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Meta-analysis of randomized controlled trials challenging the usefulness of purgative preparation before small-bowel video capsule endoscopy

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Appendix e1 – e3, Table e2, Figs. e5 – e7
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ABSTRACT

Background The usefulness of purgative preparation before small-bowel video capsule endoscopy is controversial. We aimed to examine the effect of purgative preparation on small-bowel video capsule endoscopy outcomes.

Methods We performed literature searches in MEDLINE and the Cochrane library for randomized controlled trials evaluating the effect of purgative preparation (polyethylene glycol, sodium phosphate, others) vs. clear-liquid diet/fasting in patients undergoing small-bowel capsule endoscopy. Meta-analysis outcomes included the examination's diagnostic yield, small-bowel mucosal visualization quality, the examination's completion rate, and gastric and small-bowel transit times. The effect size on study outcomes was calculated using a fixed- or random-effect model, as appropriate, and is shown as the risk ratio (RR) with 95 % confidence interval (CI).

Results We identified 12 eligible trials with 17 sets of data including 1221 subjects. Significant heterogeneity was detected with no evidence of publication bias. As compared with clear-liquid diet, purgative bowel preparation did not increase capsule endoscopy diagnostic yield (RR 1.17 [95 % CI 0.97 to 1.40]; $P = 0.11$). Neither the small-bowel mucosal visualization quality (RR 1.14 [95 %CI 0.96 to 1.35]; $P = 0.15$) nor completion rate for the examination (RR 0.99 [95 %CI 0.95 to 1.04]; $P = 0.76$) significantly improved after purgative preparation. Purgatives also had no effect on video capsule endoscopy gastric and small-bowel transit times.

Conclusions Our analysis challenges the usefulness of purgative preparation for improving the diagnostic yield of small-bowel video capsule endoscopy and the quality of small-bowel mucosal visualization.

Introduction

Meticulous mucosal visualization is a prerequisite for the unequivocal assessment of patients undergoing small-bowel video capsule endoscopy (VCE). However, intraluminal presence of food debris, air bubbles, bile or mucus often significantly decreases the diagnostic accuracy of the examination. Although the device's manufacturer proposes a preparation regimen of 12 hours of clear liquids and/or fasting overnight, several studies evaluating different agents, including purgative bowel preparation with polyethylene glycol (PEG) and sodium phosphate (Na-P), and antifoaming agents such as simethicone and prokinetics, have been conducted.

To date, six meta-analyses have tried to pool the results of the aforementioned studies with outcomes that have been difficult to interpret because of the inclusion of different study designs, variable preparation protocols, and inconsistent endpoints [1 – 6]. Because purgative bowel preparation is the most widely used preparation in clinical practice today and in order to overcome the inconveniences that the previous meta-analy-

ses introduced, we decided to exclusively meta-analyze randomized controlled studies evaluating the effects of purgative bowel preparation – given before capsule ingestion – on the main outcomes of VCE.

Methods

Data identification and extraction

A thorough computer-assisted search of the medical literature was conducted across MEDLINE and the Cochrane Central Register of Clinical Trials databases from January 2001 to July 2017 combining the terms "capsule endoscopy" and "bowel preparation." Both terms were searched as medical subject headings (MeSH) and free-text terms. The complete search strategy can be found in ▶ **Appendix e1** (available online). We further hand searched all references from review articles, editorials, and all original studies to identify additional citations fulfilling the inclusion criteria. Data were extracted in a predefined worksheet by two of the authors (P.G. and G.T.) working in parallel but independently.

Data extracted included: name of first author, year of publication, country of origin, study design, number of participants, population characteristics, regimen of bowel preparation provided and its comparator, device used, diagnostic yield of the examination, small-bowel mucosal visualization quality (SBVQ), gastric transit time (GTT), small-bowel transit time (SBTT), and number of completed (capsule entered the cecum) examinations. Data were extracted as originally presented or following appropriate calculations, if applicable. For studies with missing or unavailable data, an attempt to contact the corresponding author to provide additional information was made. Any disagreements between the two authors were settled by discussion with the senior author (K.T.).

The search was initially performed on 12 February 2017, and repeated twice on 2 May, and 31 July 2017. Our study complies with PRISMA guidelines [7], see ▶ **Appendix e2** (available online).

Study endpoints

The primary endpoint of our meta-analysis was to explore the effect of small-bowel preparation with cathartics compared with clear-liquid diet or fasting overnight on the diagnostic yield of VCE.

Secondary endpoints included the effects of purgative bowel preparation on SBVQ, VCE completion rate, GTT, and SBTT.

Definitions

Diagnostic yield

This is defined as the likelihood that a test or procedure will provide the information needed to establish a diagnosis. In the field of VCE, the definition of a positive study incorporates any examination with findings that explain a patient's complaints or symptoms, as well as any examination with findings that lead to modification of a patient's management.

Small-bowel mucosal visualization quality

Investigators have used various definitions to determine SBVQ. Because no official consensus exists, we arbitrarily bisected the proposed "qualities of visualization" into two broad groups: adequate and inadequate. The "adequate" group consisted of a quality of mucosal visualization characterized as adequate, excellent, or good by the authors; visualization characterized as inadequate, moderate, fair, or bad comprised the "inadequate" group. A study was considered eligible to be included in SBVQ analysis only if it reported data for the visualization of the entire small bowel. For studies that traced SBVQ using a score that could not be dichotomized and consequently homogenized in the adequate vs. inadequate preparation, it was predecided that these would be excluded from the meta-analysis of the respective endpoint.

Completion rate

An examination was considered to have been completed when the capsule reached the cecum.

Gastric transit time

The time needed for the capsule to reach the duodenal bulb.

Small-bowel transit time

The time needed for the capsule to traverse the entire small bowel and reach the cecum.

Inclusion criteria

Inclusion criteria were determined before the beginning of the literature search. A study was considered eligible for inclusion in the meta-analysis if it met the following criteria: (i) published as a full article in English; (ii) randomized controlled design with adult participants; (iii) contained raw data regarding at least one of the five endpoints; (iv) purgative bowel preparation regimen given before capsule ingestion; (v) anti-foaming (e. g. simethicone) and prokinetic agents excluded; (vi) same type of capsule used for all arms in the study.

Quality assessment of studies

Cochrane collaboration's risk of bias assessment tool [8] evaluates six domains of potential source of bias namely: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); and selective reporting (reporting bias). Authors reviewed and judged studies according to each domain as having a high, low, or unclear risk of bias, providing at the same time support for their judgement. In the absence of a validated quality scale for VCE studies, we modified the performance bias domain of the tool in order to judge only personnel blinding, because VCE studies evaluating bowel preparation cannot be double blinded.

Two authors (P.G. and G.T.) independently assessed all of the studies for risk of bias and any discrepancies were resolved after discussion with the senior author (K.T.).

Statistical analysis

Extracted data were entered in a suitable form (number of events, means, medians, etc.) and meta-analyzed using the statistical software Review Manager (RevMan 5.3.5. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

For diagnostic yield, SBVQ, and completion rate, the risk ratios (RRs) and their 95 % confidence intervals (95 %CIs) were calculated. For continuous data in our study – GTT and SBTT – the inverse variance statistical method was used and mean difference with 95 %CI was calculated. Where necessary, mean value and standard deviation (SD) were calculated, taking into account the median and variance, as proposed by Hozo et al. [9].

All meta-analytic outcomes were further compared using either the fixed-effects model (Mantel and Haenszel method) or the random-effects model (DerSimonian and Laird method) in the absence or presence of significant heterogeneity, respectively. Finally, appropriate forest plots were created to visually display the results.

Assessment of heterogeneity and sensitivity analyses

Heterogeneity among studies was measured using I^2, with lower values representing lower levels of heterogeneity. In case of significant heterogeneity ($P<0.1$), we examined potential excessive influence of a sole study in our results. Sensitivity analysis was therefore performed by repeating the meta-analysis excluding one study at a time to assess the effect of exclusion in the heterogeneity's significance. For each outcome, we performed additional predefined subgroup analyses for each type of purgative regimen.

Publication bias

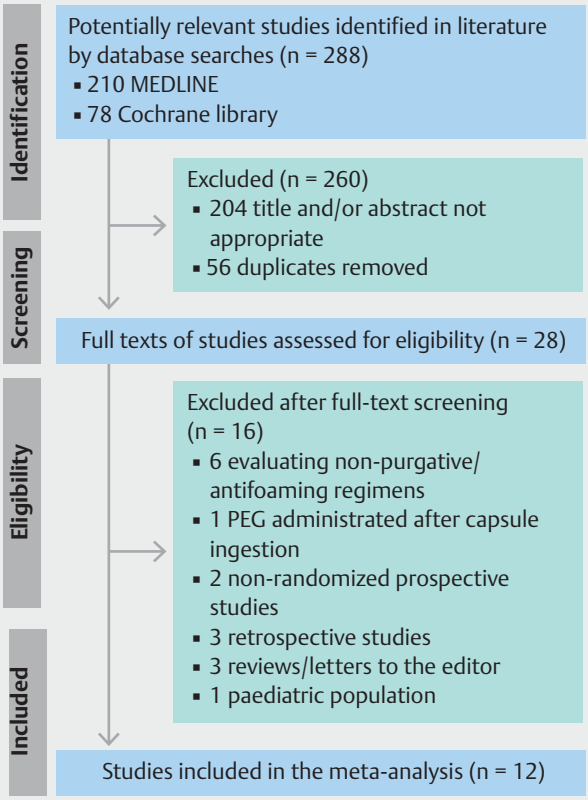
In order to estimate potential publication bias, funnel plots were constructed by plotting the log odds ratios (ORs) vs. precision of individual studies per outcome and visually assessing these for symmetry [10].

Results

Descriptive assessment and study characteristics

The search strategy yielded 288 citations from the two databases. No other article was identified from the searching of reference lists. After preliminary title and abstract review, 260 articles were excluded as non-relevant and/or duplicates; therefore, 28 articles were further assessed for eligibility. Among these, 16 were deemed to be ineligible for a variety of reasons, which left 12 articles [11 – 22] that met all of the eligibility criteria to be included in the meta-analysis. The flow chart describing the process is depicted in ▶ **Fig.1**.

The 12 meta-analyzed studies included 17 sets of data that compared VCE outcomes in 736 and 485 individuals who had received purgative bowel preparation and clear liquids/fasting, respectively.



▶ **Fig. 1** Flowchart showing study inclusion and exclusion.

Among the retrieved sets of data, 10 evaluated PEG [11 – 18], four were for regimens based on Na-P [13, 18, 20, 21] (in one study [20], Na-P was combined with bisacodyl), while magnesium-based regimens were evaluated in three studies [11, 19, 22]. More precisely, magnesium citrate (MgC) was evaluated as the sole preparation regimen [19], and in combination with sodium picosulfate (P/MgC) [11], while magnesium carbonate/anhydrous citric acid with the anthraquinone stimulant laxative senna was administered in one study [22]. In two studies, a small identical amount of simethicone was used as complementary therapy in both arms of the study [11, 22]. Because simethicone was not comparatively evaluated, we decided to include these two studies (three sets of data) in the meta-analysis.

Eight studies were conducted in Western countries [11, 13 – 16, 20 – 22] (seven of these in Europe) and four in the East [12, 17 – 19]; there were only two multicenter studies [18, 21].

Nine studies reported on the device used and participants received M2A capsules (Given Imaging Ltd., Yoqneam, Israel) in five studies [13, 15 – 18], PillCam SB1 (Given Imaging Ltd.) in three [19, 21, 22], and PillCam SB2 (Given Imaging Ltd.) in one study [14].

▶ **Table1** presents the main characteristics of the included studies.

▶ **Table 1** Characteristics of the included studies.

Author (Year)	Country of origin	Capsule model	Study design	Type of small-bowel preparation		Participants, n		Outcomes reported				
				Purgative	Comparator	Purgative	Comparator	DY	SBV-Q*	CR	GTT	SBTT
Viazis (2004) [16]	Greece	M2A	Prospective, randomized, controlled, single-blinded, single center	2 L PEG 16 hours before VCE, clear liquids the day before VCE, overnight fasting	Clear liquids the day before VCE and overnight fasting	40	40	•	•	•	•	•
Van Tuyl (2007) [15]	The Netherlands	M2A	Prospective, randomized, controlled, single-blinded, single center	A) 1 L PEG the evening before VCE, overnight fasting; B) 2 L PEG the evening before VCE, overnight fasting	Clear liquids for 12 hours the day before VCE and overnight fasting	A) 30 B) 30	30	•	–	•	•	•
Wei (2008) [17]	China	M2A	Prospective, randomized, controlled, single-blinded, single center	1 L PEG 12 hours before VCE	1 L clear water 12 hours before VCE, then fasting	30	30	–	•	•	–	•
Franke (2008) [20]	Germany	N/A	Prospective, randomized, controlled, single blinded, single center	12 hours of fasting followed by 30 mL Na-P 3 hours before VCE and 20 mg bisacodyl just before VCE ingestion	At least 8 hours of fasting before, water allowed till 2 hours before VCE	26	26	–	–	–	•	•
Lapalus (2008) [21]	France	Pillcam SB1	Prospective, randomized, controlled, single-blinded, multicenter	45 mL Na-P and 2 L clear liquids the evening before VCE, plus 45 mL Na-P the morning of the procedure	Clear liquids the evening before VCE followed by 8 hours fasting	63	64	•	–	•	•	•
Wi (2009) [18]	Korea	M2A	Prospective, randomized, controlled, single-blinded, multicenter	A) 45 mL Na-P at 15:00 h and 45 mL Na-P at 19:00 h on the day before capsule ingestion, followed by 2 L of clear liquids till midnight; B) 2 L PEG 16 hours before capsule ingestion	12 hours of fasting	A) 45 B) 45	44	•	•	•	•	•

▶ **Table 1** (Continuation)

Author (Year)	Country of origin	Capsule model	Study design	Type of small-bowel preparation		Participants, n		Outcomes reported				
				Purgative	Comparator	Purgative	Comparator	DY	SBV-Q*	CR	GTT	SBTT
Postgate (2009) [22]	United Kingdom	Pillcam SB1	Prospective, randomized, controlled, single-blinded, single center	Two packets of senna at 14:00 h and two packets magnesium carbonate/ anhydrous citric acid (one at 14:00 h and one at 18:00 h) on the day before capsule ingestion. VCE ingested with 0.5 mL add-on simethicone	Clear liquids on the evening before capsule ingestion followed by 10 hours of fasting. VCE ingested with 0.5 mL add-on simethicone	40	38	•	–	•	•	•
Park (2011) [12]	Korea	N/A	Prospective, randomized, controlled, single center	A) Overnight fasting and 2 L PEG 4 hours before capsule ingestion; B) Overnight fasting and 4 L PEG 4 hours before capsule ingestion	12 hours of fasting	A) 20 B) 25	23	•	–	•	•	•
Pons Beltran (2011) [13]	Spain	M2A	Prospective, randomized, controlled, single-blinded, multicenter	A) 90 mL Na-P and 4 L clear liquid 24 hours before VCE, followed by 8 hours of fasting; B) 4 L PEG 24 hours before VCE, followed by 8 hours of fasting	4 L of clear liquids during 24 hours before VCE, followed by 8 hours of fasting	A) 89 B) 92	92	•	•	•	•	•
Ninomiya (2012) [19]	Japan	Pillcam SB1	Prospective, randomized, controlled, single-blinded, single center	34 g MgC 12 hours before VCE, then fasting	12 hours of fasting	22	22	•	–	•	–	–
Rosa (2013) [14]	Portugal	Pillcam SB2	Prospective, randomized, controlled, single-blinded, single center	24 hours of liquid diet, followed by 2 L PEG the evening before capsule ingestion	24 hours of liquid diet, followed by overnight fasting	20	20	•	•	•	•	•

▲ **Table 1** (Continuation)

Author (Year)	Country of origin	Capsule model	Study design	Type of small-bowel preparation		Participants, n		Outcomes reported				
				Purgative	Comparator	Purgative	Comparator	DY	SBV-Q*	CR	GTT	SBTT
Hookey (2017) [11]	Canada	N/A	Prospective, randomized, controlled, single-blinded, single center	A) 2 L PEG the evening before VCE and overnight fasting; B) One sachet P/MgC at 16:00 h and one sachet P/MgC at 21:00 h the day before VCE, and overnight fasting. Patients received 80 mg simethicone 10 minutes before capsule ingestion	12 hours of clear liquids the day before and overnight fasting. Patients received 80 mg simethicone 10 minutes before capsule ingestion	A) 58 B) 61	56	•	•	•	–	–

VCE, video capsule endoscopy; PEG, polyethylene glycol; Na-P, sodium phosphate; MgC, magnesium citrate; P/MgC, sodium picosulfate plus magnesium citrate; DY, diagnostic yield; SBVQ, small-bowel visualization quality; CR, completion rate; GTT, gastric transit time; SBTT, small-bowel transit time; N/A, not available; • outcome reported; – outcome not reported.
* Applicable if adequate vs. inadequate classification was possible and data for evaluation of the whole small bowel were available.

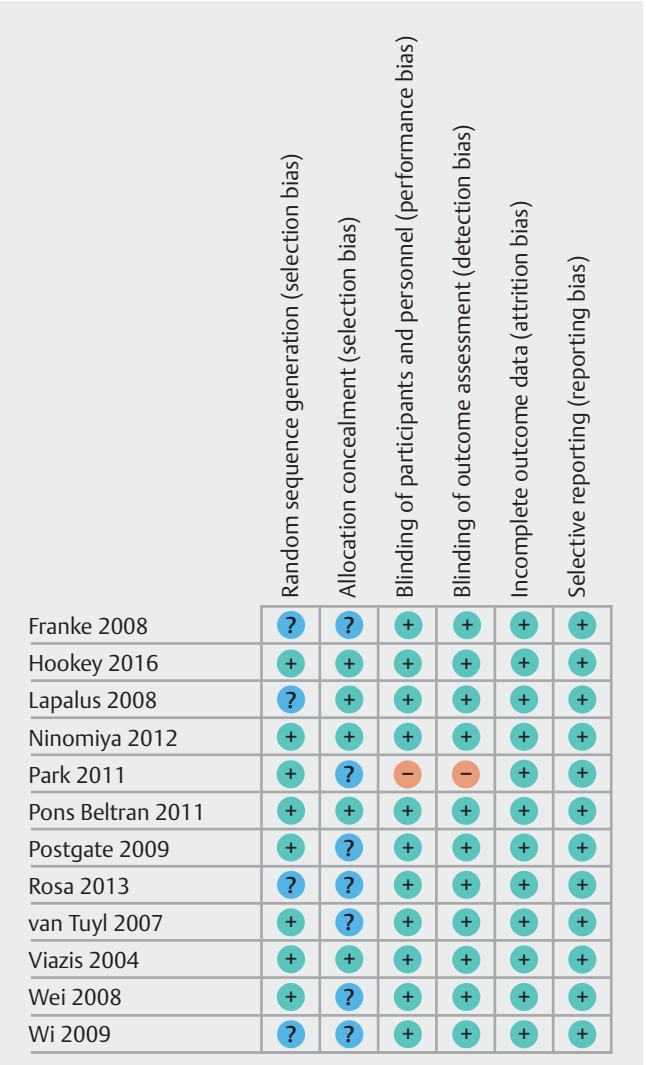
Quality assessment

▶ **Fig. 2** summarizes the assessment of per-study risk of bias according to Cochrane collaboration's risk of bias assessment tool. Exact judgement per study and per quality domain can be found in ▶ **Appendix e3** (available online). It is remarkable that in four [14, 18, 20, 21] and seven [12, 14, 15, 17, 18, 20, 22] of the studies detailed methods of randomization and allocation concealment were not described (uncertain selection bias).

Primary endpoint

VCE diagnostic yield

There were 10 studies [11 – 16, 18, 19, 21, 22] with 15 data sets that investigated the effect of cathartics on the diagnostic yield of VCE. Overall, 677 and 673 patients received purgative bowel preparation and clear liquids/fasting, respectively. Using the



▶ **Fig. 2** Illustration of the risk of bias for the 12 included studies. + low risk of bias; – high risk of bias; ? unknown risk of bias.

random-effects model because of the presence of significant heterogeneity (I^2 = 41 %; P = 0.05), no statistically significant difference was detected regarding the diagnostic yield between the two arms, overall. There were 289 (42.7 %) and 245 (36.4 %) positive studies in the cathartics and in the clear liquids/fasting arms, respectively (overall RR [95 %CI] was 1.17 [0.97 to 1.40]; P = 0.11) (▶ **Fig. 3a**). We did not detect any publication bias (▶ **Fig. 3b**).

Sensitivity analysis by excluding one study every time revealed that there were two studies [16, 22] responsible for the significant heterogeneity. However, exclusion of only one [22] of these two studies changed the significance of our results in slight favor of purgative bowel preparation overall (RR 1.23 [95 %CI 1.07 to 1.40]; P = 0.002).

Overlapping confidence intervals (▶ **Fig.3a**) and testing for subgroup differences (χ^2 = 2.32, df = 2; P = 0.31) did not indicate differences in the per-regimen subgroup analysis.

Secondary endpoints

Small-bowel mucosal visualization quality

We retrieved data regarding SBVQ from six studies [11, 13, 14, 16 – 18] (nine sets of data) including 478 patients prepared with cathartics and 474 receiving only clear liquids/fasting. Six more studies [12, 15, 19 – 22] provided data regarding SBVQ, but were not included in the meta-analysis because they either evaluated SBVQ using a composite score that could not be dichotomized or reported segmental outcomes only (▶ **Table e2**; available online).

Three of the included studies [16 – 18] evaluated the adequateness of SBVQ according to the scoring system of Viazis et al. [16]. Small-bowel cleansing was considered "adequate" if the objective score (the percentage of SBTT during which less than 25 % of the intestinal mucosa was clean) was less than 10 % and "inadequate" if it was more than 10 %. The rest of the studies used either a 4 – or 5-point scale (ranging from inadequate to excellent mucosal visualization) using either qualitative [13] or quantitative criteria [11, 14]. As predefined, we homogenized the available data by grouping "good" and "excellent" mucosal visualization along with "adequate." All other characterizations were grouped as "inadequate."

After data homogenization, no difference was detected regarding SBVQ between the two arms. Overall, adequate mucosal visualization was achieved in 300 of the patients who received purgatives (62.7 %) and in 268 of those receiving only clear liquids/fasting (56.5 %). Significant heterogeneity was present (I^2 = 59 %; P = 0.01) and the effect size of the analysis (▶ **Fig. 4a**) did not indicate any favor of purgative bowel preparation over clear liquids/fasting (RR 1.14 [95 %CI 0.96 to 1.35]; P = 0.15). No publication bias was detected (▶ **Fig. 4b**).

The significance of analysis results did not change by excluding one study at a time.

No differences were detected in the per-regimen subgroup analysis, overlapping confidence intervals (▶ **Fig. 4a**), or test for subgroup differences (χ^2 = 5.61, df = 2; P = 0.06).

Completion Rate

A total of 11 studies [11 – 19, 21, 22] with 16 sets of data provided data that the examination was completed in 711 and 709 patients administered purgative bowel preparation and clear liquids/fasting, respectively. Overall, we detected no heterogeneity (I^2 = 0 %; P = 0.96) and no difference in the completion rate of the examination between patients receiving purgatives (588 / 711 [82.7 %]) and those receiving clear liquids/fasting (590 / 709 [83.2 %]); RR 0.99 [95 %CI 0.95 to 1.04]; P = 0.76) (▶ **Fig. e 5a**; available online).

Visual inspection of the funnel plot (▶ **Fig. e 5b**) did not reveal publication bias. The per-regimen subgroup analysis did not reveal any difference among the used regimens (▶ **Fig. e 5a**).

Gastric transit time

There were 13 sets of data from nine studies [12 – 16, 18, 20 – 22] that reported on GTT. Overall, GTT was evaluated in 559 and 558 patients prepared with purgative bowel preparation and clear liquids/fasting, respectively. For two studies [12, 22], mean (SD) GTTs were calculated using the provided median, range, and sample size. Data were characterized from significant heterogeneity (I^2 = 93 %; P < 0.001). Analysis revealed no difference in GTT between the two groups (mean difference = −2.71 [95 %CI −7.87 to 2.46]; P = 0.30) (▶ **Fig. e 6a**; available online) with no evidence of publication bias (▶ **Fig. e 6b**).

The significance of heterogeneity was not attributed to any of the meta-analyzed studies in the step-by-step sensitivity analysis.

The significance detected in the test for per-regimen subgroup differences (▶ **Fig. e 6a**) should be interpreted cautiously as it may simply reflect a lack of information rather than a different effect.

Small-bowel transit time

SBTT was reported in 10 studies [12 – 18, 20 – 22] (14 sets of data). SBTT was recorded in 581 and 584 patients prepared with purgative bowel preparation and clear liquids/fasting, respectively. For two of the studies [12, 22], we used median, range, and sample size to calculate the mean (SD) SBTT according to Hozo et al. [9]. Significant heterogeneity (I^2 = 95 %; P < 0.001) was present and analysis did not reveal any difference in SBTT between the two arms (mean difference = −8.35 [95 % CI −20.41 to 3.70], Z = 1.36; P = 0.17) (▶ **Fig. e 7a**; available online). No publication bias was identified (▶ **Fig. e 7b**).

During the step-by-step sensitivity analysis, we did not detect any study that if excluded would diminish the heterogeneity's significance.

The per-regimen subgroup analysis did not reveal any difference among the used regimens (▶ **Fig. e 7a**).

Discussion

In our center and in contrast to the recommendation of the manufacturer, we instruct patients to consume a clear-liquid diet on the day before their examination but they additionally receive 2 L of PEG on the evening before the procedure. How-

Study or subgroup	Purgatives Events	Purgatives Total	Clear liquids Events	Clear liquids Total	Weight	Risk ratio M-H, random, 95% CI
1.1.1 PEG						
Viazis 2L PEG 2004	26	40	12	40	7.5%	2.17 [1.28, 3.66]
van Tuyl 1L PEG 2007	6	30	8	30	3.3%	0.75 [0.30, 1.90]
van Tuyl 2L PEG 2007	9	30	8	30	4.1%	1.13 [0.50, 2.52]
Wi 2L PEG 2009	19	45	11	44	6.1%	1.69 [0.91, 3.13]
Park 4L PEG 2011	12	25	9	23	5.7%	1.23 [0.64, 2.36]
Park 2L PEG 2011	9	20	9	23	5.1%	1.15 [0.57, 2.32]
Pons Beltran 4L PEG 2011	50	92	43	92	12.9%	1.16 [0.87, 1.55]
Rosa 2L PEG 2013	8	18	12	20	6.0%	0.74 [0.40, 1.39]
Hookey 2L PEG 2016	11	58	16	56	5.4%	0.66 [0.34, 1.30]
Subtotal (95% CI)		**358**		**358**	**56.0%**	**1.16 [0.91, 1.49]**
Total events	150		128			
Heterogeneity: Tau² = 0.05; Chi² = 12.31, df = 8 (*P* = 0.14); I² = 35%						
Test for overall effect: Z = 1.18 (*P* = 0.24)						
1.1.2 Sodium Phosphate Regimens						
Lapalus Na-P 2008	34	63	26	64	10.6%	1.33 [0.91, 1.93]
Wi Na-P 2009	22	45	11	44	6.4%	1.96 [1.08, 3.54]
Pons Beltran Na-P 2011	50	89	43	92	12.9%	1.20 [0.90, 1.60]
Subtotal (95% CI)		**197**		**200**	**30.0%**	**1.33 [1.06, 1.66]**
Total events	106		80			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 2 (*P* = 0.34); I² = 7%						
Test for overall effect: Z = 2.50 (*P* = 0.01)						
1.1.3 Magnesium Regimens						
Postgate MgCO3/citric acid/senna 2009	5	39	13	37	3.3%	0.36 [0.14, 0.92]
Ninomiya MgC 2012	5	22	8	22	3.2%	1.63 [0.24, 1.61]
Hookey P/MgC 2016	23	61	16	56	7.5%	1.32 [0.78, 2.23]
Subtotal (95% CI)		**122**		**115**	**14.0%**	**0.72 [0.32, 1.62]**
Total events	33		37			
Heterogeneity: Tau² = 0.35; Chi² = 6.32, df = 2 (*P* = 0.04); I² = 68%						
Test offor**Total (95% CI)**	**677**		**673**		**100.0%**	**1.17 [0.97, 1.40]**
Total events	289		245			
Heterogeneity: Tau² = 0.05; Chi² = 23.54, df = 14 (*P* = 0.05); I² = 41%						
Test for overall effect: Z = 1.61 (*P* = 0.11)						
Test for subgroup differences: Chi² = 2.32, df = 2 (*P* = 0.31); I² = 13.7%						

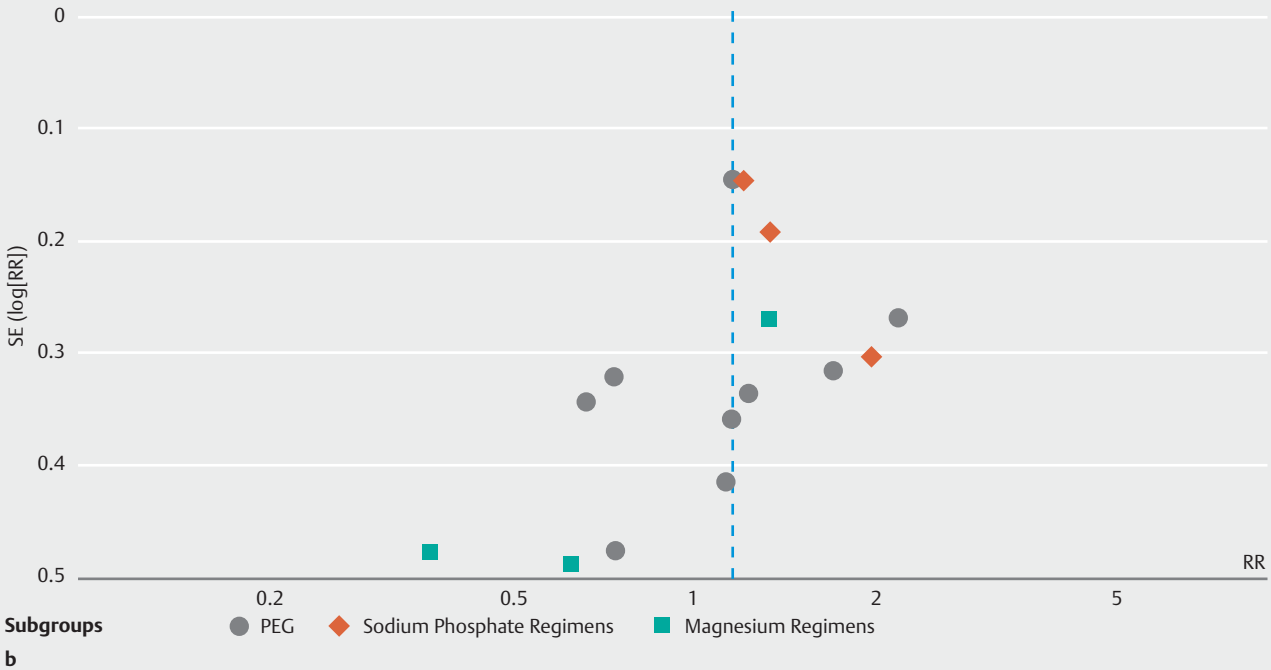
Risk ratio M-H, random, 95% CI

Risk of bias A B C D E F

0.2 0.5 1 2 5

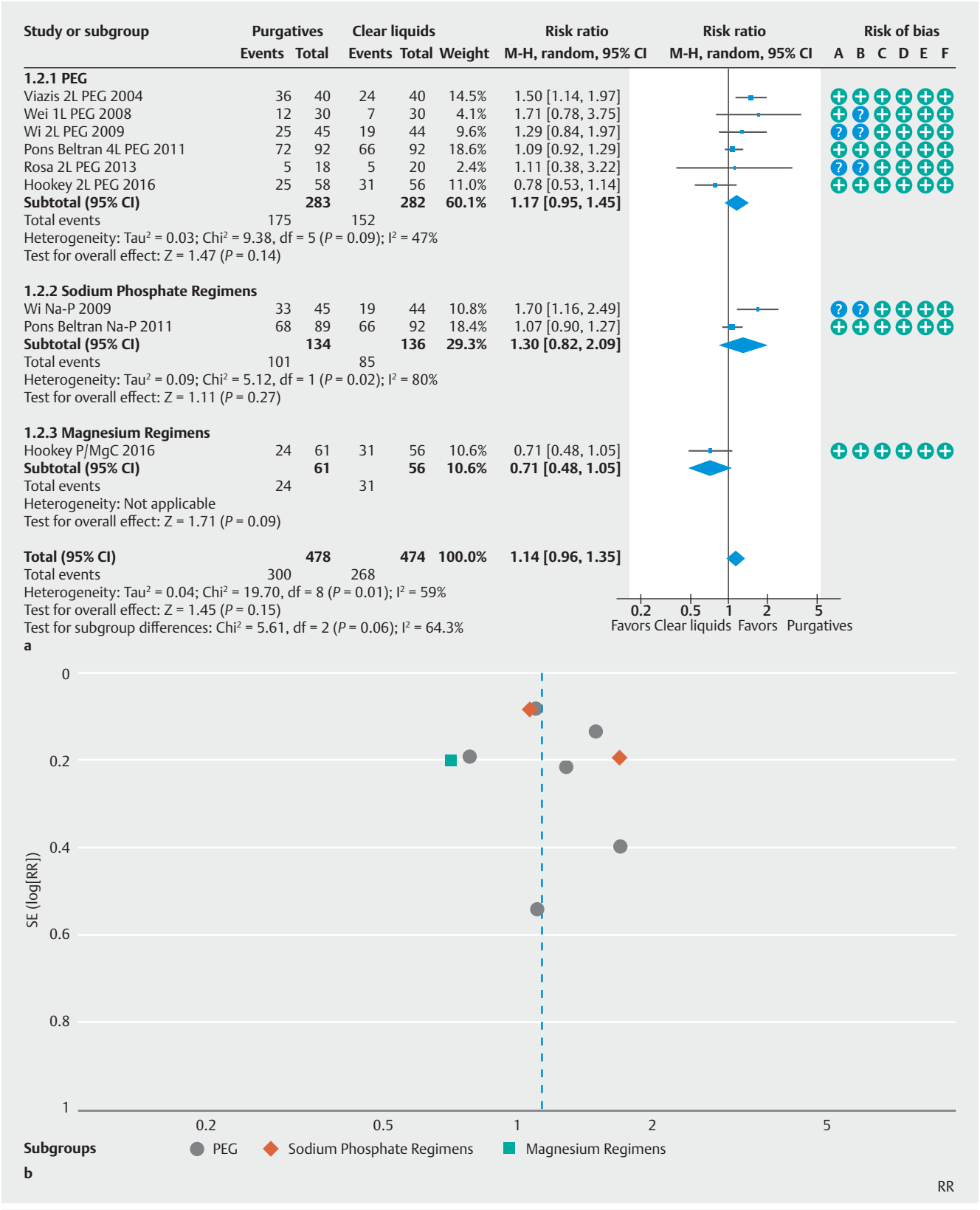
Favors Clear liquids Favors Purgatives

a



b

▶ **Fig. 3** Results for studies that assessed the diagnostic yield of small-bowel video capsule endoscopy shown as: **a** a forest plot; **b** a funnel plot. CI, confidence interval; PEG, polyethylene glycol; Na-P, sodium phosphate; $MgCO_3$, magnesium carbonate; MgC, magnesium citrate; RR, risk ratio.



▶ **Fig. 4** Results for studies that assessed small-bowel mucosal visualization quality with video capsule endoscopy shown as: **a** a forest plot; **b** a funnel plot. CI, confidence interval; PEG, polyethylene glycol; Na-P, sodium phosphate; MgC, magnesium citrate; RR, risk ratio.

ever, the usefulness of purgative bowel preparation remains controversial.

In an era of financial barriers [23], the diagnostic yield of the examination remains the most important outcome of small-bowel VCE. In the presence of significant heterogeneity, our meta-analysis of 12 randomized controlled trials, involving more than 1200 subjects, questions the efficacy of purgative preparation compared with clear liquids and/or fasting on the diagnostic yield of small-bowel VCE. To our great surprise, the significant heterogeneity disappeared after exclusion of a single study (with only 78 participants) [22] and repetition of the analysis favored administration of purgative with regard to the diagnostic yield of VCE. One might assume that the extreme and unusually low diagnostic yield, especially in the purgative group of the aforementioned study, (5/39 [12.8%] and 13/37 [35.1%] in the purgative bowel preparation and clear liquids/fasting groups, respectively) could be responsible for the difference that was noticed.

Our primary endpoint result is not in accordance with the results of four previous meta-analyses [1–4] (▶ **Table 3**) that revealed a significant benefit of active bowel preparation (pooled ORs ranging from 1.68 to 1.88); the sensitivity analysis in the most recent of these meta-analyses [4] showed that the benefit of the purgative bowel preparation was attributed merely to a single study [16]. In contrast, our findings are in line with the two most recently published meta-analyses [5, 6], which also failed to detect any benefit of active bowel preparation on the diagnostic yield of the examination giving ORs (95%CI) of 1.55 (0.79 to 3.04) and 1.11 (0.85 to 1.44), respectively.

While all of these meta-analyses – ours included – suffer from significant heterogeneity, the discrepant results among them could be attributed to different methodological design, type of included studies, small sample sizes, and variable endpoints. In particular, the first meta-analysis included prospective and retrospective studies for all types of preparation [1], while the two subsequent studies examined the role of purgative bowel preparation regardless of the study design [2,6]. Two more studies meta-analyzed only randomized controlled trials [3,4], investigating the role of purgatives, antifoaming agents, prokinetics and/or their combinations on VCE outcomes, while the most recent network meta-analysis [5] – including both retrospective and prospective studies – tried to identify the most efficient PEG schema.

The "immaturity" of physicians in interpreting VCE findings during the first years of VCE utilization, as shown recently in a multicenter retrospective study that revealed that the rate of positive studies progressively declined in a period between 2002 and 2014 [23], and the lack of standardized definitions for findings comprise other potential explanations of the discrepant meta-analysis results with regarding to the diagnostic yield of VCE.

Our analysis of six RCTs enrolling more than 950 individuals failed to confirm the findings of Rokkas et al. [2] who meta-analyzed RCTs and cohort studies with 653 patients and showed that administration of cathartics resulted in improved small-bowel mucosal inspection. Our findings are consistent with the largest meta-analysis so far [6], which regardless of the design of studies showed no benefit of purgative administration on SBVQ, with the exception of a minimal SBVQ improvement in patients receiving Na-P or simethicone alongside their preparation [6]; this finding was not replicated in our per-regimen sensitivity analysis.

Our results are in line with previous meta-analytic findings [2,4–6] showing that the rate of complete examinations does not increase after the administration of purgatives. Moreover, as previously reported [2], the GTT and SBTT are not accelerated by purgative bowel preparation. Nevertheless, the issues of accelerating the passage of the capsule in the small bowel and of increasing the completion rate of VCE in order to potentially improve the diagnostic yield of the examination may be out of date given the advent of new-generation capsule endoscopes with longer battery life, the use of which has a significant impact on VCE completion rate [24,25]. In addition, the latest generation capsules (PillCam SB3; Given Imaging Ltd.) offer not only prolonged video recording (up to 12 hours), but also advanced optics, with better image resolution and a variable adaptive frame rate (ranging from 2 to 6 frames per second). It is obvious that these characteristics could affect not only completion rate but also small-bowel mucosal visualization and the diagnostic yield of the examination.

The major strength of this systematic review and meta-analysis is the inclusion of RCTs evaluating the effect of purgative bowel preparation only before capsule ingestion on the outcomes of VCE. In this way, we abolished any potential bias attributable to study design (retrospective studies, cohort studies missing comparator arms, etc.) and to non-purgative preparation agents (anti-foaming agents and/or prokinetics) that might have influenced the outcomes of previous meta-analyses. Moreover, rigorous quality assessment of the studies, absence of publication bias, and sensitivity and subgroup analyses applied to minimize heterogeneity comprise additional advantages of our study.

The main limitation of our meta-analysis is the significant heterogeneity among the included studies. In an effort to blunt this problem, we performed sensitivity analyses, but heterogeneity originates from multiple and diverse sources that are difficult to deal with. First, the heterogeneous mixture of populations and indications that might be related to different VCE outcomes. Of the 12 included studies, seven originated from the West, while there were only two multicenter studies and three of the studies enrolled less than 30 individuals per arm.

Second, there is an absence of standardized and validated definitions for diagnostic yield and SBVQ. Although diagnostic yield is more or less "self-defined," several authors classify their VCE findings as "positive," "relative," or even "suspicious," and the classification proposed by Saurin et al. [26], although adapted in some studies, has never been validated. Regarding SBVQ, multiple simple or composite scores, as well as the arbitrary judgments of authors, have been used. In addition, we were unable to reclaim SBVQ data from six of the 12 included studies, because the authors provided evidence in a very heterogeneous manner.

Finally, the fact that studies with different purgative regimens have been included in our meta-analysis might be consid-

▶ **Table 3** Meta-analyses evaluating small-bowel preparation and video capsule endoscopy (VCE) outcomes.

Author (Year)	Intervention	Outcomes	Number of studies	Type of studies	Number of patients	Regimens evaluated	Quality assessment	Sensitivity analyses
Niv (2008) [1]	Preparation of any kind vs. no preparation	SBVQ; CR; GTT; SBTT	8	2 RCTs; 2 prospective non-randomized; 4 retrospective	437	PEG; Na-P; simethicone; erythromycin	None mentioned	None performed
Rokkas (2009) [2]	PBP vs. CL/F	Primary: DY and SBVQ; Secondary: CR, GTT, and SBTT	12	6 RCTs; 6 retrospective	1162	PEG; Na-P	Self-proposed score: 1) Study design: prospective (1 point), retrospective/ cohort (0); 2) Number of examiners: >1 (1), one (0); 3) Examiners blinded to preparation: yes (1), no (0); 4) Grades for overall bowel cleansing: ≥3 (1), <3 (0); 5) Entire small-bowel evaluation: yes (1), no (0)	1) Step-by-step one study removed if heterogeneity present; 2) Full paper vs. abstracts; 3) Prospective vs. retrospective; 4) PEG vs. Na-P
Belsey (2012) [3]	Impact of PBP, antifoaming agents and their combination on VCE outcomes	SBVQ; DY	8	8 RCTs	746	PEG; Na-P; simethicone; bisacodyl	No specific score or tool mentioned	PEG vs. Na-P
Kotwal (2014) [4]	Impact of PBP, antifoaming agents, their combination or prokinetics on VCE outcomes	SBVQ; DY; CR	15	15 RCTs	1468	PEG; Na-P; simethicone; mannitol; dimethylpolysiloxane; erythromycin; mosapride; metoclopramide (either alone or as different combinations)	Modified Jadad Scale (maximum of 9 points): Randomization (2 points) Blinding procedures (4 points) Extent of attrition (3 points)	Step-by-step one study removed if heterogeneity present
Wu (2017) [5]	Network meta-analysis for the efficacy of bowel preparation with different doses of PEG vs. CL/F	Primary: SBVQ; Secondary: DY and CR	9	9 RCTs	982	PEG	Cochrane Collaboration's tool	None performed

▶ **Table 3** (Continuation)

Author (Year)	Intervention	Outcomes	Number of studies	Type of studies	Number of patients	Regimens evaluated	Quality assessment	Sensitivity analyses
Yung (2017) [6]	Laxatives vs. no laxatives	Primary: DY; Secondary: SBVQ and CR	40	24 RCTs; 5 prospective non-randomized; 11 retrospective	6565	PEG; Na-P; MgC; mannitol	Score as proposed by Rokkas et al: 1) Study design: prospective (1 point), retrospective/ cohort (0) 2) Number of examiners: >1 (1), one (0) 3) Examiners blinded to preparation: yes (1), no (0) 4) Grades for overall bowel cleansing: ≥ 3 (1), < 3 (0); 5) Entire small-bowel evaluated: yes (1), no (0) High quality: 4/5 and above; Moderate quality: 3/5; Low quality: 2/5 and below	1) Repetition of meta-analysis with exclusion of outliers if heterogeneity present; 2) Type of laxatives used; 3) Use of simethicone and/or prokinetics; 4) Timing of administration of laxatives; 5) Large studies only (≥ 30 VCEs in both laxative and control groups)

ered a limitation of our work, although it does reflect clinical practice; we tried to eliminate this issue by performing per-regimen subgroup analysis.

In conclusion, our study challenges the usefulness of purgative bowel preparation before small-bowel VCE. Performing VCE without any prior bowel preparation could lead – from a patient's perspective – to a more convenient examination and at the same time save some costs for the healthcare system. However, significant heterogeneity among meta-analyzed studies owing to the lack of standardized definitions, different patients demographics, different study indications, unjustified sample sizes, and use of older generation capsules may weaken a recommendation for abandoning purgative bowel preparation for VCE.

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Competing interests

None.

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