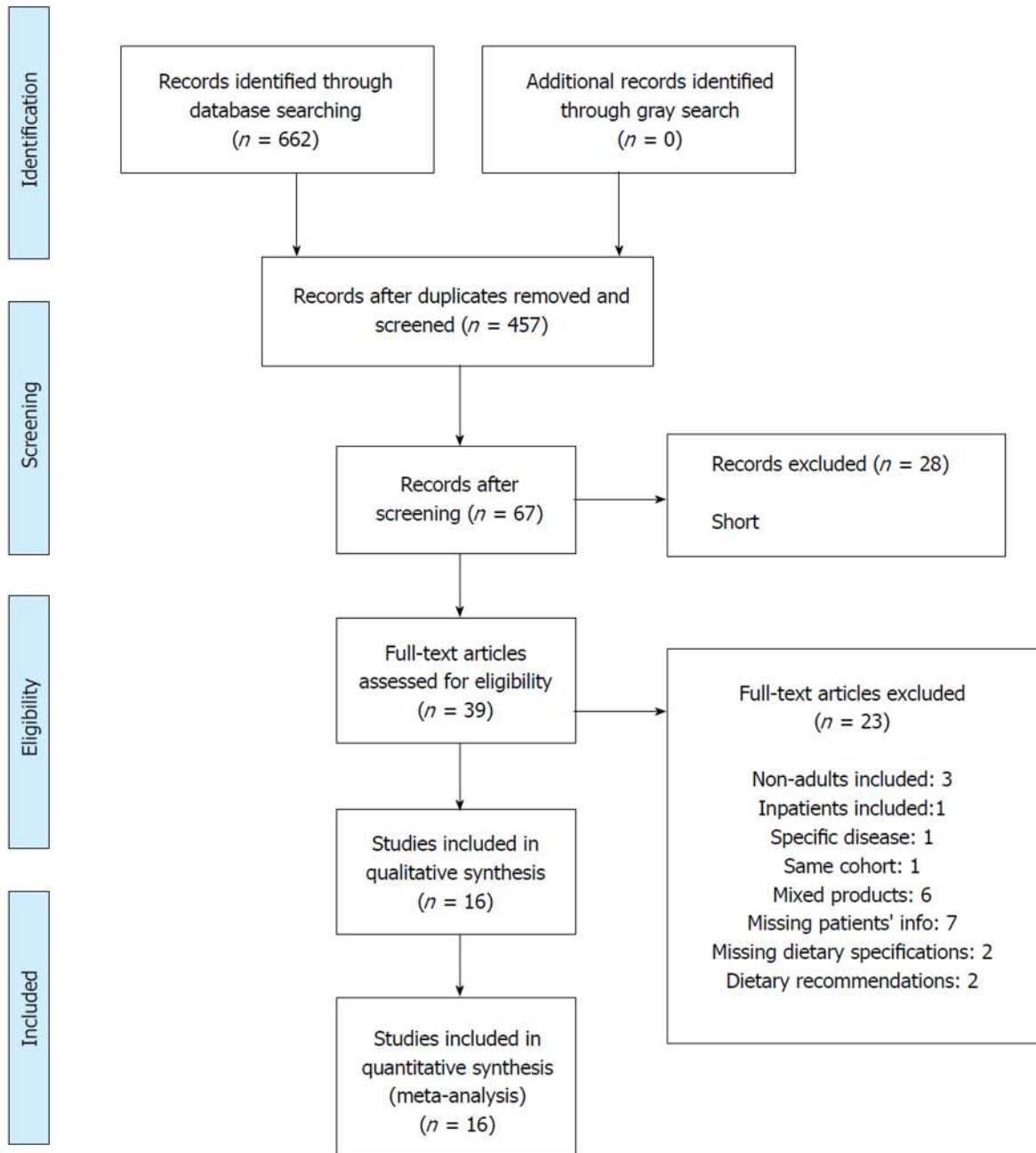
Figure 1 Flow diagram of included studies.

One study (Kim *et al*[40]) presented four different treatment arms, two of which were SPMC arms (with 2 or 3 sachets in split dose regimen) and two others of PEG arms (4 L of solution in a split or in a same-day dose regimen). For the analysis, the study was dismembered into two based on treatment regimens (Kim *et al*[40], SPMC split dose arms *vs* PEG split dose; and Kim *et al*[40], SPMC split dose *vs* PEG same-day dose).

Another study (Kojecky *et al*[33]) presented three different treatment arms (PEG, PEG plus ascorbic acid and SPMC) with two subgroups each (day-before dose and split dose). PEG and PEG-A treatment arms were grouped and the study dismembered into two according to the regimen (Kojecky *et al*[33], day-before dose; and Kojecky *et al*[33], split dose).

Bowel cleansing success: Twelve studies (corresponding to fourteen comparisons) demonstrated that sodium picosulphate and PEG had the same efficacy in bowel cleaning[13,29,33-40], two studies demonstrated that sodium picosulphate was better[15,41] and one study demonstrated that PEG was better[31].

Tolerability: Three studies (four comparisons) demonstrated that both obtained the same tolerability level[37,39,40], seven demonstrated that SPMC was better

Table 1 Studies characteristics

STUDY	SITE	POPULATION	INTERVENTION (ITT/PP)	COMPARISON (ITT/PP)	OUTCOMES
Regev et al[34]	1	29 to 86 y	Pico-Salax (1+1+1)/0 sachets	New-Meroken® 3/0 L	Bowel cleansing quality
	Israel		+ (200/h for 16h)/0 mL of water		Cecal intubation
		ITT: 68	+ clear liquid diet	+ clear liquid diet	General discomfort
		PP: 68	39/39	29/29	Medication Intake
					Adverse events
Lawrance et al[35]	1	18 to 75 y	Pico® (1+1)/0 sachets for morning procedure or	ColonLytely® 4/0 L for morning procedure or	Bowel cleansing quality
	Australia		Pico 1/1 sachets for afternoon procedure	ColonLytely® 4/0 L for afternoon procedure	
			+ liquid	+ clear liquid 2/0	
		ITT: 634	+ low residue diet	284/279	Medication Intake
		PP: 625	171/169		
			CB fleet® (45+45)/0 mL		Mucosal inflammation
			+ (750+750)/0 mL of water for morning procedure or		
			CB fleet® 45/45 mL		
			+ 750/750 mL of water for afternoon procedure		
			+ low residue diet		
			179/177		
Kao et al[36]	1	18 to 75 y	SPMC (1+1+MC)/0 sachets for morning procedure or	PEG 4/0 L for morning procedure or	Bowel cleansing quality
	Canada		SPMC (1+1)/MC sachets for afternoon procedure	PEG 2/2 L for afternoon procedure	Bowel cleansing quality according to the procedure time
		ITT: 834	+ liquid	+ liquid	Tolerability
		PP: 790	+ clear liquid diet	+ clear liquid diet	
			194/194	218/210	Adherence
			NaP 45/45/0 mL for morning procedure or	PEG 2/0 L + bisacodyl 20/0 mg for morning procedure or	Sleeping hours
			NaP 0/45/45 mL for afternoon procedure	PEG 0/2 L + bisacodyl 20/0 mg for afternoon procedure	Willingness to reuse
			+ liquid	+ liquid	Safety
			+ clear liquid diet	+ clear liquid diet	
			164/164	214/210	Ischemic colitis
Katz et al[15]	12	18 to 80 y	Prepopik® (1+1)/0 sachets	Half-Lytely e bisacodyl Tablets® 2/0 L	Bowel cleansing quality
	USA		+ (1200+720)/0 mL of liquid	+ 10/0 mg bisacodyl	Acceptability
					Tolerability
		ITT: 603	+ clear liquid diet	+ clear liquid diet	Medication Intake
		PP: 598			Ease to use medication
			300/296	303/302	General experience
					Taste
					Willingness to reuse
					Adverse events
Manes et al[37]	3	18 to 85 y	CitraFleet® (1+1)/0 sachets	Moviprep® 2/0 L	Bowel cleansing quality
	Italy		+ 3/0 L of liquid for morning procedure or	+ 1/0 L of liquid for morning procedure or	Bowel cleansing quality of right colon
		ITT: 293	CitraFleet® 1/1 sachets	Moviprep® 1/1 L	Polyps detected

Study	Centers/Country	Age	Intervention	Comparison	Outcomes
			PP: 285	+ 1.5/1.5 L of liquid for afternoon procedure	+ 500/500 mL of liquid for afternoon procedure	Acceptance
				+ low-fiber diet	+ low-fiber diet	Tolerability
				145/140	148/145	Adherence
						Adverse events
Rex *et al*[15]	10 USA	18 to 80 y	Prepopik® 1/1 sachets	Half-Lytely e bisacodyl Tablets® 2/0 L	Bowel cleansing quality
			+ 1200/720 mL of liquid	+ bisacodyl 10/0 mg	Acceptability
				+ clear liquid diet	Tolerability
		ITT: 608	+ clear liquid diet		Ease to use medication
		PP: 601			Medication Intake
					Taste
			NA/305	NA/298	Willingness to reuse medication
					Adverse events
					Colonoscopy before
Jeon *et al*[38]	1 South Korea	20 to 80 y	Picolight powder® (1+1)/1 sachet	Coolprep powder® 1/1 L	Bowel cleansing quality
			+ (1+1)/1 L of water	+ 500/500 mL of water	Cecal intubation
			+ low-fiber diet	+ low-fiber diet	Withdrawal time
		ITT: 430			ADR
		PP: 388			PDR
					Tolerability
			215/195	215/193	Satisfaction
					Adverse events
Kang *et al*[39]	1 South Korea	18 to ou mais	Picolight® 0/(1+1)	Colyte® 2/2 L	Bowel cleansing quality
			+ 0/≥ 1 L of water	+ low-fiber diet	Tolerability
		ITT: 197	+ low-fiber diet	99/99	Adverse events
		PP: 197	98/98		Sleep time quantity
					PDR
					ADR
Kim *et al*[40]	1 South Korea	18 to 75 y	SPMC 1/1 sachets	PEG 0/4 L	Bowel cleansing quality
			+ 1/1 L of liquid		Adherence
			+ low-fiber diet	+ low-fiber diet	Medication Intake
		ITT: 200	50/50	50/50	
		PP: 200	SPMC (1+1)/1 sachets	PEG 2/2 L	Tolerability
			+ (1+1)/1 L of liquid		Taste
			+ low-fiber diet	+ low-fiber diet	Biochemical changes
			50/50	50/50	Adverse events
Kim *et al*[41]	1 South Korea	18 to 80 y	Picolight (1+1)/0 sachets	Standard PEG 4/0 L	Acceptability
			+ 2L of water		Adherence to instructions
		ITT: 194	+ bisacodyl 10/0 mg	+ bisacodyl 10/0 mg	Bowel cleansing quality
		PP: 184	+ low-fiber diet (ZeroCol)	+ semi-fluid diet	Adverse events
			97/94	97/90	Willingness to reuse medication
Leitao *et al*[28]	3 Norway	18 to 80 y	CitraFleet® 1/1 sachets	Enddealk® 2/1L	Bowel cleansing quality
			+ 2/2 L of water	+ 0/1 L of liquid	Tolerability
		ITT: 368	+ no-grains diet	+ diet without crops	Adherence
		PP: 368			PDR
			179/179	189/189	Cecal intubation time
					Cecal intubation
Kim *et al*[29]	13 South Korea	20 to 75 y	sachets	Standard PEG 2/2 L	Bowel cleansing quality
			+ 2/2 L of water	no bisacodyl	Satisfaction
			+ bisacodyl 10/0 mg	+ low-fiber diet	Tolerability
			+ low-fiber diet		Medication Intake

Study	Centers	Population	Intervention	Control	Outcomes
		ITT: 387	193/181	194 / 184	Ease to use
		PP: 365			Taste
					Willingness to reuse
					Adverse events
Munsterman *et al*[30]	1	18 to 80 y	Picoprep® 1/1 sachets for morning procedure or	Kleanprep® 3/1 L for morning procedure or	Bowel cleansing quality
	Netherlands	ITT: 173	Picoprep® 1/1 sachets for afternoon procedure	Kleanprep® 2/2 L for afternoon procedure	
		PP: 172	+ 2/2 L of water	+ additional liquid	Tolerability
			+ low-fiber diet	+ low-fiber diet	
			88/87	85/85	
Pohl *et al*[31]	17	40 to 80 y	CitraFleet® (1+1)/0 sachets	Moviprep® 1/1 L	Patients with at least one polyp or flat lesion
	Germany	ITT: 399	+ 250mL/h of water after sachet	+ 500/500 mL of liquid	Patients with at least one adenoma
		PP: 398			Cancer detection rate
			+ fibers restriction diet	+ fibers restriction diet	Flat lesion detection rate
			NA/197	NA/201	Advanced lesions detection rate
Yoo *et al*[32]	1	18 to 80 y	Picolight® 1/1 sachets	Coolprep® 1/1 L	Bowel cleansing quality
	South Korea		+ 1/1 L of water	+ 500/500 mL of water	Bubble score
		ITT: 200	+ low-fiber diet	+ low-fiber diet	Tolerability
		PP: 200			
			100/100	100/100	Satisfaction
Kojecky *et al*[33]	3	18 to 99 y	Picoprep® 2/0 sachets	Fortrans™ 4/0 L	Length of preparation
	Czech Republic		+ 2L of water	94/102	
		ITT: 612	92/102	Fortrans™ 3/1 L	Time to colonoscopy
				87/102	
		PP: 584	OR	Moviprep™ 2/0 L	
				+ 1/0 L of fluids	
			Picoprep® 1/1 sachets	96/102	Bowel cleansing quality
			+ 1/1 L of water		
			86/102	Moviprep™ 1/1	
				+ 0.5/0.5 L of fluids	
				93/102	Tolerability score
			+ low residue diet	+ low residue diet	

* In intervention and control columns, slash separates different days and plus sign separates different doses on the same day; * ITT: number of randomized patients (intention to treat); * PP: number of treated patients (per protocol); * NR: not reported in full-text; * PDR: polyp detection rate; * ADR: adenoma detection rate.

tolerated[13,15,28,34,35,40,41] and one that PEG was better than SPMC[39].

Adverse events prevalence: Eight studies reported adverse events prevalence as a dichotomous outcome. Five of them showed that both products regimens presented the same adverse events prevalence[13,15,28,34,38] and three of them that SPMC regimens achieved fewer adverse events[29,31,41].

PDR: Five studies (corresponding to six comparisons) demonstrated that PDR was the same with both products regimens[31,37,38,40,41]. In one study there was statistical difference in favor of SPMC[28].

ADR: Only five studies assessed ADR and none of them showed difference between SPMC and PEG[31,32,38,39,41].

Syntheses of results
The overall meta-analysis for each outcome was performed with heterogeneity assessment and cumulative treatment effect.

Bowel cleaning success: An asymmetrical funnel plot and high heterogeneity (I^2 = 91%, $P < 0.00001$) were observed among the 15 studies included. An outlier study

Table 2 Assessment of risk of bias by JADAD scale

#	STUDY	Randomize-d? (1 pt)	Randomiza-tion method	Adequate randomizat ion? (1 pt)	Double blind? (1 pt)	Masking method	Adequate masking? (1 pt)	Loss description ? (1 pt)	Jadad (0-5 pts)	GENERAL QUALITY
1	Regev *et al*[34]	Yes	Randomizati-on per patients' ID (odd or even numbers)	No	No	Endoscopist blind for the preparation regimen	No	Yes	2	Intermidiate
2	Lawrance *et al*[35]	Yes	Randomized using Generator Pro 1.69 (Segobit software) in ratio 2:1:1 (PEG:NaP:Pi-co)	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
3	Kao *et al*[36]	Yes	Randomizati-on in blocks of 8 and stratified per AM/PM using a computer-generated table	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
4	Katz *et al*[15]	Yes	Randomizati-on numbers allocated sequentially by voice system	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
5	Manes *et al*[37]	Yes	Randomizati-on by computer-generated sequence	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
6	Rex *et al*[15]	Yes	Randomizati-on numbers allocated sequentially by voice system	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
7	Jeon *et al*[38]	Yes	Randomizati-on by computer-generated table	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
8	Kang *et al*[39]	Yes	Randomizati-on in blocks using website randomizati-on.com	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
9	Kim *et al*[40]	Yes	Not described	No	No	Endoscopist blind for the preparation regimen	No	No	1	Low
10	Kim *et al*[41]	Yes	Randomizati-on by computer-generated sequence	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
11	Leitao *et al*[28]	Yes	Randomizati-on 1:1 with blocks of 10 by endoscopy-unit secretary	Yes	No	Endoscopist blind for the preparation regimen	No	No	2	Intermidiate

12	Kim et al[29]	Yes	Randomizati-on by computer-generated table	Yes	No	Not described	No	No	2	Intermidiate
13	Munsterman et al[30]	Yes	Randomizati-on by computer-generated 1:1 stratified by age (18-64) or (65-80)	Yes	No	Endoscopist blind for the preparation regimen	No	No	2	Intermidiate
14	Pohl et al[31]	Yes	Randomizati-on 1:1 in blocks of 4 by statistician list-generated	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
15	Yoo et al[32]	Yes	Randomizati-on 1:1 in blocks of 4 by a a computer-generated list	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
16	Kojecky et al[33]	Yes	Randomizati-on 1:1 using a software generated random table	Yes	No	Endoscopist blind for the preparation regiment	No	Yes	3	High

responsible for reporting bias was identified through sensitivity analysis (Pohl *et al*[31]). After its exclusion ($I^2 = 35\%$, $P = 0.09$) and through the use of FE model, there was statistical difference in favor of SPMC. More cases of success were obtained with SPMC compared to PEG [MH FE, RD 0.03, IC (0.01, 0.05), $P = 0.003$, $I^2 = 33\%$] with a NNT of 34 (34 people need to be treated with SPMC to obtain 1 additional benefit over PEG) (Figures 2 and 3).

Patient tolerability: Sensitivity analysis of the eleven included studies revealed true heterogeneity ($I^2 = 88\%$, $P < 0.00001$) and RE model was adopted. SPMC was better tolerated than PEG [MH RE, RD 0.08, IC (0.03, 0.13), $P = 0.002$, $I^2 = 88\%$], with a NNT of 13 (Figure 4). As Manes *et al*[37] and Jeon *et al*[38] criteria for completion of intake were different from other studies (failure was defined as lower than 70% and 50% of ingestion of the solutions, respectively), additional analysis was performed without them. The result still favored SPMC [MH RE, RD 0.09, IC (0.03, 0.15), $P = 0.002$, $I^2 = 91\%$] and lower NNT (NNT of 11).

Adverse events prevalence: A RE model analysis was conducted due to the high heterogeneity among the ten included studies ($I^2 = 88\%$, $P < 0.00001$). Fewer adverse events occurred using SPMC [MH RE, RD 0.13, IC (0.05, 0.22), $P = 0.002$, $I^2 = 88\%$], and the NNT obtained was 7 (7 people need to be treated with SPMC to avoid 1 adverse event over PEG) (Figure 5).

PDR: An asymmetric funnel and inconsistency in the upper limit ($I^2 = 50\%$, $P = 0.06$) were observed among the seven included studies. Sensitivity analysis identified the study responsible for the heterogeneity (Leitao *et al*[28]). The study was not excluded due to the small number of studies included (fewer than 10) and a RE model analysis was conducted. There was no difference between SPMC and PEG for polyp detection [MH RE, RD -0.03, IC (-0.09, 0.02), $P = 0.30$, $I^2 = 50\%$] (Figure 6).

ADR: Heterogeneity was null among the five studies included and a FE model analysis showed no statistical difference between SPMC and PEG, but a trend in favor of PEG was present [MH FE, RD -0.05, IC (-0.11, -0.00), $P = 0.05$, $I^2 = 0\%$] (Figure 7).

Subgroups analyses
Additional analyses were performed by subgroups based on type of regimen, volume of PEG solution and dietary recommendations for the day prior to colonoscopy.
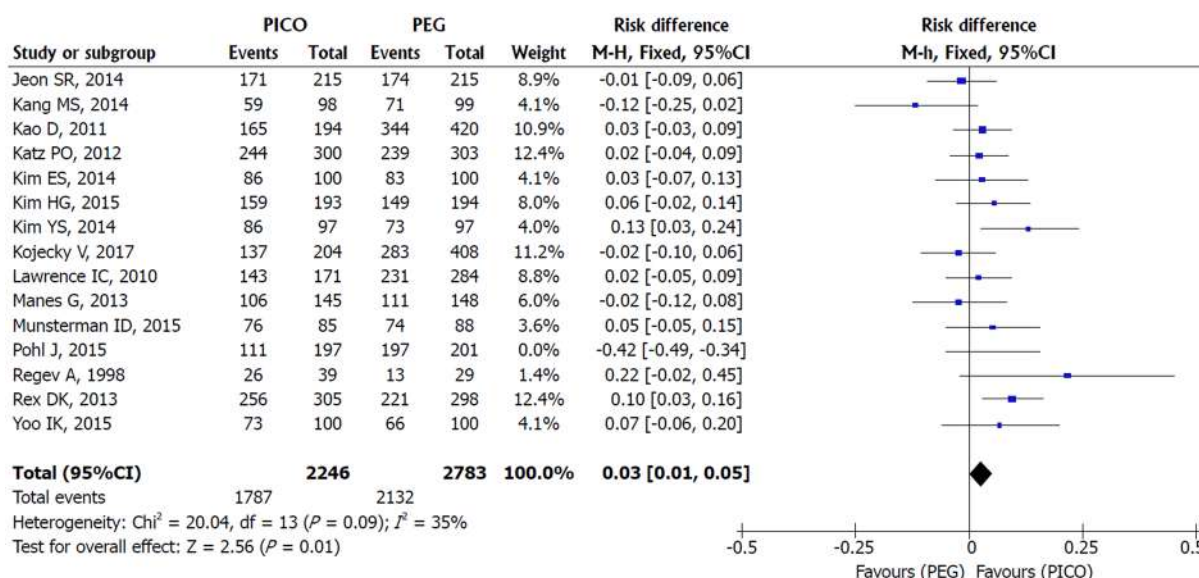
Study or subgroup	PICO Events	Total	PEG Events	Total	Weight	Risk difference M-H, Fixed, 95%CI	Risk difference M-h, Fixed, 95%CI
Jeon SR, 2014	171	215	174	215	8.9%	-0.01 [-0.09, 0.06]	
Kang MS, 2014	59	98	71	99	4.1%	-0.12 [-0.25, 0.02]	
Kao D, 2011	165	194	344	420	10.9%	0.03 [-0.03, 0.09]	
Katz PO, 2012	244	300	239	303	12.4%	0.02 [-0.04, 0.09]	
Kim ES, 2014	86	100	83	100	4.1%	0.03 [-0.07, 0.13]	
Kim HG, 2015	159	193	149	194	8.0%	0.06 [-0.02, 0.14]	
Kim YS, 2014	86	97	73	97	4.0%	0.13 [0.03, 0.24]	
Kojecky V, 2017	137	204	283	408	11.2%	-0.02 [-0.10, 0.06]	
Lawrence IC, 2010	143	171	231	284	8.8%	0.02 [-0.05, 0.09]	
Manes G, 2013	106	145	111	148	6.0%	-0.02 [-0.12, 0.08]	
Munsterman ID, 2015	76	85	74	88	3.6%	0.05 [-0.05, 0.15]	
Pohl J, 2015	111	197	197	201	0.0%	-0.42 [-0.49, -0.34]	
Regev A, 1998	26	39	13	29	1.4%	0.22 [-0.02, 0.45]	
Rex DK, 2013	256	305	221	298	12.4%	0.10 [0.03, 0.16]	
Yoo IK, 2015	73	100	66	100	4.1%	0.07 [-0.06, 0.20]	
Total (95%CI)		**2246**		**2783**	**100.0%**	**0.03 [0.01, 0.05]**	
Total events	1787		2132				

Heterogeneity: Chi^2 = 20.04, df = 13 (P = 0.09); I^2 = 35%
Test for overall effect: Z = 2.56 (P = 0.01)

Favours (PEG) Favours (PICO)

Figure 2 Metanalysis forest plot of bowel cleaning success.

Per type of regimen: Studies were divided into four subgroups according to regimens compared: day-before dose[13,33,34,41]; split dose[28-30,32,33,38,40]; according to interval time for colonoscopy[35-37]; and comparison of different regimens[15,31,39].

Bowel cleansing success: SPMC was better than PEG for bowel cleaning in day-before dose comparison [MH RE, RD 0.06, IC (0.01, 0.11), P = 0.02, I^2 = 38%], with an NNT of 17. No difference was observed in the split dose regimen [MH FE, RD 0.01, IC (-0.03, 0.05), P = 0.56, I^2 = 29%], in the according-to-interval-time regimens [MH FE, RD 0.02, IC (-0.03, 0.06), P = 0.45, I^2 = 0%] and in the different regimens subgroup [MH RE, RD -0.14, IC (-0.50, 0.21), P = 0.42, I^2 = 98%].

Additional sensitivity analysis by subgroups showed that inconsistency among all studies included in the overall meta-analysis decreased from 91% to 19% after the removal of different regimens subgroup, in which the previous outlier study for the outcome was identified (Pohl *et al*[31]). Without this subgroup, the statistical difference disappeared and there was only a trend in favor of SPMC [MH FE, RD 0.03, IC (0.00, 0.05), P = 0.03, I^2 = 19%] (Appendix 4 - Figure 1).

Patient tolerability: No difference was observed in tolerability in the split dose regimen (MH RE, RD 0.04, IC [-0.05, 0.14], P = 0.38, I^2 = 86%) and in the different regimens subgroup [MH RE, RD 0.04, IC (-0.09, 0.17), P = 0.54, I^2 = 97%]. In the day-before dose regimen [MH FE, RD 0.17, IC (0.13, 0.21), P < 0.0001, I^2 = 0%] and in the according-to-interval-time subgroups [MH RE, RD 0.08, IC (0.01, 0.15), P = 0.02, I^2 = 54%], SPMC was better tolerated than PEG, with an NNT of 6 and 13, respectively. Sensitivity analysis by subgroups did not change the overall meta-analysis results either (Appendix 4 - Figure 2).

Adverse events: Three subgroups were available (day-before dose, split dose and different regimens). No difference was found in day-before dose [MH RE, RD -0.18, IC (-0.50, 0.14), P = 0.26, I^2 = 96%] and in split dose subgroups [MH RE, RD -0.07, IC (-0.16, 0.02), P = 0.15, I^2 = 62%], but there were fewer adverse events with SPMC in the different regimens subgroup [MH RE, RD -0.10, IC (-0.19, -0.02), P = 0.01, I^2 = 60%], with a NNT of 10 (Appendix 4 - Figure 3).

PDR: The analysis showed no difference in PDR in the split dose subgroup [MH FE, RD 0.04, IC (-0.03, 0.10), P = 0.28, I^2 = 43%] and superiority of PEG over SPMC in the different regimens subgroup [MH FE, RD -0.09, IC (-0.17, -0.01), P = 0.02, I^2 = 0%], with a NNT of 12 (Appendix 4 - Figure 4).

ADR: Only two subgroups (split dose and different regimens) with 2 studies each were available. There was no statistical difference in ADR between them [split dose: MH FE, RD -0.02, IC (-0.11, 0.07), P = 0.70, I^2 = 0%; different regimens: MH FE, RD -0.06, IC (-0.14, 0.01), P = 0.09, I^2 = 0%] (Appendix 4 - Figure 5).

Per volume of PEG solution: Eight studies were included in low-volume subgroup[13,15,31-33,36-38] and nine in high-volume subgroup[29,30,33-36,39-41].
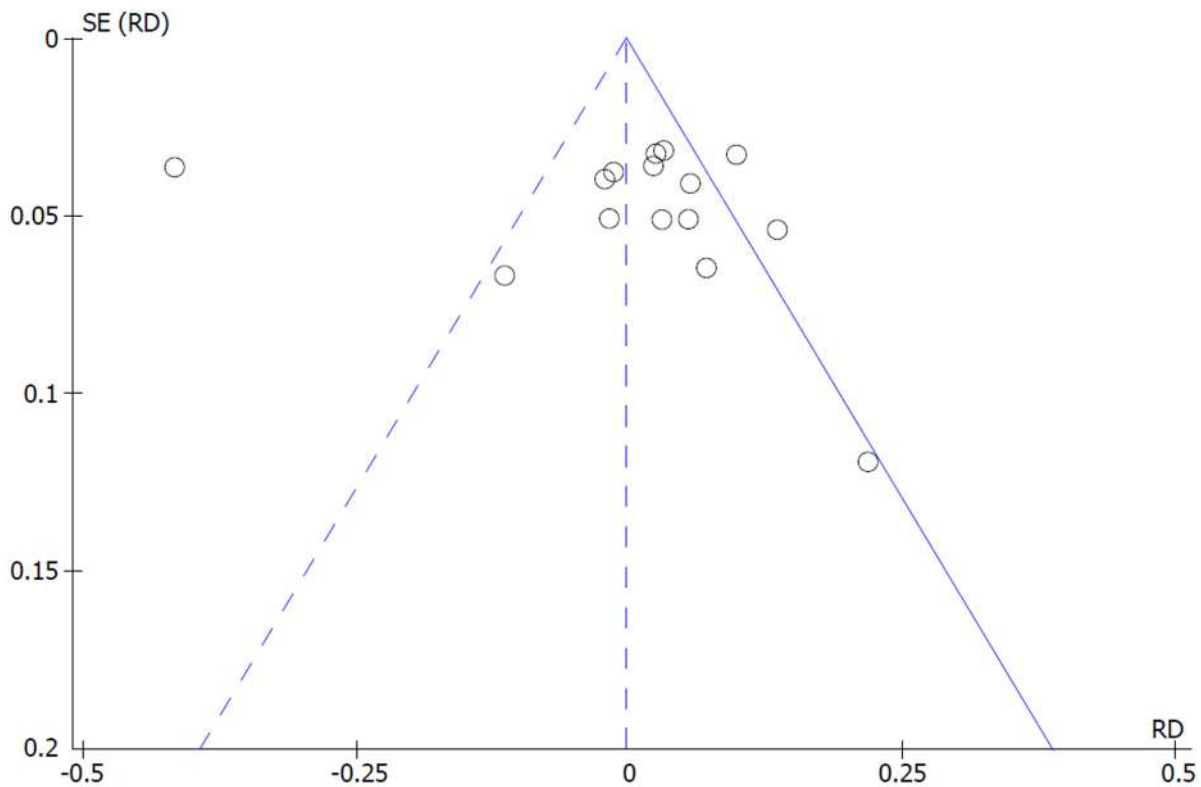
Figure 3 Metanalysis funnel plot of bowel cleaning success.

Bowel cleansing success: Low-volume PEG subgroup presented high heterogeneity (I^2 = 96%, P < 0.00001) and sensitivity analysis identified one study (Pohl *et al*[31]) as the responsible for funnel asymmetry and high heterogeneity. Considering the small number of studies, it was maintained for the analysis and RE model was adopted. No difference was observed in bowel cleaning between SPMC and low-volume PEG [MH RE, RD -0.03, IC (-0.16, 0.09), P = 0.61, I^2 = 95%]. High-volume subgroup analysis also showed no difference between them [MH FE, RD 0.03, IC (-0.01, 0.06), P = 0.09, I^2 = 42%] (Appendix 4 - Figure 6).

Patient tolerability: SPMC was better tolerated than high-volume PEG solution [MH RE, RD 0.08, IC (0.01, 0.14), I^2 = 89%, P = 0.02], with a NNT of 13, and a trend in favor of SPMC was observed in the low-volume PEG subgroup [MH RE, RD 0.08, IC (0.00, 0.16), I^2 = 87%, P = 0.05]. (Appendix 4 - Figure 7).

Adverse events: After the performance of a sensitivity analysis, a study responsible for the heterogeneity in the high-volume subgroup was identified (Kim *et al*[41]), but was not excluded due to the small number of studies (fewer than 10 studies). RE model analysis showed SPMC caused fewer adverse events than PEG in the high-volume subgroup [MH RE, RD -0.18, IC (-0.30, -0.07), P = 0.002, I^2 = 79%], with a NNT of 6. There was no difference in adverse events prevalence in the low-volume subgroup [MH RE, RD 0.09, IC (-0.02, 0.20), P = 0.12, I^2 = 91%] (Appendix 4 - Figure 8).

PDR: Sensitivity analysis was carried out for high-volume subgroup and the study responsible for the inconsistency was identified (Leitao *et al*[28]). It was not removed due to the small number of included studies. There was no difference in PDR in the low-volume subgroup [MH FE -0.05, IC (-0.11, 0.01), P = 0.11, I^2 = 0] or in the high-volume subgroup [MH RE, RD -0.03, IC (-0.14, 0.09), P = 0.65, I^2 = 71%] (Appendix 4 - Figure 9).

ADR: No difference was observed between SPMC and PEG in both subgroups [low-volume: MH FE, RD -0.04, IC (-0.11, 0.02), P = 0.17, I^2 = 0%; high-volume: MH FE, RD -0.07, IC (-0.17, 0.02), P = 0.12, I^2 = 0%] (Appendix 4 - Figure 10).

Per dietary recommendations: Four studies were included in liquid diet subgroup[13,15,34,36] and twelve studies[23-28,30,32-36] in the low residue diet subgroup.
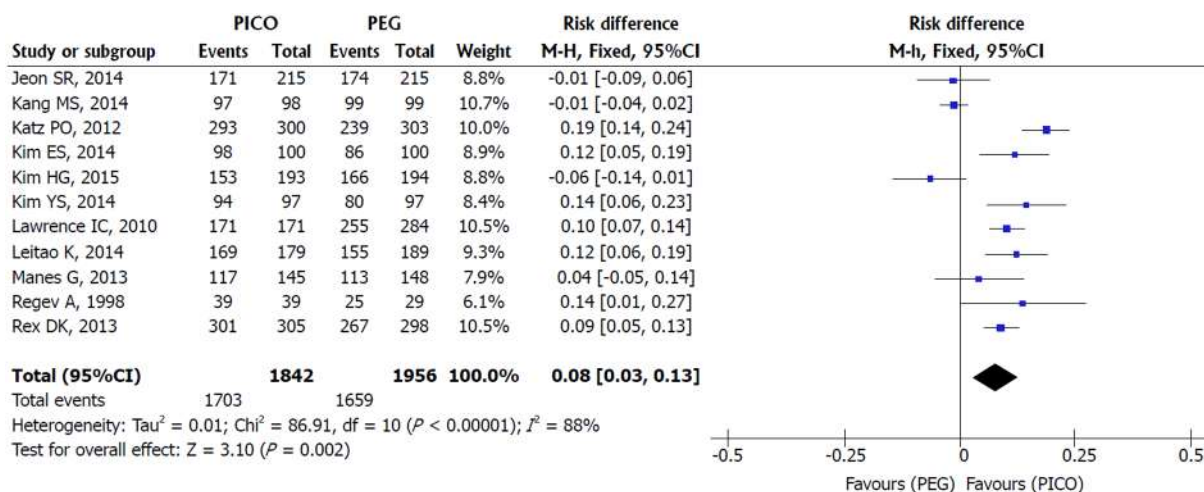
Study or subgroup	PICO Events	PICO Total	PEG Events	PEG Total	Weight	Risk difference M-H, Fixed, 95%CI
Jeon SR, 2014	171	215	174	215	8.8%	-0.01 [-0.09, 0.06]
Kang MS, 2014	97	98	99	99	10.7%	-0.01 [-0.04, 0.02]
Katz PO, 2012	293	300	239	303	10.0%	0.19 [0.14, 0.24]
Kim ES, 2014	98	100	86	100	8.9%	0.12 [0.05, 0.19]
Kim HG, 2015	153	193	166	194	8.8%	-0.06 [-0.14, 0.01]
Kim YS, 2014	94	97	80	97	8.4%	0.14 [0.06, 0.23]
Lawrence IC, 2010	171	171	255	284	10.5%	0.10 [0.07, 0.14]
Leitao K, 2014	169	179	155	189	9.3%	0.12 [0.06, 0.19]
Manes G, 2013	117	145	113	148	7.9%	0.04 [-0.05, 0.14]
Regev A, 1998	39	39	25	29	6.1%	0.14 [0.01, 0.27]
Rex DK, 2013	301	305	267	298	10.5%	0.09 [0.05, 0.13]
Total (95%CI)		**1842**		**1956**	**100.0%**	**0.08 [0.03, 0.13]**
Total events	1703		1659			

Heterogeneity: Tau^2 = 0.01; Chi^2 = 86.91, df = 10 (*P* < 0.00001); *I*^{2} = 88%
Test for overall effect: Z = 3.10 (*P* = 0.002)

Figure 4 Metanalysis forest plot of tolerability.

Bowel cleansing success: The analysis showed that SPMC was better than PEG for bowel cleaning in the liquid diet subgroup [MH FE, RD 0.06, IC (0.02, 0.09), *P* = 0.002, *I*^{2} = 40%], with a NNT of 17. In the low residue diet subgroup, high heterogeneity and an asymmetrical funnel plot were initially observed (*I*^{2} = 93%, *P* < 0.00001). After sensitivity analysis, one study (Pohl *et al*[31]) was identified as the responsible for reporting bias. After its exclusion, heterogeneity decreased to an acceptable level (*I*^{2} = 31%) and analysis using FE model showed that SPMC and PEG were similar in the low residue subgroup [MH FE, RD 0.01, IC (-0.02, 0.04), *I*^{2} = 30%, *P* = 0.38] (Appendix 4 – Figure 11).

Patient tolerability: SPMC was better tolerated than PEG in the liquid diet group [MH RE, RD 0.14, IC (0.06, 0.22), *I*^{2} = 81%, *P* = 0.0006], with an NNT of 8, and a trend in favor of SPMC was identified in the low residue subgroup [MH RE, RD 0.06, IC (0.00, 0.11), *I*^{2} = 86%, *P* = 0.05] (Appendix 4 - Figure 12).

Adverse events: There was low heterogeneity (*I*^{2} = 43%, *P* = 0.17) among the three studies included in the liquid diet subgroup and high heterogeneity (*I*^{2} = 86%, *P* < 0.00001) among the seven studies included in the low residue subgroup. FE and RE models were used for liquid diet and low residue subgroups, respectively. There was no difference between SPMC and PEG in the liquid diet subgroup [MH FE, RD -0.02, IC (-0.08, 0.05), *P* = 0.59, *I*^{2} = 43%], but the low residue subgroup SPMC presented fewer adverse events than PEG [MH RE, RD -0.17, IC (-0.27, -0.07), *P* = 0.0008, *I*^{2} = 86%], with a NNT of 6 (Appendix 4 - Figure 13).

Polyp and adenoma detection rates: PDR and ADR subgroups were the same for SPMC *vs* PEG comparison because all the included trials in this comparison recommended only low residue diet on the day before.

DISCUSSION

Summary of evidence

Results from the meta-analysis of the 16 included studies (with 6200 subjects from ten different countries) indicate that for adult outpatients before elective colonoscopy, SPMC is at least similar to PEG in bowel cleaning efficacy, better in tolerability and in adverse events prevalence and similar in polyp and adenoma detection rate.

As high inconsistency and true heterogeneity were present among the included studies despite the strict inclusion criteria adopted, caution for interpretation of data is recommended. Populations of different countries with different dietary patterns, different options of dosage and schedule for bowel preparation and different scales and different instruments to measure outcomes may have contributed to increase heterogeneity. As bowel cleaning protocols vary between different institutions worldwide, variations across trials are inherent and expected.

As this meta-analysis provided an overall impression by grouping different bowel cleaning protocols and did not consider confounding factors, such as type of regimen, volume of solution ingested and dietary restrictions, additional analyses by subgroups were conducted to elucidate these aspects and to help decision-making in
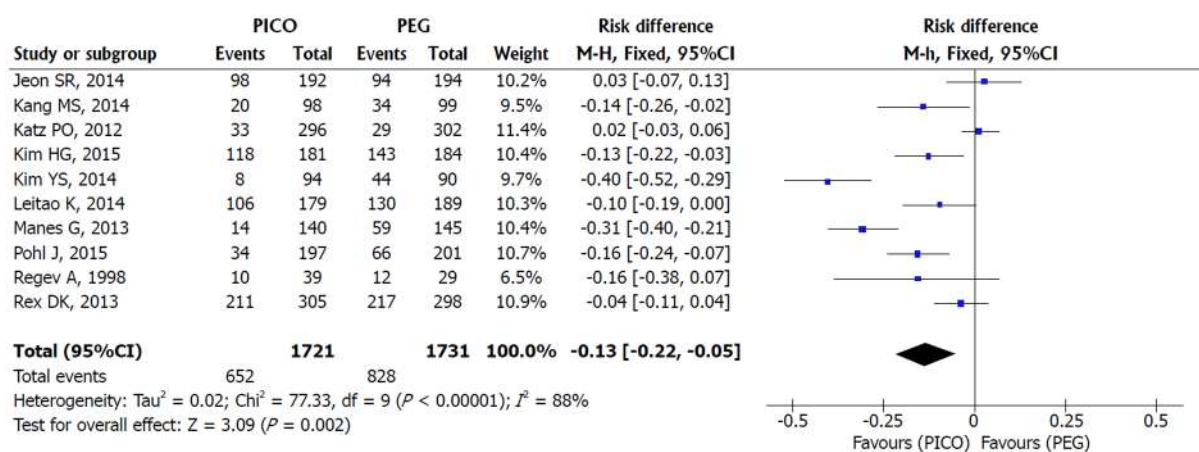
Study or subgroup	PICO Events	Total	PEG Events	Total	Weight	Risk difference M-H, Fixed, 95%CI
Jeon SR, 2014	98	192	94	194	10.2%	0.03 [-0.07, 0.13]
Kang MS, 2014	20	98	34	99	9.5%	-0.14 [-0.26, -0.02]
Katz PO, 2012	33	296	29	302	11.4%	0.02 [-0.03, 0.06]
Kim HG, 2015	118	181	143	184	10.4%	-0.13 [-0.22, -0.03]
Kim YS, 2014	8	94	44	90	9.7%	-0.40 [-0.52, -0.29]
Leitao K, 2014	106	179	130	189	10.3%	-0.10 [-0.19, 0.00]
Manes G, 2013	14	140	59	145	10.4%	-0.31 [-0.40, -0.21]
Pohl J, 2015	34	197	66	201	10.7%	-0.16 [-0.24, -0.07]
Regev A, 1998	10	39	12	29	6.5%	-0.16 [-0.38, 0.07]
Rex DK, 2013	211	305	217	298	10.9%	-0.04 [-0.11, 0.04]
Total (95%CI)		1721		1731	100.0%	-0.13 [-0.22, -0.05]
Total events	652		828			

Heterogeneity: Tau^2 = 0.02; Chi^2 = 77.33, df = 9 (P < 0.00001); I^2 = 88%
Test for overall effect: Z = 3.09 (P = 0.002)

Figure 5 Metanalysis forest plot of adverse events.

daily clinical practice.

Sensitivity analyses provided additional information on the influence of the studies in the meta-analysis, helping with the confounding factors. Pohl *et al*[31] was identified as the main outlier study for bowel cleaning due to its methodological bias of treatment: the comparison of different regimens of bowel preparation.

As previously known in a meta-analysis by Bucci *et al*[43], the interval time between the last drink of bowel preparation and the beginning of colonoscopy (also known as "runway time") is a key factor for cleaning quality. When Pohl *et al*[31] compared different regimens (a split regimen of PEG and a day-before regimen of SPMC), the difference between treatment effects was increased and favored that one with the shorter "runway time" (PEG).

The sensitivity analysis by subgroups of regimen confirmed the impact of including trials comparing different regimens. Through the exclusion of this subgroup (Rex *et al*[15], Kang *et al*[39], Kim *et al*[40] and Pohl *et al*[31]), a more reliable analysis with less heterogeneity was obtained and the difference in bowel cleaning and the trend in favor of PEG for adenoma detection disappeared. Hence, the more rational approach was to assume SPMC and PEG were similar for both outcomes.

Statistical difference in favor of SPMC was also identified in the sub-analysis in the following situations: (1) bowel preparation was made on the day before (better bowel cleaning success and better tolerability); (2) bowel preparation was made based on the interval time to colonoscopy (also better tolerability); (3) when compared to high-volume solution of PEG (better tolerability and fewer adverse events); (4) liquid diet was the option on the day before (with better bowel cleaning success and better tolerability); and (5) low residue diet was the option on the day before (fewer adverse events).

Although there was statistical difference in these outcomes, it is also important to observe the number needed to treat to evaluate treatment effectiveness properly and to help deciding about changes in daily clinical practice. If the NNT is high, there is low chance of benefits for the patient with the alternative treatment, which might not justify its adoption.

The high NNTs of SPMC for bowel cleaning (NNT of 34) and for tolerability (NNT of 13) result in a small chance of benefit for the patient (2.9% and 7.6%, respectively). However, the small NNT for adverse events (NNT of 7) reveals a significant reduction of 14.2% when SPMC is used, this being its main advantage and the reason for its adoption over PEG.

Benefits of using SPMC are also obtained in day-before preparations (16.6% more chance of tolerability), against high-volume solutions of PEG (reduction of 16.6% in chance of adverse events) and with prior-day dietary restrictions (a 12.5% greater chance of tolerability with the use of liquid diet and a 16.6% reduction in the chance of adverse events with low residue diet).

Despite the potential benefits of SPMC demonstrated in this meta-analysis, care should be taken in regard to some of the product faults. Because of the potential electrolyte shifts, SPMC is not recommended in patients with renal insufficiency, end-stage liver disease, heart failure and electrolyte abnormalities[44,45]. PEG is the product of choice for those patients as it is an inert molecule and isosmotic solution, which also induces less mucosal damage (inflammation or ulceration) by ten times when compared to SPMC[35].

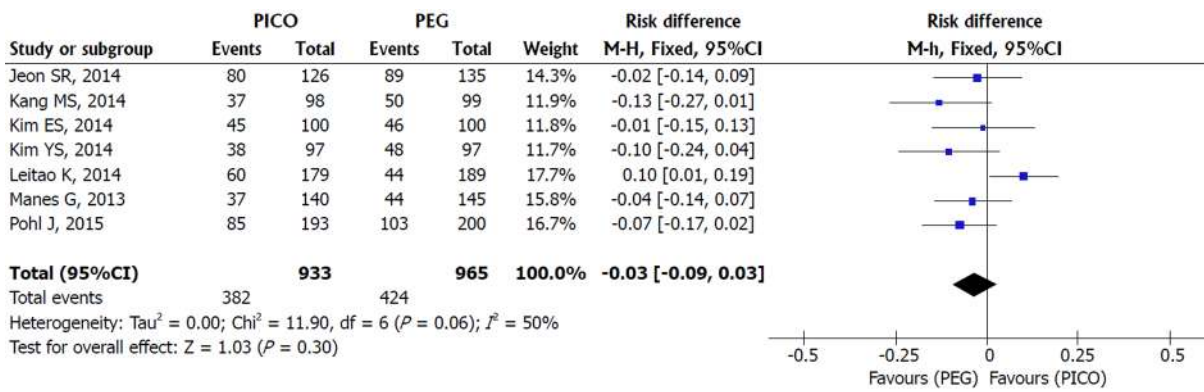The main disadvantage of PEG consists in the amount of solution to be ingested as

Study or subgroup	PICO Events	PICO Total	PEG Events	PEG Total	Weight	Risk difference M-H, Fixed, 95%CI	Risk difference M-h, Fixed, 95%CI
Jeon SR, 2014	80	126	89	135	14.3%	-0.02 [-0.14, 0.09]	
Kang MS, 2014	37	98	50	99	11.9%	-0.13 [-0.27, 0.01]	
Kim ES, 2014	45	100	46	100	11.8%	-0.01 [-0.15, 0.13]	
Kim YS, 2014	38	97	48	97	11.7%	-0.10 [-0.24, 0.04]	
Leitao K, 2014	60	179	44	189	17.7%	0.10 [0.01, 0.19]	
Manes G, 2013	37	140	44	145	15.8%	-0.04 [-0.14, 0.07]	
Pohl J, 2015	85	193	103	200	16.7%	-0.07 [-0.17, 0.02]	
Total (95%CI)		**933**		**965**	**100.0%**	**-0.03 [-0.09, 0.03]**	
Total events	382		424				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 11.90, df = 6 (P = 0.06); I^2 = 50%
Test for overall effect: Z = 1.03 (P = 0.30)

Favours (PEG) Favours (PICO)

Figure 6 Metanalysis forest plot of polyp detection rate.

observed in the meta-analysis by Xie *et al*[46]. Further sub-analyses by volume of PEG solution presented in this meta-analysis reinforce this drawback. High-volume PEG presented less tolerability and more adverse events than SPMC whereas no difference was found between low-volume PEG and SPMC. As tolerability and adverse events are correlated factors that can affect bowel cleaning, SPMC appears as an interesting alternative.

An extensive search strategy, well-defined eligibility criteria, careful inclusion of the studies and analyses based on "intention-to-treat" data are the strength of this study. Results obtained by additional analyses focusing on subgroups based on regimen schedule, volume of PEG solution and dietary restriction bring new information and complement two recent meta-analyses.

Jin *et al*[20] and van Lieshout *et al*[47] showed that SPMC was equally effective or slightly superior to PEG in terms of bowel cleaning efficacy and that it was better tolerated than PEG. However, they did not consider patient status (if inpatient or outpatient) for studies selection and grouped different types of patients. This is the first meta-analysis for this specific group of patients and the first communicating effectiveness of bowel preparation using NNT.

Limitations

Nine full-text trials identified in the search were not included in this meta-analysis due to the lack of essential information concerning eligibility criteria[48-56]. Their absence may have contributed to borderline results in some sub-analyses with few included studies, but it assured the assertiveness of the results for this specific population.

Quality of bowel cleaning measured by different cleanliness scores and patients' preferences and impressions of the products are other important outcomes that were not evaluated. Due to the different instruments to collect data used by trials, matching these data is prejudiced.

The type and severity of adverse events were also not explored. Owing to the methodological feature of RCTs and the characteristics of those products, the events are generally mild to moderate gastrointestinal symptoms (nausea, vomiting, abdominal pain, bloating and dizziness). Serious adverse events after bowel preparation are rare[57].

In addition, results obtained by this meta-analysis should be only inferred to healthy patients or those with mild disease as the included trials excluded other types of patients. This is especially important for the use of SPMC, as it is known for the occurrence of electrolyte disturbances which could have a repercussion in moderately or severely diseased patients.

Finally, although all the included studies were randomized clinical trials, five of them presented problems regarding randomization and masking, the description of losses and failure in reporting the outcomes, which compromised the quality of the evidence. Therefore, the quality of the evidence obtained was moderate for bowel cleaning efficacy, tolerability and adverse events prevalence, and low for polyp and adenoma detection rates[58]. Future studies might influence some outcomes and sub-analyses, especially those with borderline differences, with high NNTs or few studies included.

Conclusion

According to data published until now, SPMC seems to be a better product than PEG for bowel preparation in healthy or mildly diseased adult outpatients before
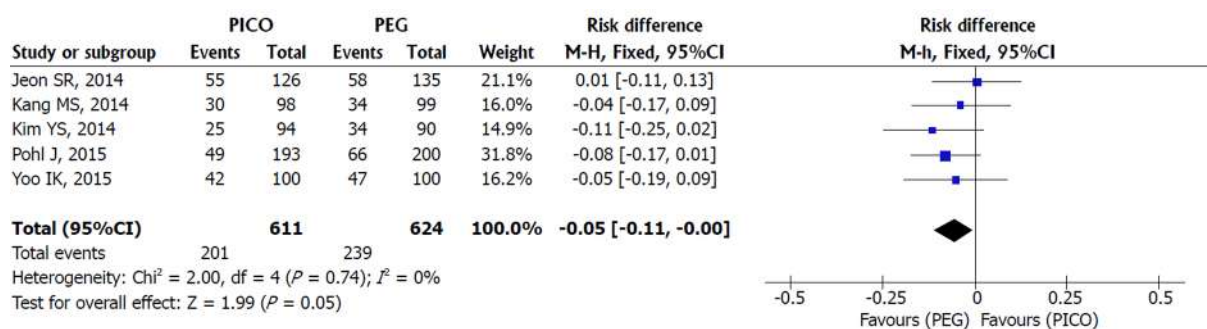
| Study or subgroup | PICO | | PEG | | Weight | Risk difference | Risk difference |
	Events	Total	Events	Total		M-H, Fixed, 95%CI	M-h, Fixed, 95%CI
Jeon SR, 2014	55	126	58	135	21.1%	0.01 [-0.11, 0.13]	
Kang MS, 2014	30	98	34	99	16.0%	-0.04 [-0.17, 0.09]	
Kim YS, 2014	25	94	34	90	14.9%	-0.11 [-0.25, 0.02]	
Pohl J, 2015	49	193	66	200	31.8%	-0.08 [-0.17, 0.01]	
Yoo IK, 2015	42	100	47	100	16.2%	-0.05 [-0.19, 0.09]	
Total (95%CI)		611		624	100.0%	-0.05 [-0.11, -0.00]	
Total events	201		239				

Heterogeneity: Chi^2 = 2.00, df = 4 (P = 0.74); I^2 = 0%
Test for overall effect: Z = 1.99 (P = 0.05)

Figure 7 Metanalysis forest plot of adenoma detection rate.

colonoscopy as its bowel cleaning efficacy is at least equal to that of PEG, its tolerability is better and adverse events prevalence is lower. The latter corresponds to the main advantage of using SPMC instead of PEG. Both SPMC and PEG can be used for split preparations as there are no difference in bowel cleaning success, tolerability and adverse events prevalence, but SPMC should be the choice for day-before preparations because of its better tolerability.

ARTICLE HIGHLIGHTS

Research background
Colonoscopy reduces the incidence and mortality for colorectal cancer. Bowel preparation is the cornerstone for colonoscopy as the quality of bowel cleaning directly affects the effectiveness for detecting neoplastic lesions. Different options of purgatives exist as a result of the search for the ideal product and none of them have all the ideal features. PEG solutions are the most widely used and studied bowel cleanser, while SPMC is a recently developed one to overcome PEG's poor palatability and large volume of solution to be ingested. Meta-analyses of RCTs are the best evidence for medical practice, but none of them compared SPMC and PEG for outpatients before colonoscopy, leaving a gap in the literature.

Research motivation
Most of elective colonoscopies are performed in outpatients and inpatient status is an independent risk factor for inadequate bowel preparation. As previous meta-analyses comparing SPMC and PEG before elective colonoscopy did not consider patient status for inclusion criteria, there is no established evidence for this subset of patients.

Research objectives
To determine the best option for bowel preparation in adult outpatients before elective colonoscopy by comparing cleaning efficacy, tolerability, AE prevalence, PDR and ADR between SPMC and PEG. This is the first meta-analysis to include only outpatients and to communicate effectiveness using NNT.

Research methods
Systematic review and meta-analysis followed PRISMA Statement. Eligibility criteria were based on PICOS strategy. Search was performed in MEDLINE, Scopus, EMBASE, CENTRAL/Cochrane, CINAHL and LILACS. Jadad scale was the tool adopted to evaluate the methodological quality of included RCTs and heterogeneity among studies was assessed by Higgins' test (I^2). Meta-analysis was preferably performed using intention-to-treat data by computing risk difference (RD) for dichotomous outcomes using Mantel-Haenszel (MH) method and NNT calculated for each outcome with statistical difference.

Research results
Sixteen RCTs with 6200 subjects were included for the meta-analysis and high heterogeneity was found among them. Sensitivity analysis and sub analysis by type of regime, volume of PEG solution and dietary recommendations were performed to interpret data. In the overall analysis, SPMC was better for bowel cleaning [RD 0.03, IC (0.01, 0.05), NNT 34], for tolerability [RD 0.08, IC (0.03, 0.13), NNT 13] and for adverse events [RD 0.13, IC (0.05, 0.22), NNT 7]. The small NNT for adverse events (NNT of 7) reveals a reduction of 14.2% when SPMC is used. Better tolerability for SPMC was also found in "Day-before preparations" [RD 0.17, IC (0.13, 0.21), NNT 6], "According to interval time" [RD 0.08, IC (0.01, 0.15), NNT 13], "Against high-volume of PEG" [RD 0.08, IC (0.01, 0.14), NNT 13] and "Liquid diet subgroup" [RD 0.14, IC (0.06,0.22), NNT 8].

Research conclusions
Data from published RCTs suggests SPMC is a better bowel cleanser than PEG before elective colonoscopy for healthy and mildly diseased adult outpatients because of its better tolerability,

lower AE prevalence and cleaning efficacy at least equal to that of PEG. For split preparations, SPMC and PEG can be equally use, but for day-before preparations SPMC should be the standard choice.

Research perspectives

Future RCTs might influence the outcomes of this meta-analysis with few studies included and/or with borderline differences obtained (*e.g.*, PDR, ADR, per type of regimen and per dietary recommendations) since Meta-analyzes are limited by the number of studies available and by the quality of the studies included. More homogeneous and definitive results should be obtained through a large intercontinental multi-center RCT, with the same bowel preparation protocol and tools for evaluating results. Although expensive and hard-working, it would be the best study format to compare purgatives and determine the best conditions for each of the available purgatives.

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