TECHNICAL REVIEW

Optimal bowel cleansing for colonoscopy: split the dose! A series of meta-analyses of controlled studies

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Background: Colonoscopy is considered the criterion standard for detecting colorectal cancer; adequate preparation is crucial for an effective colonoscopy, but definitive data on the optimal preparation are lacking.

Objective: Our aim was to assess the efficacy of split-dose versus non-split–dose preparations, the rate of adequate preparation according to type and dose of laxatives, the role of "runway time" (the interval time between the last drink of purgative and the beginning of colonoscopy), and to evaluate compliance as an additive risk factor for colon cleansing.

Design: A series of meta-analyses of controlled studies.

Setting: Randomized clinical trial of split dose regimen versus entire dose taken on the day preceding colonoscopy.

Patients: Published trials (1960-2013) comparing split-dose versus non-split–dose preparations in adults undergoing colonoscopy were selected by using MEDLINE, the Cochrane Central Register of Controlled Trials, clinicaltrial.gov, ISI Web of Science, and Scopus.

Interventions: Colonoscopy.

Main Outcome Measurements: Rate difference of the degree of colon cleansing between split dose and whole dose was the primary measure of treatment effect.

Results: We included 29 studies. Overall, an adequate preparation was obtained in 85% of patients in the split-dose group and in 63% of the non-split–dose group (rate difference 22%). The heterogeneity was caused by 5 factors: the runway time (the longer, the worse the cleansing), type of diet, male sex, use of polyethylene glycol 4 L, and the Jadad score. Compliance was significantly higher in the split-dose group.

Limitations: Average quality of the included studies and publication bias.

Conclusion: We provided further evidence of the superiority of a split-dose regimen over a non-split–dose regimen and showed that, regardless of type and dose, the superiority of split-dose regimens remains valid if the "golden 5 hours" rule is preserved. (Gastrointest Endosc 2014;80:566-76.)

Colonoscopy is considered the criterion standard in detecting colorectal cancer and, more importantly, its precursors such as polypoid or flat lesions. The first step toward a high-quality colonoscopy is a clean colon. Indeed, inadequate cleansing can result in missed lesions, aborted procedures, increased procedure time and, potentially, adverse events, together with reduced patient comfort.[1,2] Commercially available bowel cleansing preparations contain osmotic components (sodium phosphate [NaP]), isotonic solution (polyethylene glycol [PEG]), or irritant laxatives (sodium picosulphate). In literature, many studies show that all those laxatives are associated with good colon cleansing, but there is no clear-cut superiority or a specific dosing regimen that is better than another. Also, alternative dosages (eg, PEG 2 L or low volume [PEG-low]) or different regimens (splitting the dose, in which the laxative is split into 2 half doses between the day before and the day of the examination or same day

Abbreviations: ESGE, European Society of Gastrointestinal Endosocopy; G/E, good and/or excellent; NaP, sodium phosphate; PEG, polyethylene glycol; PEG-high, PEG high volume (4 L); PEG-low, PEG low volume (2 L); RD, rate difference.

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regimen, suggested for afternoon colonoscopies) were tested recently, with an apparent increase in efficacy and patient compliance, but definitive data are still missing.[3]

Objectives

The primary endpoints were to compare the efficacy in terms of colon cleansing of the split-dose regimen compared with the non-split–dose regimen, regardless of the type and doses of laxative and the efficacy of different laxatives in patients undergoing colonoscopy. Secondary endpoints were (1) to compare the rate of good and/or excellent (G/E) bowel preparation in different subgroups of patients according to the type and dosage of the laxative, (2) to assess the role of "runway-time" (the interval time between the last drink of laxative and the beginning of colonoscopy), and (3) to evaluate the rate of compliance as an additive risk factor for colon cleansing.

METHODS

Study selection

A systematic review of published articles (1960-2013) comparing split-dose versus non-split–dose regimens in adults undergoing colonoscopy by using MEDLINE, the Cochrane Controlled Trials Register, clinicaltrial.gov, ISI Web of Science, and Scopus was performed. Search terms included "bowel," "preparation," "colon," "cleaning," and "colonoscopy." Studies were identified also by scanning reference lists of articles. No limits were applied for language, and foreign articles were translated, when possible. Abstracts were screened separately by 2 authors and selected if the following inclusion criteria were fulfilled: (1) randomized clinical trials, (2) split-dose versus non-split–dose regimens, and (3) patient age >18 years. Abstracts were excluded if they did not fulfill the inclusion criteria and/or if there was a special interest in a subgroup of patients (older, inpatients, pediatrics, etc). Then the full texts of selected articles were retrieved in extenso. A predefined data extraction sheet (containing a pilot test on 10 randomly selected included studies performed in advance) was used. Two authors extracted independently the following data from each article: patient characteristics (age; sex; diet before preparation; time of colonoscopy; use of cathartics; compliance to the laxative; type, dose, and regimen of preparation; scale used to evaluate colon cleansing; degree of colon cleansing (grouping; excellent-good vs poor-fair); study quality indicators for the Jadad score[4] and analysis type (intention to treat or per protocol). If one or more variables was not immediately inferable, principal investigators were contacted by e-mail. If primary outcomes were not available, the study was then excluded. The Jadad score was rated for each trial by 2 authors, and then the final ratings were determined by consensus.

Data synthesis

The rate difference (RD) of the degree of colon cleansing between split dose and whole dose was the primary measure of treatment effect. The meta-analyses were performed by computing RD by using a random-effects model, if heterogeneity was present. Quantitative analyses were performed on an intention-to-treat basis. Absolute rate of colon cleansing for split-dose and non-split–dose regimens, RD between them and 95% confidence intervals for each treatment arm, and pooled effect estimated were calculated.

Measures of treatment effect

Analysis was carried out for all patients undergoing split-dose versus non-split–dose regimens (overall analysis) for colonoscopy and according to specific type of laxative comparisons (subgroup analysis). The second analysis was realized by estimating the difference in colon cleansing degree between patients in the split-dose and in the non-split–dose groups.

Assessment of heterogeneity

To explore the heterogeneity, we specified the following hypotheses before conducting the analysis. We hypothesized that effect size may differ according to the methodologic quality of the studies, to the type of purge, to the time elapsed between the end of purge intake and the beginning of colonoscopy, the type of diet before laxative use, patient compliance, frequency of male sex, the scale used to evaluate colon cleansing, and the type of analysis performed (intention to treat vs per protocol).

Assessment of biases

We assessed the possibility of publication bias by evaluating a funnel plot of the trial effect rate for asymmetry. We conducted an Egger-Hardbord regression test as a formal predefined statistical test for publication bias, and we conducted the contour-enhanced funnel plots to aid in interpreting the funnel plot.

Subgroup analysis

A subgroup analysis was planned to test the secondary endpoints among groups of patients who took different laxatives. We tested for heterogeneity as described for the overall effect and calculated confidence intervals and *P* values for differences between the effect measure parameters for different subpopulations.

Sensitivity analysis

Sensitivity analyses were prespecified. The treatment effects were examined according to quality components (concealed treatment allocation, blinding of patients and caregivers, blinded outcome assessment). Appendix 1 (available online at www.giejournal.org) extensively describes the statistical methods applied.

TABLE 1. Study and patient characteristics included in the quantitative systematic revision

Ref	Jadad score	Split-dose regimen	Non-split–dose regimen	Diet	Total no. split-dose	Total no. non-split–dose	Time lapse, h	Good preparation split-dose, no.	Fair preparation split-dose, no.	Good preparation non-split–dose, no.	Fair preparation non-split–dose, no.
30	1	PEG H	NaP	L	54	48	NA	44	10	10	38
24	1	NaP	PEG H	L	70	73	3	60	10	66	7
25	2	PEG H	Castor oil	LFD	61	71	NA	51	10	45	26
20	1	NaP	PEG H	L	34	38	NA	27	7	23	15
11	1	NaP	PEG H	L	143	141	2	128	15	102	39
11	1	NaP	PEG H	L	143	138	2	128	15	93	44
33	2	NaP	PEG L	L	154	127	NA	131	23	86	41
7	1	NaP	PEG H	LFD	100	100	5	68	32	50	50
7	1	NaP	$MgSO_4$	LFD	100	100	5	68	32	38	62
19	2	NaP	PEG H	NA	420	425	4	354	66	326	29
8	3	NaP	NaP	L	297	160	3	252	45	117	43
8	3	NaP	$MgSO_4$	L	297	140	3	252	45	132	8
16	2	PEG H	NaP	L	59	60	2	49	10	15	45
16	2	PEG H	PEG H	L	59	54	2	49	10	27	27
15	1	PEG H	PEG H	L	91	96	2	75	16	66	30
6	2	PEG H	PEG H	L	68	73	2	52	16	41	32
13	2	NaP	PEG L	LFD	79	96	5	53	26	48	48
13	2	NaP	Se + Mg	LFD	79	90	5	53	26	35	55
18	2	PEG H	NaP	L	38	40	1	30	8	33	7
27	3	NaP	PEG H	LFD	45	45	2	36	9	12	33
27	3	NaP	NaP	LFD	45	44	2	36	9	3	41
32	2	NaP	NaP	NA	29	32	4	26	3	23	9
32	2	NaP	NaP	NA	33	30	4	32	1	27	3
31	3	PEG L	Pico + Mg	NA	32	33	1	27	5	24	9
5	5	PEG H	PEG H	L	92	94	2	85	7	37	57
5	5	PEG H	PEG H	L	107	89	2	92	15	41	48
14	3	PEG L	NaP	L	183	194	NA	175	8	159	31
14	3	PEG L	PEG L	L	183	193	NA	175	8	155	38
14	3	NaP	NaP	L	181	194	NA	175	6	159	31
14	3	NaP	PEG L	L	181	193	NA	175	6	155	38
21	3	NaP	PEG L	LFD	40	41	5	39	1	31	10
21	3	NaP	PEG L	LFD	40	41	5	35	5	31	10
12	1	PEG L	PEG H	L	85	87	NA	79	6	77	10
26	2	PEG H	PEG H	L	80	79	NA	61	19	40	39
26	2	PEG L + Mg	PEG H	L	73	79	NA	55	18	40	39

TABLE 1. Continued

Ref	Jadad score	Split-dose regimen	Non-split–dose regimen	Diet	Total no. split-dose	Total no. non-split–dose	Time lapse, h	Good preparation split-dose, no.	Fair preparation split-dose, no.	Good preparation non-split–dose, no.	Fair preparation non-split–dose, no.
28	2	NaP	PEG H	L	63	67	3	62	1	61	6
10	3	PEG L	PEG L	L	52	55	6	48	4	49	6
23	3	PEG H	PEG L	LFD	218	218	2	160	58	91	127
23	3	PEG L	PEG L	LFD	217	218	2	167	50	91	127
23	3	PEG H	PEG H	LFD	218	215	2	160	58	95	120
23	3	PEG L	PEG H	LFD	217	215	2	167	50	95	120
17	3	Pico + Mg	Pico	L	119	117	4	111	8	78	39
29	3	PEG L	PEG H	L	54	60	NA	41	13	19	41
29	3	PEG H	PEG L	L	51	60	NA	42	9	19	41
29	3	PEG L	PEG H	L	54	57	NA	41	13	11	46
29	3	PEG H	PEG H	L	51	57	NA	42	9	11	46
22	3	PEG H	PEG H	LFD	168	168	3	160	8	156	12
9	3	PEG H	PEG L	L	49	52	NA	27	23	32	20

PEG H, Polyethylene glycol high volume (4 L); *NaP*, sodium phosphate; *L,* liquid; *NA,* not available; *LFD,* low-fiber diet; *PEG L,* polyethylene glycol low volume (2 L); *$MgSO_4$,* magnesium sulfate; *Se + Mg,* senna plus magnesium sulfate; *Pico,* picosulphate.

RESULTS

Characteristics of included studies

Between 1967 and 2013, 144 articles were published on this topic; 60 articles were evaluated as full text, and 29 randomized clinical trials were finally included,[5-33] with a total of 48 treatment arms (Table 1). Figure 1 depicts the overall results of the search strategy. According to the inclusion criteria, participants of the studies were inpatients and outpatients who had undergone colonoscopy. We assumed that all underwent the purge the day before (non-split–dose group, n = 4040) or took a half dose the day before and half dose the morning of the examination (split-dose group, n = 3679), regardless of the type of purge assumed or the timing of the colonoscopy or endoscopy session. Fifteen types of comparisons among different laxatives were tested in those 29 trials, with a major predominance of PEG (both PEG-low and high-volume PEG of 4 L [PEG-high]) or NaP-based regimens (Table 2). Specifically, the most frequent comparisons were between split-dose PEG-high (no. of patients tested = 934) and non-split–dose PEG-high (no. of patients tested = 925) and split-dose NaP (no. of patients tested = 1019) versus non-split–dose PEG-high (no. of patients tested = 1027). Appendix 2 (available online at www.giejournal.org) extensively describes the characteristics of the included studies.

ANALYSIS OF SPLIT-DOSE VERSUS NON-SPLIT–DOSE BOWEL PREPARATION REGIMENS

Overall

A G/E preparation was obtained in 0.85 (95% confidence interval [CI], 0.82-0.88) of patients undergoing a split-dose regimen, whereas in the non-split–dose group, this rate was 0.63 (95% CI, 0.55-0.71) (Fig. 2), with a raw RD of 0.22 (95% CI, 0.16-0.27). All trials but 1[8] were in favor of the split-dose regimen, and only in 4 studies[8,9,18,24] did the mean value cross the null line (Fig. 3). Although all studies clearly showed a direction of the effect toward the split-dose regimen, a significant heterogeneity ($P < .001$) was present, with an I^2 of 91.4% and a significant publication bias (Egger test; $P < .001$).

Meta-regression analysis

In an attempt to explain the huge difference among trial outcomes, we performed a meta-regression analysis. The results were that, although studies had apparently comparable protocols, 5 factors significantly influenced the quality of colon cleansing: the runway time, the type of diet before colonoscopy (liquid or low-fiber), male sex, the comparisons between PEG-high preparations versus other laxatives, and the Jadad score (I^2 residual = 65.24%; adjusted R^2 = 82.72%). In contrast, the use of different

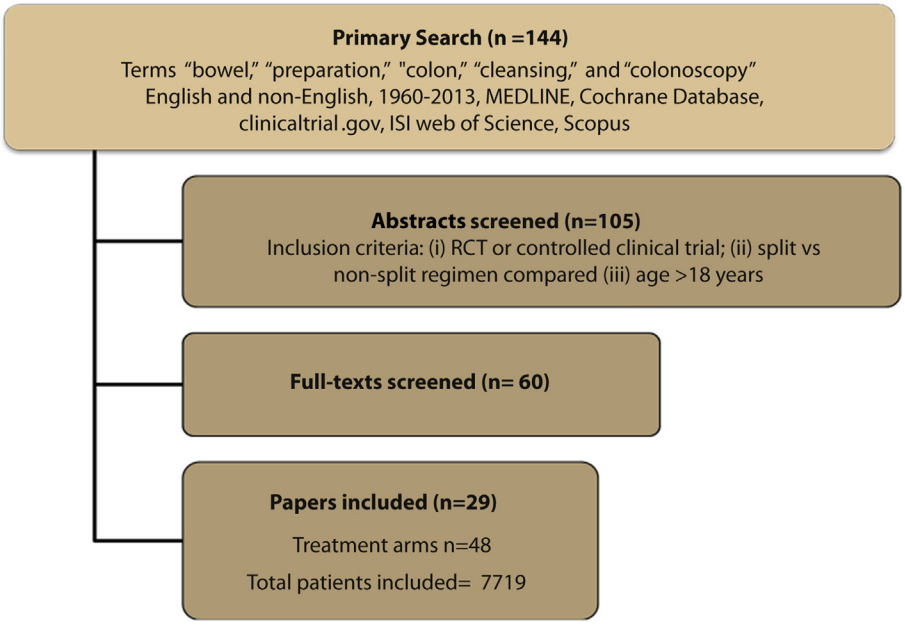

Figure 1. Search strategy.

scales did not influence the variance of the degree of colon cleansing (Table 3). When examining the role of runway time, we found that as this time increased, the gain of the split-dose over the non-split–dose regimen decreased. In fact, the overall RD of 0.23 was maintained when the colonoscopy was performed within 3 hours from the end of purge intake ($P < .001$), whereas it decreased after 4 to 5 hours (RD 0.18; $P < .001$) and became statistically not significant at >5 hours (RD 0.03; $P = .56$) (Table 4).

Also, the type of diet before the endoscopic examination had a role in our meta-regression analysis. In fact, the use of a low-fiber diet provided a better colon cleansing when compared with a liquid diet (Table 3). The cumulative analysis (Fig. 4) indicates that all trials published since 2006 proved the gain of the split-dose versus the non-split–dose regimen, with roughly 22% in favor of the split-dose regimen. Compliance analysis showed that, regardless of the laxative type, the highest compliance was obtained by using the split-dose regimen, with an RD of 9.4% (95% CI, 0.06-0.13; $P < .001$) versus the non-split–dose regimen.

Subgroup analysis based on type of laxative used

A subgroup analysis was carried out according to the type of laxative used in the 2 groups (Table 2).

PEG-high split-dose versus PEG-high non-split–dose regimens. Nine treatment arms compared the split-dose versus non-split–dose PEG-high regimen (split-dose group = 934 patients, male 55%, median age 57.3 years; 95% CI, 50.6-64; non-split–dose group = 925 patients, male 56.7%, median age 56.4 years; 95% CI, 55.3-57.5).[5,6,15,16,22,23,26,29] The RD between groups was 0.30 (95% CI, 0.16-0.45) toward the split-dose regimen. Moreover, 83% (95% CI, 0.78-0.89) of the split-dose group had a G/E cleansing, compared with 55% (95% CI, 0.39-0.70) of the non-split–dose group ($P < .001$; heterogeneity 130.6; I^2 93.9%; $P < .001$). Overall, 94% of patients in the split-dose group were fully compliant to the scheduled regimen versus 84% of those in the non-split–dose group (RD 0.08; 95% CI, 0.03-0.12; $P < .001$; heterogeneity 25.9; I^2 73%; $P = .001$).

NaP split-dose versus PEG-high non-split–dose regimens. Eight treatment arms compared split-dose NaP versus non-split–dose PEG-high regimens (split-dose group = 1019 patients, male 45%, median age 58.1 years; 95% CI, 53.6-72.5; non-split–dose group = 1027 patients, male 46.6%, median age 57.5 years; 95% CI, 44.0-71.1).[7,11,19,20,24,27,28] In the NaP group, a G/E preparation was obtained in 85% (95% CI, 0.77-0.90) of cases, whereas in the other group, only 70% (95% CI, 0.54-0.83) achieved the same preparation quality (RD 0.15; 95% CI, 0.07-0.24; $P < .001$; heterogeneity 39.3; I^2 82.2%; $P < .001$). Compliance was 94% in the NaP split-dose group and 58% in the PEG-high non-split–dose group (RD 0.26; 95% CI, 0.029-0.494; $P = .028$; heterogeneity 708.2; I^2 99.2%; $P < .001$).

Split-dose NaP versus non-split–dose NaP regimens. Five treatment arms were included in this analysis (split-dose group = 586 patients, male 45%, median age 57.2 years; 95% CI, 55.5-68.9; non-split–dose group = 460 patients, male 48.4%, median age 55.6 years; 95% CI, 45.6-65.6).[8,14,27,32] The use of the split-dose NaP regimen gave a G/E cleansing in 91.0% (95% CI,

TABLE 2. Absolute rate of good and/or excellent colon cleansing prior to colonoscopy and compliance according to type of comparison among laxatives

	Split-dose, no.	Non-split–dose, no.	RD, 95% CI	Split-dose, G/E % (range)	non-split–dose, G/E % (range)	*P* value
PEG-high vs PEG-high	934	925	0.30 (0.16-0.45)	83 (0.78-0.89)	55 (0.39-0.70)	< .001
NaP vs PEG-high	1019	1027	0.15 (0.07-0.24)	85 (0.77-0.90)	70 (0.54-0.83)	< .001
NaP vs NaP	586	460	0.23 (0.02-0.42)	91.0 (0.82-0.96)	67 (0.31-0.90)	.024
NaP vs PEG-low	313	305	0.18 (0.11-0.24)	86 (0.73-0.94)	67 (0.54-0.78)	< .001
PEG-low vs PEG-high	429	444	0.26 (0.08-0.45)	81 (0.69-0.89)	56 (0.30-0.79)	< .001
Low volume vs low volume preparations	386	398	0.15 (0.05-0.24)	93 (0.89-0.95)	78 (0.68-0.85)	< .001

RD, Rate difference; *CI,* confidence interval; *G/E,* good and/or excellent; *PEG,* polyethylene glycol; *high,* high volume (4 L); *NaP,* sodium phosphate; *low,* low volume (2 L).

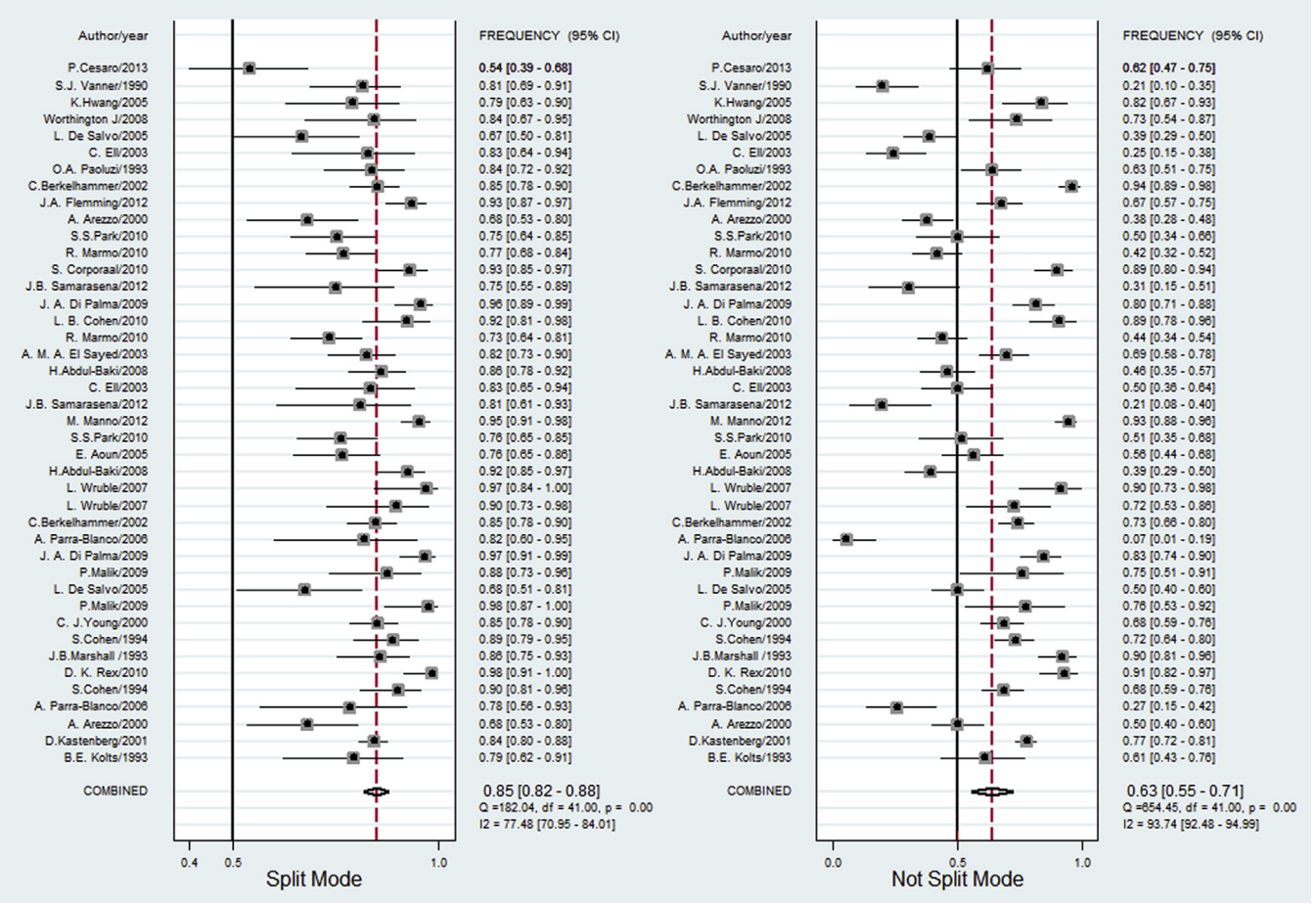

Figure 2. Colon cleansing rate (good or excellent) before colonoscopy in included studies in patients consuming split-dose or non-split–dose bowel preparation.

0.82-0.96) of patients, compared with 67% (95% CI, 0.31-0.90) in the non-split–dose group (RD 0.23; 95% CI, 0.02-0.42; $P = .024$; heterogeneity 70.07; I^2 94.3%; $P < .001$). In this comparison, patients were slightly more compliant to the non-split–dose regimen (99.5%) than to the split-dose (99.2%) regimen, with an RD of -0.001 (95% CI, -0.010–0.008; $P = .75$; heterogeneity 0.71; I^2 0.0%; $P = .87$).

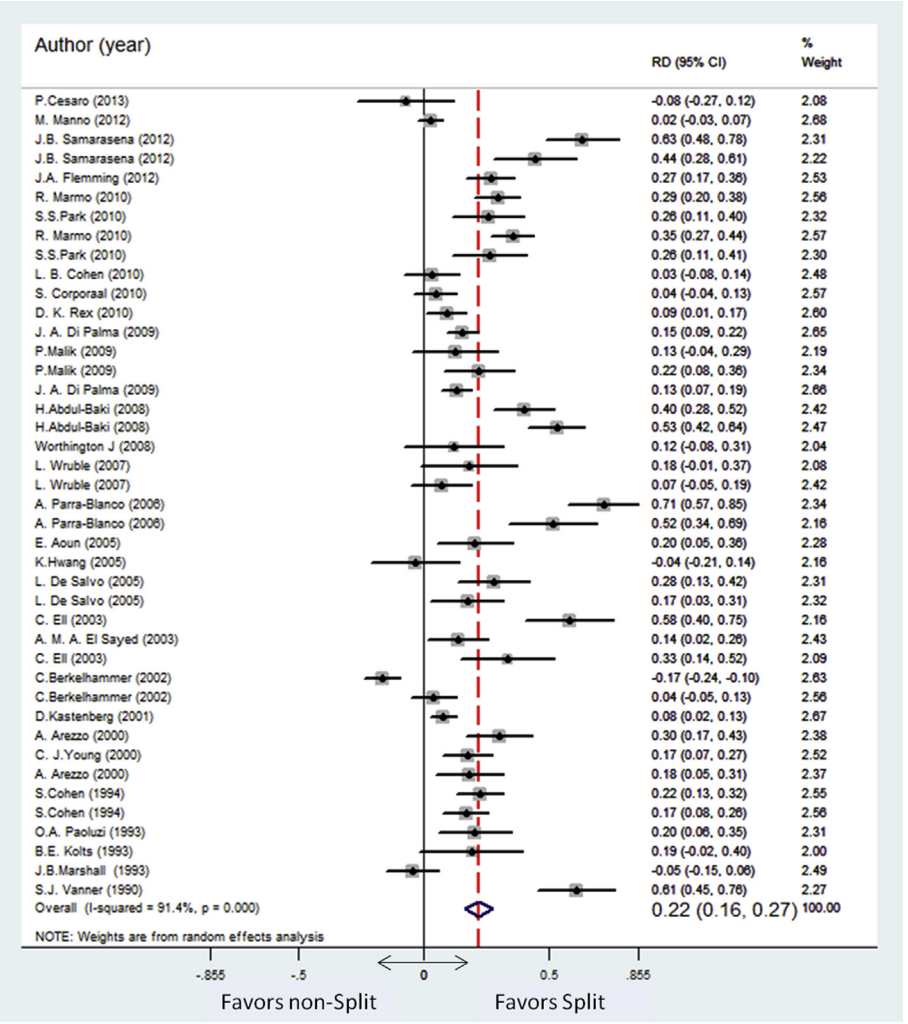

Figure 3. Good or excellent grade of colon preparation before colonoscopy pooled rate difference between split-dose and non-split–dose regimens.

NaP versus PEG-low regimens. The split-dose NaP regimen led to a G/E cleansing in 86% (95% CI, 73%-94%) versus 67% (95% CI, 54%-78%) of patients undergoing a non-split–dose PEG-low regimen, with an RD of 0.18 (95% CI, 0.11-0.24; $P < .001$; heterogeneity 0.72; I^2 0.0%; $P = .86$; arms compared 4; split-dose group = 313 patients, male 49%, median age 61.9 years, 95% CI, 37.2-86.5; non-split–dose group = 305 patients, male 51.8%, median age 60.5 years; 95% CI, 39.1-81.8).[13,14,21,33] Compliance was 96.5% in the split-dose group and 88.3% in the non-split–dose group (RD 0.075; 95% CI, 0.03-0.12; $P < .001$; heterogeneity 0.02; I^2 0.0%; $P = .90$).

PEG-low versus PEG-high regimens. Colon preparation was G/E in 81% of patients taking the split-dose PEG-low regimen (95% CI, 0.69-0.89) versus 56% (95% CI, 0.30-0.79) of those taking the non-split–dose PEG-high regimen, with an RD of 0.26 (95% CI, 0.08-0.45; $P = .004$; heterogeneity 32.9; I^2 90.7%; $P < .001$) (4 treatment arms; split-dose group = 429 patients, male 70.6%, median age 57.6 years; 95% CI, 48.8-66.5; non-split–dose group = 444 patients, male 68.9%, median age 56.9 years; 95% CI, 48.3-65.6).[12,23,29] Compliance was 93.8% in the split-dose group and 94.1% in the non-split–dose group (RD 0.005; 95% CI, -0.03–0.04; $P = .78$; heterogeneity 2.42; I^2 17.2%; $P = .29$).

Other low-volume preparation comparisons. Four articles addressed the rate of G/E preparation, comparing low-volume purgatives (split-dose group = 386 patients, male 48.2%, median age 55.8 years; 95% CI, 45.4-66.3; non-split–dose group = 398 patients, male 47.7%, median age 55.7 years; 95% CI, 43.3-60.0). Two studies compared the PEG-low regimen[10,14]; 1 PEG-low versus picosulphate plus magnesium citrate regimen[31] and 1 picosulphate plus magnesium citrate versus picosulphate regimen.[17] In all, the split dose was superior, with a G/E degree of 93% (95% CI, 0.89-0.95) versus 78% (95% CI, 0.68-0.85) in the non-split–dose group (RD 0.15, 95% CI, 0.052-0.244; $P = .003$). Heterogeneity was present only in the non-split–dose group. Compliance was 95.1% in the split-dose group versus 93.9% in the non-split–dose

TABLE 3. Meta-regression analysis of the factors affecting the rate difference heterogeneity for colon cleansing among included studies

	ES	Coef	SE	P	95% CI
Diet (0 liquid, 1 LFD)	0.170	0.048	3.55	.004	0.066-0.274
Sex (0 male, 1 female)	-0.002	0.000	-4.58	< .001	-0.004–0.001
Time elapsed	-0.125	0.020	-6.16	< .001	-0.169–0.081
Jadad score	0.061	0.020	3.03	.010	0.017-0.105

ES, Effect size; *Coef,* coefficient; *SE,* standard error; *CI,* coefficient interval; *LFD,* low-fiber diet.

group (RD 0.005; 95% CI, 0.061-0.051; $P = .86$; heterogeneity = 3.40; $P = .183$; $I^2 = 41.1\%$).

Sensitivity analysis

Twelve treatment arms scored ≥3 when evaluated by the mean of the Jadad score.[5,8-10,14,17,21-23,27,29,31] Overall, a G/E degree of colon cleansing was achieved in 86.5% for the split-dose group (95% CI, 0.82-0.91) versus 62.6% (95% CI, 0.47-0.75) for the non-split–dose group. The pooled rate difference was 24.6 (95% CI, 14.6-34.7; $P < .0000$; heterogeneity chi-square = 363.44; $P = .000$; $I^2 = 95.0\%$; Egger test for publication bias $P = .023$).

Publication bias

As for the publication bias, in our meta-analysis a significant asymmetry was present, and the Egger-Harbord regression was significant for such bias.[34] The contour-enhanced funnel plot showed that among the studies included in this meta-analysis, those leading to asymmetry are found in the areas of higher statistical significance (0.01 or less), suggesting that asymmetry could be caused by other factors that cause systematic differences in the results of large and small studies (data not shown).

DISCUSSION

Since the introduction of colonoscopy as a screening tool, the importance of a good-quality endoscopic examination has become increasingly significant to the point where major quality indicators (adenoma detection and cecal intubation rates) are associated with optimal bowel cleansing.[35] In this meta-analysis, we analyzed 29 trials comparing the efficacy of split-dose versus non-split–dose regimens and different laxatives. Results indicate a specific advantage of split-dose over non-split–dose regimens of roughly 22% because a good preparation can be obtained in 85% of patients taking the split dose and only in 63% of those taking the non-split dose, independently from the laxative. In the sensitivity analysis, such a rate difference was present even in larger studies, confirming the marked effect direction of all studies toward the superiority of the split dose.

All studies demonstrated the superiority of the split dose, although with a significant difference in terms of efficacy. The meta-regression analysis identified 5 key factors potentially related to the different magnitude of split-dose regimen efficacy. The most prominent was the runway time, that is, the time elapsed between the last dose of purge and the beginning of the colonoscopy. The role of the runway time already has been considered in previous trials. In 2009, Siddiqui et al[36] showed that patients who had an excellent preparation quality had a shorter runway time and, consequently, that the colon cleansing varied inversely with the duration of this interval. Our results confirmed that the clinical gain of the split-dose regimen is maintained within 3 hours from the end of purge intake, progressively decreases after 4 to 5 hours, and fades away at >5 hours, suggesting that it is not the type or the dose of any laxative, but the "5 golden hours" that is the key factor in performing a colonoscopy in a clean colon. The impact of the runway time on the clinical effectiveness of the split-dose regimen underlines that the superiority of the split-dose versus the non-split–dose regimen is not related to the type or volume of purge but is related to the progressive worsening of colon cleansing over time, inevitably because of the arrival of liquid stools from the ileum. This factor should be considered by the clinician when a good-quality colonoscopy is wanted. It is worth remembering that concerns about the safety of sedation in patients not compliant with preprocedure fasting were raised (eg, for those taking the second dose of laxative shortly before the endoscopic procedure). Those concerns were mainly related to the American Society of Anesthesiologists guidelines that suggest a 2-hour fast before sedation because of the risk of pulmonary aspiration.[37] In our opinion, 2 elements support the safety of the split-dose regimen: first, because the second dose is completed at least 2 hours before the colonoscopy, it can hardly interfere with these guidelines, and second, mean residual gastric volume in patients receiving a split dose is similar to that found in patients who received the whole preparation, as recently shown.[38]

The meta-regression analysis also showed that the use of a low-fiber diet instead of a liquid one is associated with the magnitude of effect variance. The European Society of Gastrointestinal Endosocopy guidelines[39] (ESGE) recommend a low-fiber diet for colon preparation, although with a weak level of recommendation because of moderate quality evidence. Furthermore, the analysis confirmed that there is an association between the low-

TABLE 4. Relationship between the time elapsed from the last dose of bowel purgative intake to colonoscopy session and the degree of colon cleansing

Time elapsed, h	Split-dose arm, no.	Non-split–dose arm, no.	RD	*P*	95% CI
≤3	1799	2044	0.23	.00	0.143-0.321
4-5	860	1031	0.18	.00	0.112-0.243
>5	52	55	0.03	.56	-0.078–0.142

RD, Rate difference; *CI,* confidence interval.

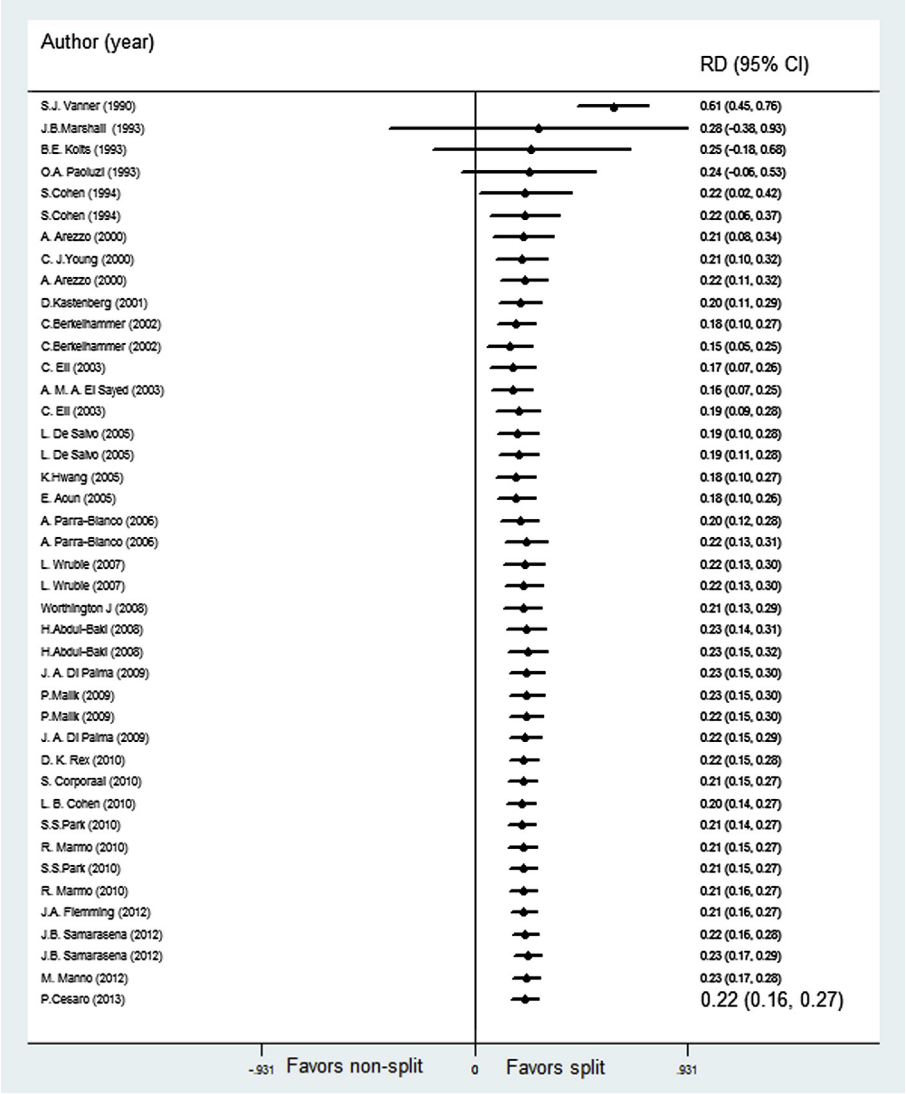

Figure 4. Cumulative meta-analysis of included studies sorted by year of publication.

fiber diet and heterogeneity of published studies, linking this diet with more consistent results for the split-dose regimen. Unfortunately, we are unable to define the best time of fiber withdrawal because diet protocols varied among studies.

Other influencing factors resulting from the meta-regression analysis were male sex; the use of PEG-high, in accordance with previous meta-analysis[40]; and the study quality according to the Jadad score. A negative correlation between male sex and colon preparation had already been

demonstrated in several papers.[41,42] Male sex together with marital status is known to be an independent predictor of poor bowel preparation. One explanation is the lower health consciousness or diversity in health perceptions of men compared with those of women, but further studies are needed to evaluate possible underlying biology divergences between sexes.

Among different products, the split-dose NaP regimen achieved a higher number of patients with an optimal colon cleansing quality when compared with full-dose PEG, full-dose NaP, or split-dose PEG. Comparisons among low-volume solutions showed that other laxatives produced a cleansing rate of 93%, but numbers were too small to generalize results. Among quality indicators, bowel cleansing is considered adequate if $\geq$90% of screening colonoscopies are described as having G/E cleansing.[43] Based on our results, NaP is the only laxative able to produce an optimal cleansing, but because of the notorious side effects, it hardly can be prescribed for screening purposes. Future studies should aim at understanding how to obtain better preparation with good safety profile laxatives.

Results of the cumulative analysis confirmed that the split-dose regimen is better than the non-split–dose regimen; therefore, it should be the first-choice regimen for morning colonoscopies. Also, the work organization of endoscopy units should be subordinate to the scheduling time in order to arrange patient preparation within the "golden hours." In fact, the gain achieved with the split-dose regimen ultimately can reduce the missing rate for lesions and adverse events, the work overload, and the costs, secondary to repeated procedures and potentially increasing patient willingness to undergo colonoscopy. The role of the same-day regimen was not investigated in the present meta-analyis and in accordance with the recent ESGE guidelines,[39] it should be suggested only for afternoon colonoscopies.

Compliance, as expected, was higher in the split-dose group, but this does not affect the heterogeneity of the results in the meta-regression analysis. One could speculate that an increased compliance to a more patient-friendly preparation is implicitly part of the split-dose regimen and not an additional factor, because compliance was excellent within the split-dose group. Subgroup analysis revealed that the compliance rate was higher for NaP than for PEG products. Again, although data support its superiority, the risk of adverse events should discourage the use of NaP, and further studies are needed to validate other low-volume products. According to recent evidence, picosulphate-based preparation seems to represent a novel alternative among low-volume products.[44]

There are several strengths and limitations to this meta-analysis. Strengths include the extensive search strategy and the inclusion of only randomized, controlled trials. Second, we analyzed which regimen is better, independently from the laxative type or dose. Limitations are essentially related to the quality of the included studies and to the publication bias. As mentioned, the Jadad score was low, and this influenced the heterogeneity, so further studies should be carried out with better methodology. In fact, most studies lack proper blinding, and randomization procedures were not fully described. We cannot exclude the possibility of subjective influences on the judgment of cleansing quality or be confident that the randomization was appropriate. Also, although the use of different cleansing scales did not seem to have an effect on primary endpoints, for future trials the use of validated scales or authors providing comparable and easily inferable results, together with scale means would be advisable.

For the publication bias, in our meta-analysis a significant asymmetry was present, and the Egger-Harbord regression was significant for such bias. But with the use of contour-enhanced funnel plots, we showed that this asymmetry may have been related to factors other than publication biases, such as true systematic differences (data not shown).

In conclusion, our meta-analysis provides evidence of the superiority of the split-dose over the non-split–dose regimen and that NaP-based laxatives have a better cleansing effect. Clinicians should remember that, regardless of the type, dose, and regimen, the superiority of the split-dose schedule is preserved only for proper runway time—meaning that the colonoscopy is started within 5 hours of the end of purgative intake.

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APPENDIX 1

METHODS

Measures of treatment effect

Analysis was carried out for all patients receiving split-dose versus non-split–dose regimens (overall analysis) for colonoscopy and according to a specific type of laxative comparisons (subgroup analysis). Moreover, we performed 2 types of pooled measures: first, we used the MIDAS procedure,[10] used in diagnostic meta-analysis or for interventional trials, to evaluat the treatment effect as excellent and/or good (E/G) or fair and/or poor (F/P) for colon cleansing rate in patients who had undergone split-dose or non-split–dose regimens (eg, patients who took all the laxative the day before the procedure versus patients who took half dose the day before and half dose the morning of the examination). Within the split-dose group, we considered patients with E/G preparation as true positive and patients with F/P preparation as true negative. Consequently, within the non-split–dose group, we considered patients with E/G preparation as false positive and patients with F/P preparation as false negative. The second analysis estimated the difference in colon cleansing degree between patients in the split-dose and non-split–dose groups. All pooled analyses were based on fixed or random-effects models concerning the heterogeneity among studies that were evaluated and measured. All measures were performed by using the STATA software 11.1 version (StataCorp 2009. Stata Statistical Software: Release 11; StataCorp LP, College Station, Tex).

Assessment of heterogeneity

To explore the variability in study results (heterogeneity) we specified the following hypotheses before conducting the analysis: that effect size may differ according to the methodologic quality of the studies, type of purge, time elapsing between the end of purge intake and the beginning of colonoscopy, type of diet prior to laxative use, patient compliance, frequency of male sex, scale used to evaluate colon cleansing, and type of analysis performed (intention to treat vs per procedure). We used the usual statistical test (Cochran Q), which is computed by summing the squared deviations of each study estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner as in the meta-analysis.[11] P values were obtained by comparing the statistic with a χ^2 distribution with k-1 degrees of freedom (where k is the number of studies).[12] To quantify the heterogeneity, we used I^2, which describes the percentage of total variation across studies that is caused by heterogeneity rather than chance. I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Meta-regression analysis was planned to examine the contribution of the covariate to the heterogeneity in the study findings.

Assessment of reporting biases

We assessed the possibility of publication bias by evaluating a funnel plot of the trial effect rate for asymmetry. Publication bias was assessed visually by using a scatter plot of the inverse of the square root of the effective sample size versus the log odds. In order to reduce a bias due to subjective graphic evaluation, we conducted an Egger-Hardbord regression test as a formal predefined statistical test for publication bias. Also, we used the contour-enhanced funnel plots, that is, a plot enhanced by adding contours of statistical significance to aid in interpreting the funnel plot by using the confunnel STATA command for the overall assessment. The contours assess the proportion of studies published in the meta-analysis at and around a statistical significance, which aids in the interpretation of whether such differences in study estimates in a meta-analysis are most likely to be caused by publication bias or other factors.

APPENDIX 2

CHARACTERISTICS OF INCLUDED STUDIES

Twenty-nine trials were included in the analysis. All were randomized clical trials, with the exception of the study conducted by Berkelammer et al, which included one observational arm and one randomized arm.

According to the inclusion criteria, participants of the studies were inpatients and outpatients who had undergone colonoscopy, and we assumed that all did the purge the day before (non-split–dose group, n = 4040) or half dose the day before and half the dose the morning of the examination (split-dose group, n = 3679), regardless of the type of purge assumed and the timing of the colonoscopy or endoscopy session. The mean age of participants was 57.4 years (95% confidence interval [CI], 53.6-61.3) among patients who received the split-dose preparation and 56.4 years (95% CI, 55.3-57.5) among patients who received the non-split–dose preparation. In all studies, there was a male predominance (60% in the split-dose group, 54% in the non-split–dose group). The exclusion criteria varied slightly among the different trials but generally included patients with cardiac, renal, or hepatic impairment or significant preexisting GI conditions; protocol deviations; and impossibility of reaching the cecum. Two authors were contacted by mail, but primary outcome data were missing, so the articles were excluded

from the analysis. Nine trials provided results on an intention-to-treat basis, whereas the others were on a per protocol basis.

Fifteen types of comparisons among different laxatives were tested in those 29 trials, with a major predominance of a polyethylene glycol (PEG) (both high [PEG-high] and low [PEG-low] volume) or a sodium phosphate (NaP)–based regimen (Table 2). Specifically, the most frequent comparisons were between split-dose PEG-high (no. of patients tested = 934), non-split–dose PEG-high (no. of patients tested = 925), and split-dose NaP (no. of patients tested = 1019) versus non-split–dose PEG-high (no. of patients tested = 1027). In 9 studies, investigators added a cathartic to the purge prescribed for only the non-split–dose patients, mainly bisacodyl (15 to 30 mg).[2-10] In 16 trials, authors compared one type of treatment to another (single-arm studies),[3,5,6,8,10-21] whereas in 13 there were several comparisons (eg, split-dose PEG-high vs non-split–dose PEG-high or vs NaP–multiple arms studies),[1,2,4,7,9,22-29] leading to the final inclusion of 48 treatment arms in this meta-analysis. Among those 48 treatment arms, 16 used a split-dose preparation of PEG-high,[3,8,12,16,17,19,20,22,24-26,28] 10 used PEG-low,[10,15,21,23,25,26,28] 21 used a NaP-based regimen,[1,2,4,5,7,9,11,13,14,18,23,27,29] and only 1 evaluated picosulphate as a split-dose regimen.[6]

All studies except one were single-blinded, in which only the endoscopist was blind to the type of purge taken. In the remaining study (22), a double blindness was stated in the title, but methods of blinding were not clear, so it scored 4 according to the Jadad score, a scale used to assess the validity of the studies.[30] On average, most of the included articles had low scores (Jadad score 1 = references 2, 3, 11, 15, 18, 20, and 27); Jadad score 2 = 5, 7, 12-14, 16, 19, 24, 28, and 29); Jadad score 3 = 1, 4, 6, 8-10, 17, 21, 23, 25, and 26), mostly because there was little indication of the methods of blinding or how randomization, sequence generation, and allocation concealment had been achieved.

All but one study (29) defined whether patients observed (yes or no) a specific diet during the days before colonoscopy, and 26 defined which kind of dietary restrictions and for how long (all except 13, 21, 29, and 31). Regardless of the regimen, the majority of patients observed dietary restrictions for the 24 hours preceding the colonoscopy without differences in the time in which patients were on a diet between split-dose and non-split–dose groups except in 5 studies (3, 9, 19, 23, 24) in which the authors used a shorter diet time for the split-dose group patients on an equal diet.

Regarding the time of colonoscopy or colonoscopy session, 28 studies (all except that from Corporaal et al[12]) provided the time in which the non-split–dose regimen was started and finished the day before the examination. Conversely, in the split-dose group, all except one (15) provided times of purge intake the day before, but only 18 studies provided the beginning and end times of laxative intake the morning of the examination (1, 2, 4, 5, 7-9, 11, 14, 16, 18-20, 23-25, 27, and 28). Also, 10 studies provided the colonoscopy session starting time (1, 2, 4, 7, 12, 15, 17, 18, 22, and 24), with only 8 of those reporting the session end (all except7 and 15), and 16 studies provided data on the runway time (1-4, 6, 7, 9, 10, 12-14, 16-18, 21, 22, 24, 25, 27, and 29). We therefore were confident to calculate the runway time only in 20 of the 29 studies included in this review.

Data on patient compliance to a specific laxative were available in 25 studies. In the remaining 4 studies (4, 6, 9, and 26), data were not clearly expressed or were not inferable from the text. Compliance was defined a priori as the consumption of more than 75% of the whole dose of the prescribed laxative. All those patients who consumed <75% were defined as noncompliant.

Regarding the scales used to grade colon cleansing, only 5 studies used a standardized scale (6, 8, 25, 26, and 28), whereas 24 used their own criteria. Regardless of the type of scale used, we pooled the reported cleansing degrees in a "good preparation group" if patients were scored by authors as having an E/G cleansing or in a "fair preparation group" if patients were scored by authors as having an F/P cleansing.