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Meta-analysis: randomized controlled trials of 4-L polyethylene glycol (PEG) and sodium phosphate solution (NaP) as bowel preparation for colonoscopy

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Abstract

BACKGROUND—Randomized controlled trials (RCTs) comparing PEG vs. NaP are inconsistent.

OBJECTIVE—Compare the efficacy of and tolerance to PEG vs. NaP for bowel preparation.

METHODS—We used MEDLINE and EMBASE to identify English-language RCTs published between 1990 and 2008 comparing 4 L PEG with two 45 ml doses of NaP in adults undergoing elective colonoscopy. We calculated the pooled odds ratios (ORs) for preparation quality and proportion of subjects completing the preparation.

RESULTS—From 18 trials (n=2792), subjects receiving NaP were more likely to have an excellent or good quality preparation than those receiving PEG (82% vs. 77%; OR=1.43; 95% CI, 1.01-2.00). Among a subgroup of 10 trials in which prep quality was reported in greater detail, there were no differences in the proportions of excellent, good, fair or poor preparation quality. Among nine trials that assessed preparation completion rates, patients receiving NaP were more likely to complete the preparation than patients receiving 4-L PEG (3.9% vs. 9.8%, respectively, did not complete the preparation; OR= 0.40; CI, 0.17-0.88).

CONCLUSION—Among 18 head-to-head RCTs of NaP vs. 4 L PEG, NaP was more likely to be completed and to result in an excellent or good quality preparation.

Keywords

Colonoscopy; Bowel preparation; Polyethylene Glycol; Sodium Phosphate

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INTRODUCTION

It is estimated that 14 million colonoscopies were performed in the United States in 2002 [1]. Adequate preparation of the bowel is necessary for optimal visualization of the colonic mucosa [2]. Patients often state that preparation (prep) for colonoscopy (CY) is the worst part of entire process. [3], [4] The difficulty with preparation may be related to taste and/or volume of the prep, resulting side effects, or use of adjunctive medications.

Of the commercially available preps, PEG and NaP are most commonly used. Introduced in 1980, polyethylene glycol (PEG) (NuLYTELY, and GoLYTELY; Braintree Laboratories, Inc, Braintree, MA; Colyte; Schwarz Pharma, Milwaukee, WI,) is an orally administered isotonic solution [5]. Since PEG is nondigestible and nonabsorbable, it cleanses the colon by washout of intraluminal contents [6]. Because it is iso-osmolar with plasma, the large volume of PEG does not result in significant fluid shifts. It has been shown to be highly effective when taken as instructed (4L of PEG solution) [7], [8]. However, the efficacy of standard 4 L PEG outside of clinical trials is compromised by poor patient compliance. The large volume and taste are the main factors that contribute to poor patient compliance and tolerability [9], [10], which led to development of reduced PEG volume solutions with or without laxatives, a sulfate-free version, and flavored PEG solutions (HalfLytely or 2-L PEG, NuLYTELY, TriLite) in an attempt to reduce the sulfate odor and improve taste [11], [12]. Despite these improvements, nausea and abdominal discomfort commonly result in poor prep quality, the need for repeat procedures and higher costs[13].

Sodium phosphate (NaP) solution, a buffered saline laxative, gained popularity as an alternative method for colonic preparation largely due to its smaller volume. Containing monobasic sodium phosphate and dibasic sodium phosphate, NaP acts as an osmotic laxative, cleansing the colon by drawing fluids into the gastrointestinal tract. In addition, NaP tablets (Visicol ®) were designed to improve the taste and reduce the volume required for bowel preparation. Several randomized trials comparing PEG and NaP suggest that NaP is safe, cost effective, better tolerated, and equally or more effective than PEG [6], [14–17].

Previous meta-analyses comparing these two preps are either not current [6], include pediatric trials and off-label doses of NaP [18], or include atypical doses of both preps [19]. The objective of this study was to use meta-analysis to compare the efficacy of and adherence to 4L PEG vs. two 45 ml doses of NaP preps for elective colonoscopy in adults.

METHODS

Search Strategy and selection criteria

We searched the medical literature from 1990 to 2008 using MEDLINE and EMBASE bibliographic databases to identify all relevant English language publications. The search strategy used the following MeSH search terms: 1) colonoscopy, 2) polyethylene glycol, 3) phosphates, 4) cathartics and 5) bowel prep. We limited these sets of articles to diagnostics and therapeutic uses and to human studies published in English that compared 4 L PEG vs. two 45 mL doses of NaP in adults undergoing elective colonoscopy. In addition, we hand-searched the reference lists of every primary study for additional publications. The following

criteria were used to select studies for inclusion: 1) study design: randomized controlled trials (RCTs), 2) patient population: adult patients undergoing elective colonoscopy, 3) dosing and frequency schedules of PEG and NaP. We excluded trials that were duplicate studies and those that lacked categorical data on both prep quality and adherence. We also excluded review articles, editorials, letters to editor, and studies published only in abstract form. Decisions about study inclusion and exclusion were made independently by two authors (R.J., T.F.I), with disagreements resolved by discussion.

Quantitative analysis

Descriptive data were abstracted to determine clinical similarity of the trials. We abstracted quantitative data for each trial, including the number of subjects in each treatment group and those with each outcome. Data extraction was performed primarily by one author, with random checks by a second author. Discrepancies in the data extraction process were resolved by discussion. Forrest plots were used to summarize the treatment effect for each trial. In combining data from the trials, we assumed the presence of heterogeneity prior to pooling the data and accordingly used the random effects model developed by DerSimonian-Laird[20] , which allows adjustment for variability among trials by providing a more conservative estimate of the range of an effect through wider confidence intervals (CIs).

The treatment effect was computed using the pooled odds ratios (ORs) and 95% confidence limits for prep quality (excellent, good, fair, and poor) and for the proportions of subjects completing the prep. Weighted proportions for each outcome were derived using the inverse of the variance for each trial. Statistical heterogeneity was assessed with Woolf's test [21]. Funnel plots, which plot the inverse of the standard error of the log-odds ratio against the log-odds ratio, were used to look for evidence of publication bias. All calculations were performed using r-meta library (version 2.14) for the statistical software R (version 2.5.1).

RESULTS

Descriptive and qualitative assessment

The MEDLIINE and EMBASE databases identified 174 abstracts from 1990-2008. We excluded 57 because they were trials where colonoscopy was not used (n=11), were published in foreign language (n=8), were not randomized trials (n=13), or were trials published prior to 1990 (n=18) and others (n=7). Of the 117 abstracts that described randomized controlled trials, we excluded 98 trials that compared either PEG or NaP to other dosing regimens of the same prep. Of 19 trials included for full text review, we excluded one trial [22] because it contained no data on either prep quality or patient adherence (Figure 1).

For analysis, we included 18 randomized controlled trials [9], [14-16], [23-36] involving 2,792 patients. Descriptive data for each trial is shown in Table 1. Mean age and gender distribution were similar for the 4L PEG and NaP solution groups. All trials were investigated-blinded and used comparable rating scales for bowel prep quality [9]: excellent: small volume of clear liquid or greater than 95% of surface seen; good: large volume of clear liquid covering 5% to 25% of the surface but greater than 90% of surface seen; fair:

some semi-solid stool that could be suctioned or washed away but greater than 90% of surface seen; poor: semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen. Of the 18 trials, 10 trials described prep quality in greater detail or in finer gradations (excellent, good, fair, poor) rather than just reporting it as a cumulative measure (excellent/good and fair/poor).

The methods of preparation of PEG and NaP were similar among the trials, with minor variation in the timing of prep consumption. Dietary recommendations on the day prior to colonoscopy varied from a regular diet to a clear liquid diet for lunch to a full clear liquid diet in the evening. In total, we found the trials to be similar enough in study design, study populations, interventions and outcomes to combine them quantitatively.

Quantitative assessment

There was statistically significant heterogeneity for the outcomes of prep quality and inability to complete the prep (*P* value for excellent/ good prep quality = 0.0003; P value for inability to complete the prep < 0.0001), indicating that there was greater-than- expected statistical variation among the trials for both outcomes [37].

Subjects who received NaP were more likely to have an excellent or good quality prep than were those who received PEG (82% vs. 77%; OR=1.43; 95% CI, 1.01-2.00). Among a subgroup of 10 trials in which prep quality was reported in greater detail between NaP and PEG, there were no significant differences in the proportions of patients with any specific level of prep quality: excellent (34% vs. 27%), good (30% vs. 30%), fair (17% vs. 17%), and poor (4.7% vs. 7.7%) (Table 2, Figure 2). Among the nine trials that assessed prep completion rates (Table 2, Figure 3), patients receiving NaP solution were more likely to complete the preparation than patients receiving 4-L PEG (3.9% vs. 9.8%, respectively, did not complete the preparation; OR= 0.40; CI, 0.17-0.88). Serious adverse effects were not described for either prep among the trials. Funnel plots for both outcomes reveal no clear evidence of publication bias (Figures 4 and 5).

DISCUSSION

This meta-analysis of 18 randomized controlled trials comparing NaP solution and 4L PEG shows that NaP solution is more likely than 4 L PEG both to be completed by patients and to result in an excellent or good quality prep. Although there were no differences in any specific level of prep quality between NaP solution and 4L PEG among those trials in which prep quality was reported in finer detail, the trends in the data indicate a higher proportion of NaP patients with excellent quality prep and a lower proportion with poor quality prep.

Previous meta-analyses of head-to-head trials of PEG vs. NaP have reported that NaP is more effective, better tolerated, and less costly than PEG [6, 19]. However, in 2007 a meta-analysis by Belsey *et al* reported that no single bowel preparation was consistently superior to the others [18]. To incorporate all the available evidence, we included trials that were either not included in previous analyses or that were more recently published [9, 23, 30, 33, 35].

This analysis has several strengths. First, our literature search was comprehensive in scope, and identified all relevant studies. Second, we included only randomized trials, which are considered to be superior to non-randomized comparisons. Third, the trials were very similar in study population recruited, in how the interventions (i.e., preps) were administered, and in the way outcomes were measured. Although the trials were statistically heterogeneous, they were clinically homogeneous from a qualitative standpoint. Fourth, we used a random effects model, which provides conservative quantitative results. Lastly, we found no clear evidence of publication bias, as supported by funnel plots.

Limitations of this analysis deserve comment. The potential for statistical heterogeneity is always present when combining trials quantitatively, and to address this issue, we assessed the trials qualitatively and determined that they were clinically similar enough to perform meta-analysis. We used a random effects model in the analysis, which provides a more conservative result with wider confidence intervals. Several factors may contribute to clinical and/or methodological heterogeneity among trials. One factor is variation in timing of bowel prep. The time at which the bowel prep was started was not uniform among the trials ranging from 48 hours [25] to 12 hours before the scheduled procedure. This was an issue, particularly for patients undergoing the procedure in the afternoon, as it may have an effect on prep quality [30], [36]. Some of the trials did not provide information about timing of the prep [34], [35].

Another factor potentially contributing to heterogeneity is variation in dietary instructions prior to and during the prep, which also were not uniform among the trials, and which ranged from a regular diet to a clear liquid diet for lunch and clear liquid diet in the evening. A third possible factor is the use of adjunctive liquids consumed during the prep.

In contrast to previous meta-analyses on this topic [6], [18], [19], we did not include an assessment of study quality. One reason for not doing so was that, based on our initial reading of the included trials, we thought they were very similar in design, with comparable study populations, interventions, and outcomes. In this case, we would have expected little variation in study quality. Secondly, there is no consensus on how best to use study quality in the quantitative part of a systematic review. Choices are to exclude the lowest quality trials, weight each study's quantitative results by a factor reflective of its quality, or stratify quantitative results based on a cut point in the quality score. While it remains unproven, our impression is that assessing and incorporating study quality would likely have had little effect on the quantitative results.

In recent years, there have been case series of renal insufficiency due to nephrocalcinosis with use of NaP for colonoscopy preparation. A total of 37 cases have been reported over a 4-year period, 4 of which progressed to end stage renal disease requiring dialysis [38-41]. The majority of these patients had one or more of the following co-morbid conditions: diabetes mellitus, hypertension treated with angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) or diuretics, preexisting renal insufficiency, older age; small bowel disease (that resulted in calcium and vitamin D malabsorption). Renal biopsies of many of the reported cases have showed nephrocalcinosis with intratubular deposition of calcium-phosphate. The term for this pathologic condition is acute phosphate nephropathy

(APN).The histopathology suggests that sodium phosphate ingestion leads to obstructive calcium-phosphate crystalluria followed by acute intratubular nephrocalcinosis. These reports raised concerns that led Food and Drug Administration (FDA) [42] to announce a safety alert in December 2008 stating that a Boxed Warning was to be added to the labeling on prescription oral phosphate solutions (Visicol and OsmoPrep). The FDA further recommended against the use of over the counter oral solution phosphate products for bowel preparation. Shortly after this announcement, all over-the-counter NaP products were voluntarily removed from the market, with a subsequent sharp decline in use of NaP solution.

Despite the FDA's action and resulting reaction, the published data suggest that absolute risk of APN is very low [43], [44]. A recent systematic review and meta-analysis of seven controlled studies (patient N=14,520) of the effects of NaP versus comparator on kidney function showed that there was significant clinical heterogeneity in the populations studied, study methods, definition of kidney injury, and results[45]. Quantitatively, the pooled odds ratio for kidney injury among NaP-treated patients ranged from 1.08 (CI, 0.71-1.62) to 1.22 (CI, 0.77-1.92), neither of which is statistically significant. The investigators concluded that it was not possible to discern whether there is a true association between NaP and kidney injury. In addition, an appropriate dosing interval of 10-12 hours in between doses of NaP may reduce the risk for APN[46].

The results of this meta-analysis apply to patients undergoing elective colonoscopy who do not have a history of co-morbid conditions like renal insufficiency, recent myocardial infarction and congestive heart failure; particularly NaP should not be used in patients suspected or with inflammatory bowel diseases because of the apthous ulcerations it may cause resulting in complexity in interpreting endoscopic and histological findings[47], [48]. Physicians should be aware of the risk of acute kidney injury with NaP preparations and should avoid its use in elderly patients and in those with preexisting renal insufficiency. In addition, NaP should be used with caution in patients on medications that can affect volume status or renal function (diuretics, ACE-I or ARBs). Further, all patients should be encouraged to adequately hydrate themselves prior to and while using NaP preparations. With the recent FDA safety alert, over the counter OSPs should not be used for bowel preparation, although they are still available for treatment of constipation. Despite the current restriction on use of NaP solution, up to nearly 75% of the patients undergoing elective colonoscopy are eligible to receive NaP preparation, given the fact that the tablet form is available by prescription[49].

In conclusion, among 18 head-to-head randomized trials of NaP solution vs. 4 L PEG, NaP solution was more likely to be completed by patients and to result in excellent or good quality prep. If and when NaP solution is once again made available for bowel preparation, this analysis may have direct implications for patient care.

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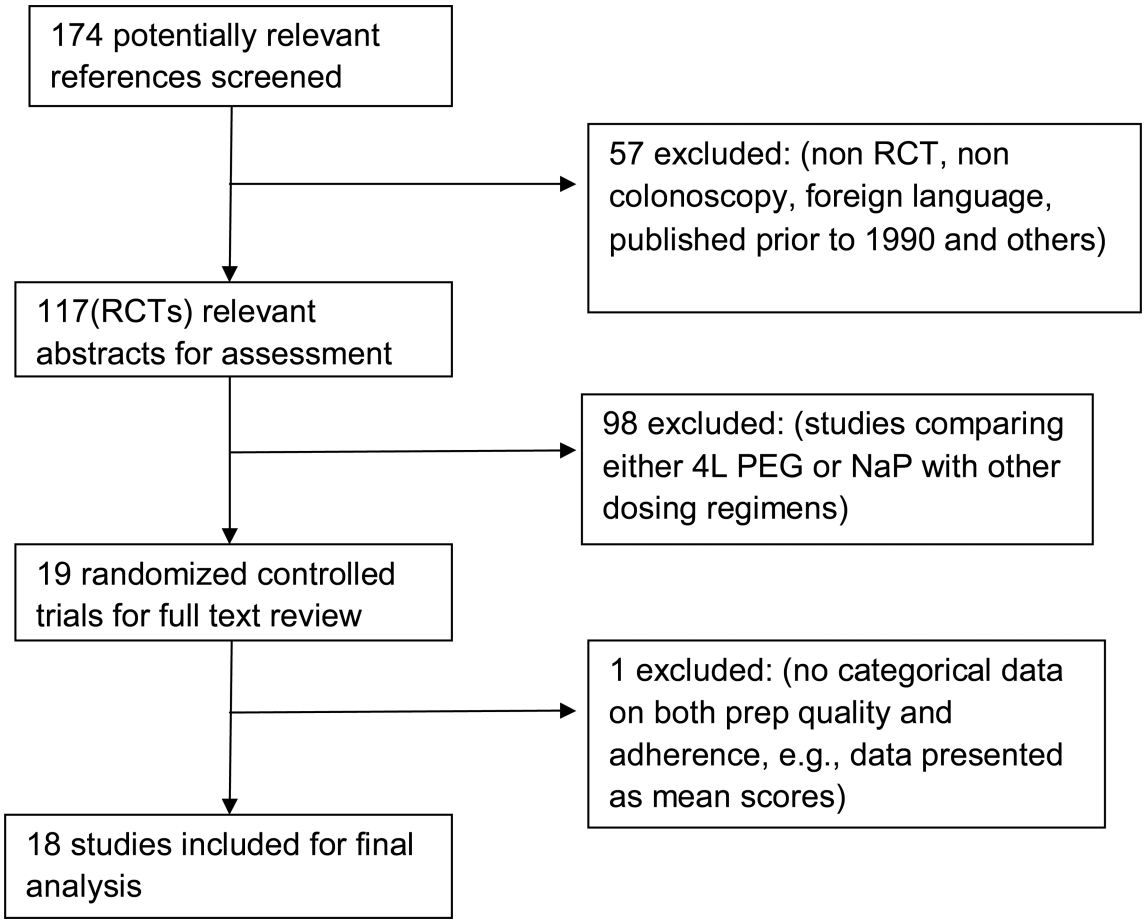

Figure 1.
Flow chart diagram of the studies identified for the meta-analysis.

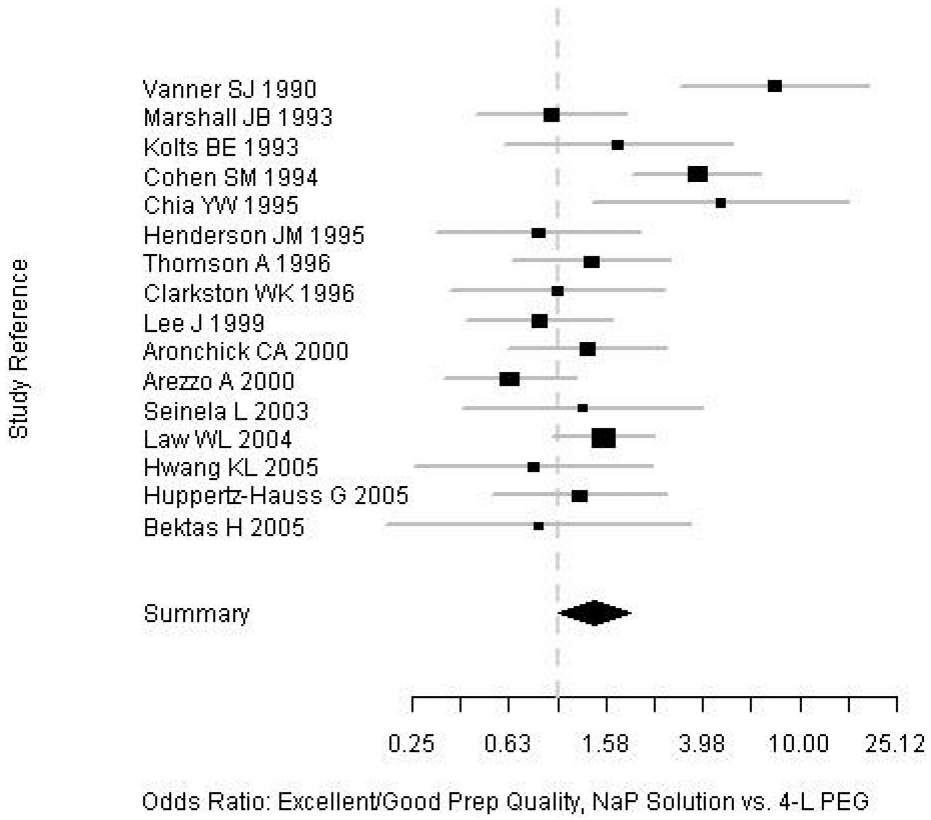

Figure 2.
Forrest plot of prep quality among the trials.

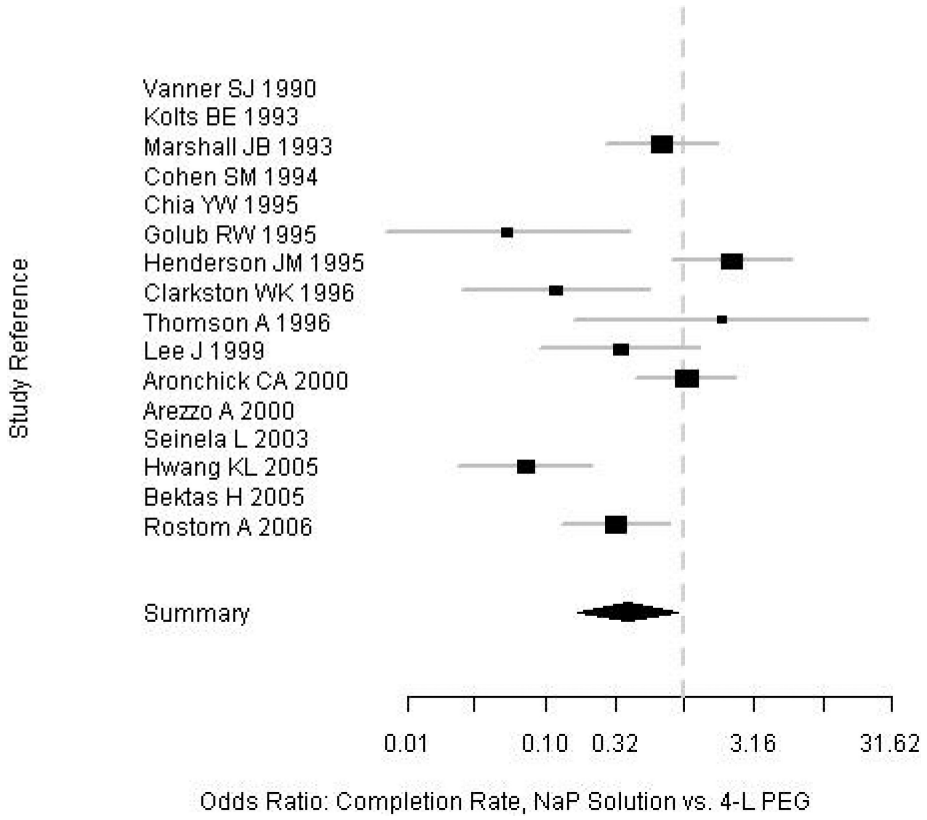

Figure 3.
Forrest plot of prep completion among the trials.

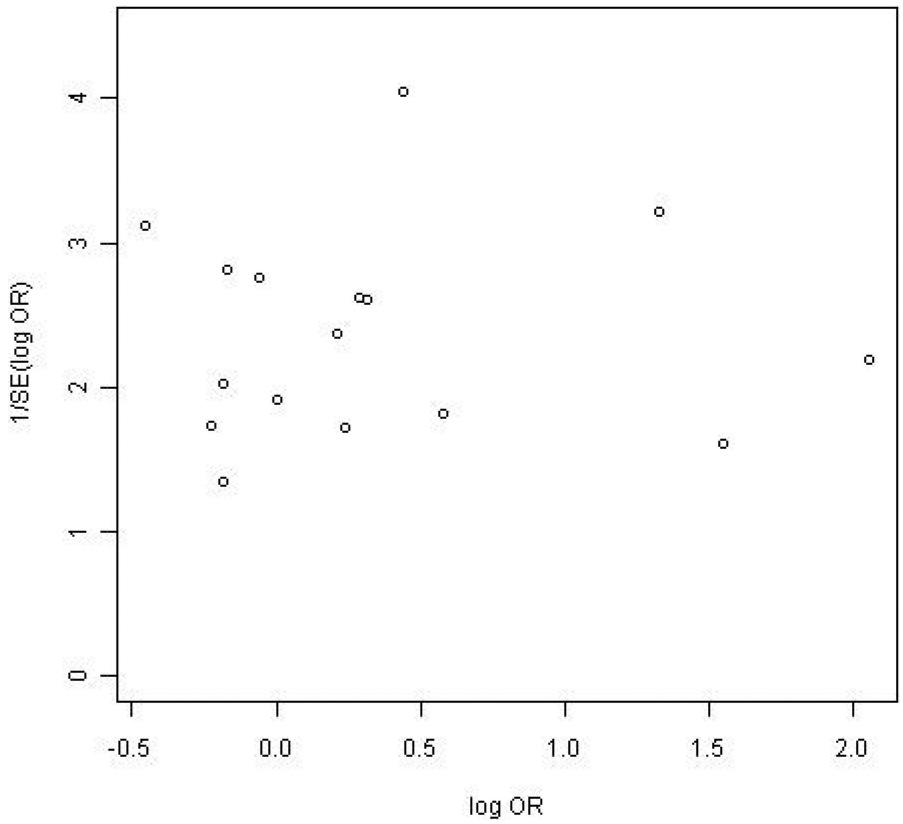

Figure 4.
Funnel plot of prep quality.

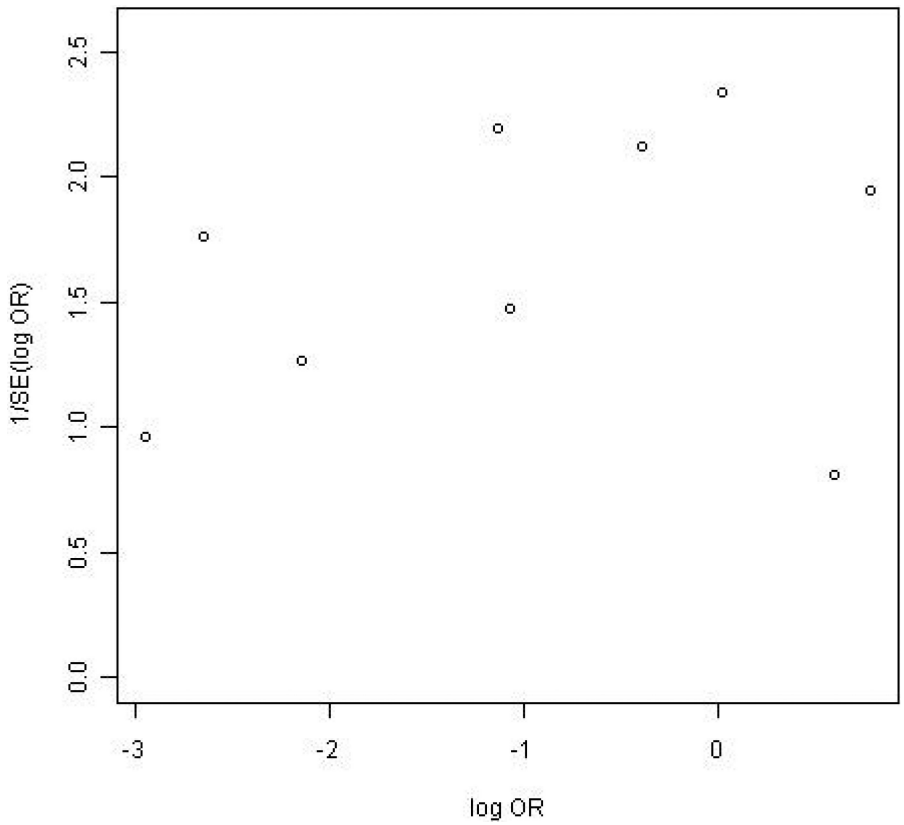

Figure 5.
Funnel plot of prep completion.

Table 1

Patient Demographics

No	Year/1st author/ref.no	Study population	Inclusion criteria	Exclusion criteria	Total number analyzed	Prep	N per group	Mean age	Male/ Female	Unable to complete prep (%)	Prep Quality			Conclusions	
											Excellent (%)	Good (%)	Exce / Good (%)	Prep Quality	Prep Completion
1	Vanner 1990[14]	Consecutive patients for elective colonoscopy	Polyps 56%, IBD 12%, bleeding 3%, others 29 %	Creatinine 2.3 mg/dL, symptomatic CHF, massive ascites, MI within 6 months	102	NaP sol	54	52	30/24	0	26	54	80	NaP better	NaP better
						4L PEG	48	58	25/23	20	6	27	33		
2	Kolts 1993[15]	Consecutive outpatients	Polyps 45%, GI bleed 32%, anemia 4%, diarrhea 4%, constipation 4%, other 11%	Unstable CV status, MI, CVA < 2 mo, creatinine > 2 mg/dL, massive ascites, active IBD, active diverticulitis, delayed gastric emptying	72	NaP sol	34	52	7/27	1	38	41	79	NaP better	NaP=PEG
						4L PEG	38	58	20/18	5	32	29	61		
3	Marshall 1993[29]	Consecutive, non-emergent patients	Not stated	Symptomatic CHF, recent MI, creatinine ≥ 2.3 mg/dL, ascites	143	NaP sol	70	57.2	64/79 for both groups	13	39	30	69	NaP=PEG	NaP=PEG
						4L PEG	73	57.2		18	47	23	70		
4	Cohen 1994[16]	Elective colonoscopy; age/sex–matched	Not stated	Not stated	422	NaP sol	143	66.5	74/69	3	65	25	90	NaP better	NaP better
						4L PEG	279	66.7	141/138	28	43	25	68		
5	Golub 1995*f*[36]	Consecutive, ambulatory patients matched for age/sex/indication	Polyps 62%, bleeding 15%, cancer 13%, family history 3%, other 8%	Not stated	230	NaP sol	106	58.4	NA	1	46	43	89	NaP=PEG	NaP better
						4L PEG	124	58.4	NA	15	48	37	85		
6	Chia 1995[31]	Elective colonoscopy	Not stated	> 60 years of age, pregnant, history of renal or cardiac diseases, acute IBD and intestinal obstruction	79	NaP sol	39	47.7	20/19	Not specified	Not specified	Not specified	85	NaP better	NaP=PEG
						4L PEG	40	53.2	15/25				63		
7	Henderson 1995[32]	Outpatient, elective colonoscopies	Not stated	Symptomatic CHF, recent MI, creatinine > 2 mg/dL, ascites	157	NaP sol	51	51	107/111 for both groups	1	Not specified	Not specified	91	NaP=PEG	NaP better
						4L PEG	106	51		10			92		

No	Year/1st author/ref.no	Study population	Inclusion criteria	Exclusion criteria	Total number analyzed	Prep	N per group	Mean age	Male/ Female	Unable to complete prep (%)	Prep Quality			Conclusions	
											Excellent (%)	Good (%)	Exce / Good (%)	Prep Quality	Prep Completion
8	Thompson 1996[28]	Outpatient colonoscopy	Not stated	Ischemic chest pain, MI, TIA/CVA in last 6 months, creatinine > 200 μg/L, ascites, CHF, colostomy, AMS	116	NaP sol	61	72	47/14	3	20	46	66	NaP better	NaP better
						4L PEG	55	70	38/17	2	15	44	58		
9	Clarkston 1996[27]	Outpatient colonoscopy	Not stated	Severe CHF, creatinine ≥ 2.3 mg/dL, prior bowel resection	98	NaP sol	49	57	22/27	4	45	36	81	NaP=PEG	NaP=PEG
						4L PEG	49	57	12/37	27	31	50	81		
10	Lee 1999[26]	Consecutive outpatients	Not stated	Not stated	159	NaP sol	71	51.5	79/80	4	40	31	71	NaP=PEG	NaP better
						4L PEG	88	57.9	for all	11	43	31	74		
11	Aronchick 2000[9]	Outpatient colonoscopy	Not stated	CHF, chronic renal failure, megacolon, severe constipation, partial or subtotal colectomy, or pre-existing electrolyte abnormalities.	206	NaP sol	106	60.3	46/60	1	77	9	86	NaP=PEG	NaP better
						4L PEG	100	58.8	52/48	12	66	16	82		
12	Arezzo 2000[30]	Consecutive patients	Not stated	Not stated	200	NaP sol	100	61.9	45/55	Not specified	Not specified	Not specified	68	NaP better	NaP=PEG
						4L PEG	100	60.5	52/48				50		
13	Seinela 2003[25]	Consecutive patients	Age > 80 years	Creatinine 2.3 mg/dL, CHF, massive ascites, MI, bowel resection	72	NaP sol	37	84	1o/62	Not specified	48	33	81	NaP=PEG	NaP=PEG
						4L PEG	35	84	for all		52	26	78		
14	Law 2004[24]	Elective colonoscopy	Age > 18 years	Intestinal obstruction, delayed gastric emptying, creatinine >0.2 mmol/L, CHF, MI in the last 6 months, massive ascites and pregnancy.	207	NaP sol	101	58.1	NA	Not specified	15	50	65	NaP better	NaP better
						4L PEG	106	58.1	NA		12	47	59		
15	Hwang 2005[23]	Elective colonoscopy	Not stated	Symptomatic CHF, MI, creatinine >1.5 mg/dL, abnormal elevation of transaminases, ileus, bowel	78	NaP sol	38	52.2	18/22	Not specified	58	21	79	NaP=PEG	NaP=PEG
						4L PEG	40	52.4	25/15		55	28	83		

No	Year/1st author/ref.no	Study population	Inclusion criteria	Exclusion criteria	Total number analyzed	Prep	N per group	Mean age	Male/ Female	Unable to complete prep (%)	Prep Quality			Conclusions	
											Excellent (%)	Good (%)	Exce / Good (%)	Prep Quality	Prep Completion
				obstruction, gastric retention, uncontrolled HTN, unstable angina, pregnancy or breast feeding and severe constipation.											
16	Bektas 2005[33]	Elective colonoscopy	Not stated	Creatinine > 2 mg/dL, pregnancy, bowel obstruction, symptomatic CHF, MI in last 3 months, emergent colonoscopy, acute IBD, ascites	97	NaP sol 4L PEG	61 36	56.7 54.3	29/32 13/23	Not specified	52 47	38 44	90 91	NaP=PEG	NaP better
17	Huppertz-Hauss 2005[¶34]	Consecutive outpatients for colonoscopy	Not stated	< 18 years, creatinine> 150mmol/L, CHF, hepatic failure, electrolyte abnormalities,	160	NaP sol 4L PEG	84 76	58.6 57.4	43/41 29/47	Not specified	Not specified	Not specified	85 81	NaP=PEG	NaP=PEG
18	Rostom 2006[†35]	Elective colonoscopy	patients 18-80 years old	Renal failure, unstable angina, acute coronary syndrome, CHF, ascites, megacolon, bowel obstruction, previous bowel resection and evaluation of diarrhea	194	NaP sol 4L PEG	144 50	52 55	39/95 16/34	8 21	Data presented as mean scores			NaP better	NaP better

Congestive heart failure-CHF, Myocardial infarction -MI, Acute coronary syndrome-ACS, Hypertension-HTN, Inflammatory bowel diseases-IBD, Altered mental status-AMS, Transient ischemic attack-TIA, Cerebrovascular attack-CVA.

[¶]Trials not included in prep completion analysis as there was no data available.

[†]Trials not included in prep quality analysis as the data was either presented as mean scores or not available.

Table 2

Comparison of percent completion and prep quality: 4L PEG vs. NaP

Outcome	Study N	NaP	4L PEG	Odds Ratio (95% CI)	Heterogeneity P-value *
Unable to complete	9	3.90%	9.83%	0.40 (0.17-0.88)	<0.0001
Execellent / good quality	16	82.42%	77.03%	1.43 (1.01-2.0)	0.0003
Excellent quality	10	33.94%	26.86%	1.26 (0.94-1.7)	0.23
Good quality	10	30.44%	29.69%	1.12 (0.8-1.56)	0.065
Fair quality	10	16.60%	17.40%	0.78 (0.59-1.04)	0.671
Poor quality	9	4.70%	7.74%	0.67 (0.36-1.23)	0.046

* P-value from the Woolf's test for heterogeneity.

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