REVIEW ARTICLE

Effectiveness of mechanical bowel preparation versus no preparation on anastomotic leakage in colorectal surgery: a systematic review and meta-analysis

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Abstract

It has been a standard practice to perform mechanical bowel preparation (MBP) prior to colorectal surgery to reduce the risk of colorectal anastomotic leakages (CAL). The latest Cochrane systematic review suggests there is no benefit for MBP in terms of decreasing CAL, but new studies have been published. The aim of this systematic review and meta-analysis is to update current evidence for the effectiveness of preoperative MBP on CAL in patients undergoing colorectal surgery. Consequently, PubMed, MEDLINE, Embase, CENTRAL and CINAHL were searched from 2010 to March 2017 for randomised controlled trials (RCT) that compared the effects of MBP in colorectal surgery on anastomotic leakages. The outcome CAL was expressed in odds ratios and analysed with a fixed-effects analysis in a meta-analysis. Quality assessment was performed by the cochrane risk of bias tool and grades of recommendation, assessment, development and evaluation (GRADE) methodology. Eight studies (1065 patients) were included. The pooled odds ratio showed no significant difference of MBP in colorectal surgery on CAL (odds ratio (OR) = 1.15, 95% CI = 0.68–1.94). According to GRADE methodology, the quality of the evidence was low. To conclude, MBP for colorectal surgery does not lower the risk of CAL. These results should, however, be interpreted with caution due to the small sample sizes and poor quality. Moreover, the usefulness of MBP in rectal surgery is not clear due to the lack of stratification in many studies. Future research should focus on high-quality, adequately powered RCTs in elective rectal surgery to determine the possible effects of MBP.

Keywords Colorectal surgery · Anastomotic leaks · Mechanical bowel preparation · Oncology · Systematic review

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Introduction

In 2014 about 10,420 colorectal surgeries were performed in the Netherlands [1]. The complication rates for this type of surgery range between 4 and 36% [2]. A part of the general postoperative complications is colorectal anastomotic leakage (CAL). This is defined as discharge of faeces from the anastomosis site, which externalises through the drainage opening or the wound incision, or can be characterised on the basis of an abscess adjacent to the site confirmed by clinical, haematological or radiological inquiry [3]. Colorectal anastomotic leakage is still a frequent and dangerous complication after gastrointestinal surgery; it occurs in 4–33% of patients and is associated with a higher risk of morbidity and mortality [4–6]. In addition, CAL has an adverse impact on late daily functional results [7–9] and long-term outcomes, such as 5-year survival rate and recurrence rate [10–12]. Moreover, it increases the 30-day re-admission rate, length

of stay, hospital costs and postoperative infections by a factor of 0.6–1.9 [13].

To reduce the risk of CAL, mechanical bowel preparation (MBP) has been a logical step prior to colorectal surgery since the first study in the seventies [14]. Various methods have been used as MBP in studies over the years, such as polyethylene glycol electrolyte solution (PEG), laxatives, enemas and low-residue diets [15]. The rationale behind these MBPs is that the mechanical removal of faeces prevents the high bacterial load content of faeces coming into contact with a newly performed anastomosis. In addition, MBP would theoretically decrease the intraluminal pressure of possible hard stool and reduce ischaemia at the new anastomosis [14, 16]. Consequently, early studies associated MBP with decreased morbidity and mortality [14].

However, over the last decade the effectiveness of MBP in elective colorectal surgery has been criticised [17]. Recent randomised clinical trials have not identified statistically significant benefits of MBP [18–22] or increased rates of infectious complications [3, 23–25]. Furthermore, patients experience an unpleasant taste, dehydration, cardiac complications, and electrolyte derangements [20, 26–29]. In addition, the latest Cochrane systematic review found no benefit for MBP in terms of decreasing CAL, mortality or other surgical complications (last search December 2010) and has not been updated yet [3]. The recommendation was to focus on MBP applied in rectal surgery. Although most colorectal surgeons accept these results, many are still reluctant to omit MBP [30, 31].

Numerous studies have been published about MBP since the latest Cochrane systematic review, which suggests that an update of available recent evidence about MBP in colorectal surgery is needed. Therefore, the aim of the study is to determine the effectiveness of preoperative MBP versus no preparation on CAL in patients undergoing colorectal surgery.

Methods

Design

The systematic review and meta-analysis followed the guidelines outlined in the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [32]. In addition, the Cochrane Handbook for Systematic Reviews of Interventions [33] was used as reference work. The findings and decisions were critically assessed by the second author, who provided feedback throughout the study.

Study identification

A systematic literature search of the medical and nursing databases Medline, Embase, the Cochrane Library for Randomised Controlled Trails (CENTRAL) and CINAHL was performed (from December 2010 to March 2017). Additional studies were identified on inspection of the reference lists of the reviewed articles.

The search terms used were: colorectal surgery, cathartic, postoperative complications, anastomosis surgical, and anastomotic leak. The full search strategy is available in Supplementary 1.

Study selection

Studies were eligible for reviewing when they contained patients undergoing colorectal surgery who had enteral, rectal or a combination of both MBP compared to no preparation, with the outcome CAL diagnosed by haematological, radiological or clinical inquiry. In addition, all studies were RCTs or observational studies, with a propensity matching analysis to adjust for selection bias, published between December 1, 2010 and the latest search on March 6, 2017.

Other inclusion criteria were: available in full-text and written in English, German or Dutch. In contrast, studies were excluded that contained colorectal surgery in children, MBP applied in other than colorectal surgery, or RCTs with fewer than ten patients per arm (pilot studies).

At first, titles and abstracts were independently screened on title and abstract by two researchers (the first and second author) to determine whether they aligned with the inclusion and exclusion criteria. Thereafter, full-text articles were independently selected for eligibility. During both stages disagreements were solved, leading to consensus.

Data extraction

Data were extracted by means of a predefined evidence table [33]. The following data per study were collected: main author, year of study, design, country, specific intervention per arm, total sample size, number of participants allocated to each intervention group, summary of findings in terms of anastomotic leaks, and associated *p* value. Patients' characteristics were: age (means in years), sex (%) and indication for surgery (*n*) divided in benign and malignant. Furthermore, method and type of colorectal surgery (*n*) were taken into account, and finally a column for the quality assessment was added.

Data were independently extracted by the main author and verified by the second author.

Data synthesis

The findings of individual studies were dichotomised and expressed as an Odds Ratio (OR) with 95% confidence interval and a *p* value of less than 0.05 considered as a statistically significant difference. Thereafter, data were analysed through a Mantel–Haenszel (M-H) analysis in a meta-analysis [34]. This type of analysis has better statistical properties then an Inverse Variance analysis, when there is a small number of events in the included studies [34] that appeared in previous meta-analysis of the effectiveness of MBP on CAL [29]. In addition, when there were different types of MBPs, studies were clustered and a subgroup analysis was performed.

The heterogeneity between studies was quantified by the I^2 and χ^2. I^2 statistic is classified as low (I^2 0–50%), moderate (I^2 50–75%), or high ($I^2 > 75\%$); a χ^2 with a *p* value of 0.10 or less is considered to indicate significant heterogeneity [35]. When heterogeneity was classified as low, a fixed-effects model was fitted. A random effects model was fitted when heterogeneity was moderate or high.

Publication bias across studies was examined through the bias indicator Kendall's Tau when a random effects model was fitted. If the test had a significant result, publication bias was assumed to be present [33]. In addition, a funnel plot was generated to examine publication bias if a fixed-effects model was fitted. Asymmetry of this plot indicated publication bias. However, at least ten studies have to be included to gain enough power to distinguish asymmetry [33].

All analyses were conducted with Review Manager version 5.3 (The Cochrane Collaboration; 2014).

Risk of bias

Two authors appraised each study critically, using the Cochrane Collaboration tool for assessing the risk of bias [36]. This tool covers six domains of bias in the form of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other biases. Each type of bias was given an assessment in the shape of low risk (circle containing a plus), high risk (circle containing a minus) or risk unclear (circle containing a question mark). Although no total score can be calculated, allocation concealment is the leading factor in the overall risk of bias of the study [33]. Disagreements were solved by discussion between the authors and led to consensus.

As an overall score of quality cannot be calculated from the cochrane risk of bias tool [36], the GRADE-approach is used for grading the overall quality of evidence in the included studies [37–39].

The highest quality rating is for randomised trial evidence. Downgrading of the included trials to moderate, low or very low-quality evidence is based on five criteria. These criteria are limitations in the design and implementation of available studies, suggesting high likelihood of bias, indirectness of evidence (indirect population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses), imprecision of results (wide confidence intervals) and high probability of publication bias [37].

Finally, the overall GRADE score for quality of evidence was formed based on four criteria: quality, consistency, directness and effect size. Each item scored a certain number of points, which were accumulated and resulted in high (at least four points), moderate (three points), low (two points) or very low (one or fewer points) quality of evidence [40].

Results

Including studies

The search resulted in 164 potentially relevant studies, of which four were accessed from the reference list of the potentially relevant studies. Screening of titles and abstracts led to 21 studies, which were reviewed in full. Eventually eight studies met the eligibility criteria and contributed to the main analyses [41–48].

Two authors from studies were asked to provide additional information. However, one of them did not respond [44]. Two studies had to be excluded merely because they were neither written in English, German or Dutch [49, 50]. A flowchart of the search is presented in Fig. 1.

Study characteristics

Study characteristics are listed in Table 1. Randomised controlled trials were conducted in all studies, although one study was a propensity score matching analysis [45] and one a subgroup analysis of a larger RCT [48]. Three of the eight studies were conducted in India and the remaining in Jordan, Japan, Taiwan and the Netherlands, respectively. The included studies were published between 2012 and 2016.

The number of participants in the individual studies ranged from 63 to 234 with a mean age of 58.5 years in a range from 43 till 69 years of age. However, one study did not calculate a mean age of the total study sample [44]. Studies featured primarily colorectal carcinoma as an indication for surgery (range 65–100%). In addition, one study was only limited to diverticulitis as the reason for surgery [48]. The main location of surgery addressed in the studies was left-colon ($n = 324$), right-colon ($n = 222$), sigmoid ($n = 303$) and rectum ($n = 205$). The main method of surgery was open ($n = 963$) versus laparoscopic ($n = 48$); however, one study did not state the method of surgery [45]. CAL was diagnosed

Fig. 1 Flowchart
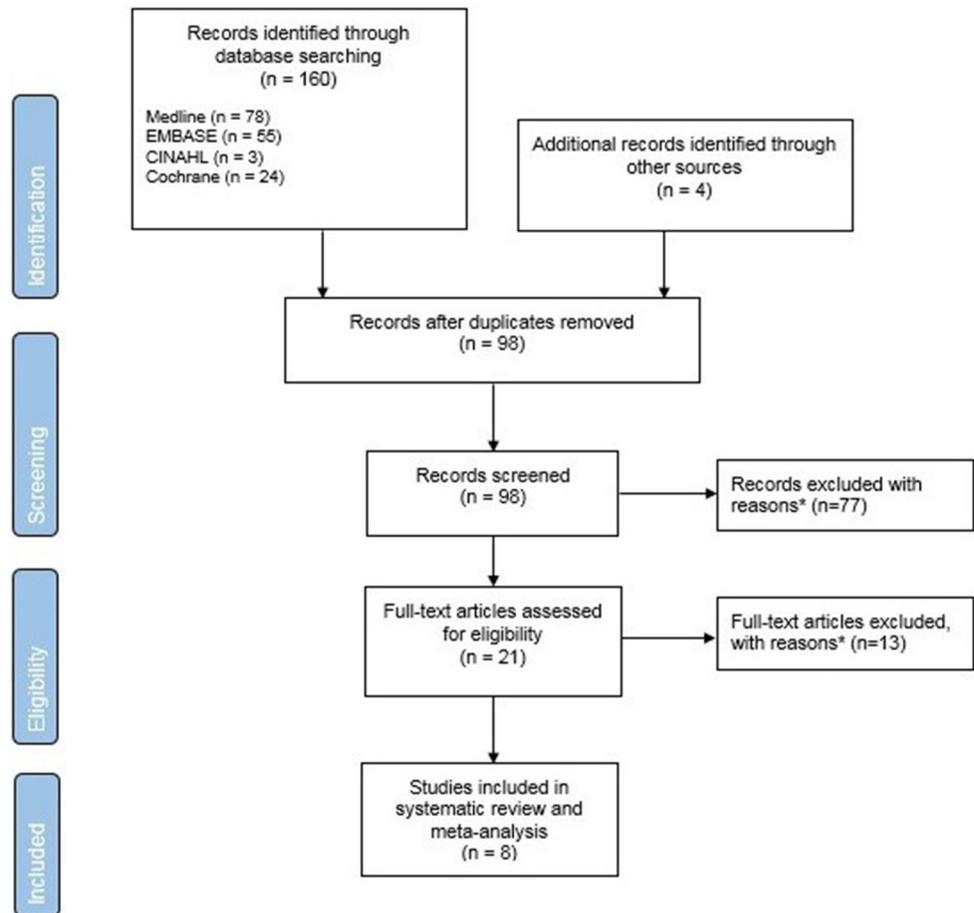
in all studies by at least two of three diagnostic inquiries, i.e., all studies used clinical inquiry, in addition to which six used haematological and four radiological inquiry.

As MBP, seven studies used polyethylene glycol (PEG), in addition to which three studies added an enema preoperative. Only the study by Tahirkheli et al. addressed a fluid diet for 3-day postoperative [46]. One study included emergency surgery as the control group [43]. All of the included studies applied antibiotics intravenously both intra- and postoperatively, both in the intervention and the control group.

Quality assessment

An overview of the risk of bias of individual studies is listed in Fig. 2. Most of the studies did not fully report information to assess the risk of bias. Nonetheless, randomisation sequence generation was conducted correctly in seven of the studies. Allocation concealment had a high risk of bias in two studies [35, 43] and remained unclear in three studies due missing reporting [41, 42, 44]. Blinding

of participants and personnel could not be executed in all studies because of the nature of the intervention and the informed consent provided.

One study had a high risk of bias at blinding of the outcome assessment, as the researchers were aware of the allocated intervention of the participants [42]. This issue remained unclear in all the other studies, as it was not reported there. However, all studies were considered free from the bias of incomplete outcome data and selective reporting. Likewise, no conflicts of interests or other biases were found.

According to the GRADE-approach, three studies were defined as moderate quality, in contrast to three low-quality studies and one very low-quality study. Conversely, none of the included individual studies were graded as of a high-quality. The reasons for downgrading the quality were based on high risks of bias or wide confidence intervals. Thus, the overall quality of evidence was defined as low. The exact arguments for the downgrading are listed in Table 1.

Table 1 Study characteristics

Author, country, design	Participants characteristics	Interventions	CAL (n/N)	GRADE
Bhat [41], India, RCT	$N = 202$	Intervention: PEG + AB	2/98 (2.0%)	+++O
	$\bar{x}$ Age: 51 years	Control: AB	3/104 (3.8%)	Moderate[a]
	Sex: 56% male		$p = 0.45$	
	Indication (%): malignant (97), benign (3)			
	Method (n): open (202), laparoscopic (0)			
	Type (n): right-colon (51), transverse-colon (5), left-colon (25), sigmoid (95), rectal (26)			
	CAL determined by: radiological and clinical inquiry			
Bhattacharjee [42], India, RCT	$N = 71$	Intervention: PEG + AB	4/38 (10.5%)	++OO
	$\bar{x}$ Age: 47 years	Control: AB	2/33 (6.1%)	Low[b]
	Sex: 58% male		$p = 0.68$	
	Indication (%): malignant (80), benign (20)			
	Method (n): open (71), laparoscopic (0)			
	Type (n): subtotal (11), left-colon (6), right-colon (27), sigmoid (13), rectal (14)			
	CAL determined by: haematological and clinical inquiry			
Beerdawood [43], Japan, RCT	$N = 130$	Intervention: PEG + AB	3/66	+OOO
	$\bar{x}$ Age: 57 years	Control: AB	2/64	Very low[c]
	Sex: 57% male		$p > 0.05$	
	Indication (%): malignant (69), benign (31)			
	Method (n): open (130), laparoscopic (0)			
	Type (n): subtotal (6), left-colon (54), right-colon (40), sigmoid (33), rectal (7)			
	CAL determined by: haematological and clinical inquiry			
Saha [44], India, RCT	$N = 63$	Intervention: PEG + enema + AB	2/32 (6.25%)	++OO
	$\bar{x}$ Age: N/A	Control: AB	2/31 (6.45%)	Low[b]
	Sex: 62% male		$p > 0.05$	
	Indication (%): malignant (71), benign (39)			
	Method (n): N/A			
	Type (n): left/right-colon (12), sigmoid (29), rectal (22)			
	CAL determined by: haematological, radiological and clinical inquiry			

Table 1 (continued)

Author, country, design	Participants characteristics	Interventions	CAL (n/N)	GRADE
Kim [45], Korea, Propensity score	$N = 234$	Intervention: PEG + enema + AB	6/117 (5, 1%)	++OO
	$\bar{x}$ Age: 66 years	Control: AB	3/117 (2.6%)	Low[b]
	Sex: 58% male		$p = 0.31$	
	Indication (%): malignant (100)			
	Method (n): open (234), laparoscopic (0)			
	Type (n): left-colon (84), right-colon/ sigmoid (50), rectal (100)			
	CAL determined by: clinical and radiological inquiry			
Tahirkheli [46], Pakistan, RCT	$N = 96$	Intervention: fluid diet for 3 days + AB	8/48 (16.7%)	++OO
	$\bar{x}$ Age: 41 years	Control: AB	6/48 (12.5%)	Low[d]
	Sex: 54% male		$p = 0.56$	
	Method (n): open (96), laparoscopic (0)			
	Indication (%): malignant (65), benign (35)			
	Type (n): left-colon (31), right-colon (31), sigmoid/rectal (34)			
	CAL determined by: haematological, radiological and clinical inquiry			
Sasaki [47], Japan, RCT	$N = 79$	Intervention: PEG + AB	1/41 (2, 4%)	+++O
	$\bar{x}$ Age: 69 years	Control: AB	3/38 (7, 9%)	Moderate[a]
	Sex: 52% male		$p = 0.35$	
	Indication (%): malignant (100)			
	Method (n): open (31), laparoscopic (48)			
	Type (n): left-colon/rectal (37), right-colon (42)			
	CAL determined by: clinical and radiological inquiry			
van't Sant [48], Netherlands, RCT	$N = 190$	Intervention: PEG + enema + AB	8/103 (7.8%)	+++O
	$\bar{x}$ Age: 67 years	Control: AB	5/87 (5.7%)	Moderate[a]
	Sex: 45% male		$p = 0.79$	
	Indication (%): benign (100)			
	Method (n): open (190), laparoscopic (0)			
	Type (n): left-colon (99), sigmoid (91)			
	CAL determined by: clinical and radiological inquiry			

CAL colorectal anastomotic leaks, *PEG* polyethylene glycol, *AB* antibiotics, *n* events, *N* total participants subgroup, *N/A* not assigned, *CI* Confidence Interval, *GRADE* Grades of Recommendation, Assessment, Development and Evaluation divided in very low (+), low (++), moderate (+++) and high (++++)

[a]Imprecision of results

[b]High risk of bias and imprecision of results

[c]High risk of bias, imprecision of results and control group contained only emergency surgery

[d]Unclear risk of bias and imprecision of results

Meta-analysis

All of the eight studies were included in the meta-analysis, which resulted in a total of 61 events (CAL) with 1065 participants (Fig. 2).

The results in terms of CAL are listed in Table 1. None of the included studies could demonstrate a significant difference between MBP and no preparation on the incidence of CAL, with a p value of 0.05. In the individual studies the p values ranged from 0.31 till 0.76. However, two studies only reported that the p value was greater than 0.05 [43, 44].

A fixed-effects model was fitted because of the assumption of low heterogeneity of studies based on I^2 of 0% with a χ^2 of 2.87 ($p = 0.90$).

Publication bias could not be determined through a Kendall's Tau because a fixed-effects model was used. Therefore, a funnel plot was fitted, which showed to be symmetric.

However, there were fewer than ten studies included to determine valid publication bias (Supplement 3).

The test for overall effect was 0.53, with a $p = 0.60$. In addition, the OR of the individual studies ranged from 0.70 to 2.05. However, all studies contained the null value and could not show statistically significant differences between MBP and no MBP ($p > 0.05$). The pooled OR was 1.15 in favour of the no preparation group, but did not show any significant difference either (95% CI = 0.68–1.94; $Z = 0.53$; $p = 0.60$).

Based upon the difference between the delivered interventions, three subgroups could be formed. The first subgroup analysis of PEG in combination with AB involved 482 participants with twenty events in total, and had an OR of 0.95 (95% CI = 0.39–2.33; $Z = 0.12$; $p = 0.91$) in favour of the MBP group.

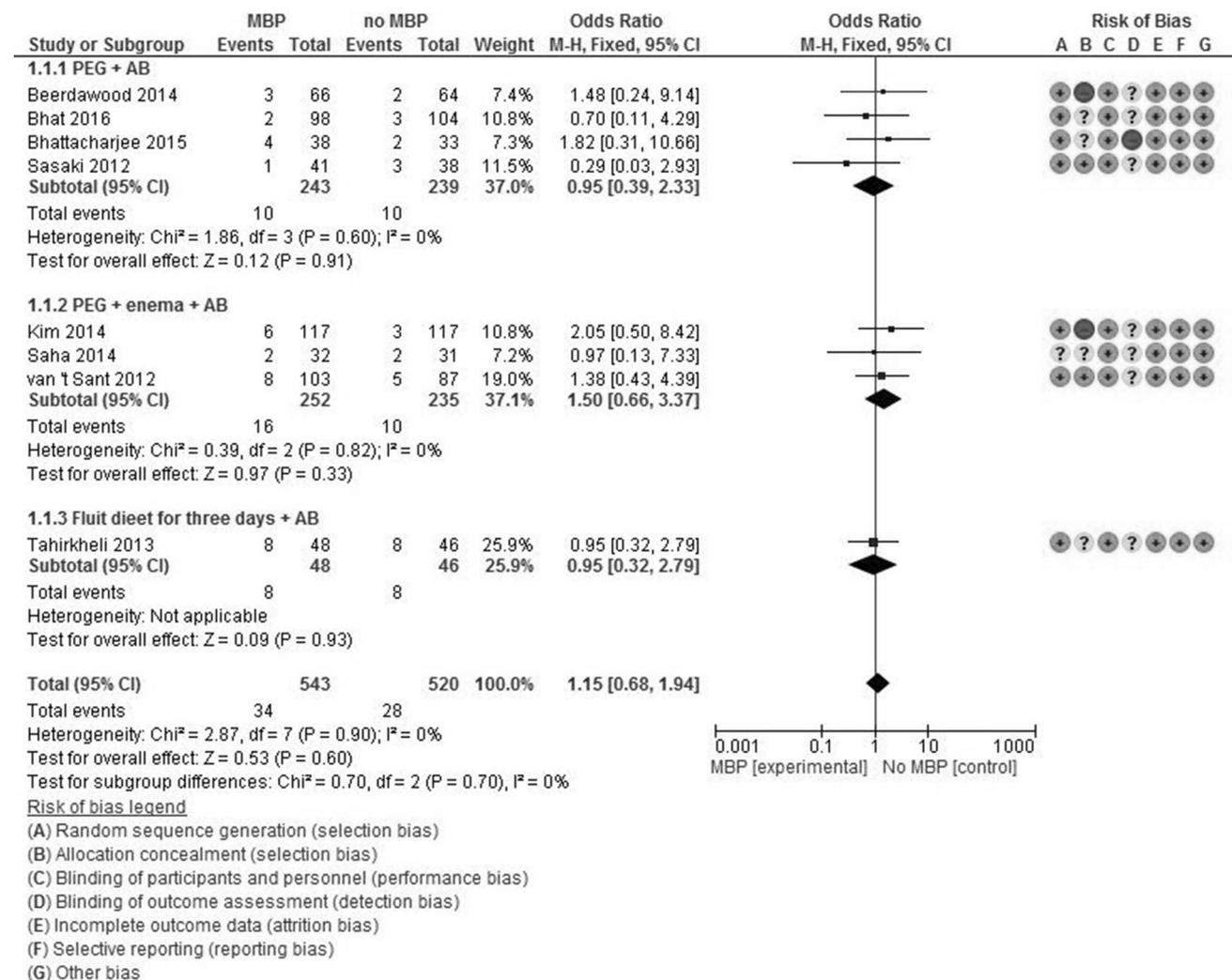The second subgroup analysis was the intervention PEG, an enema and AB and included 487 participants

Fig. 2 Meta-analysis

and 26 events. This resulted in a pooled OR of 1.50 (95% CI = 0.66–3.37; $Z = 0.97$; $p = 0.33$) in favour of the control group. The last group had as intervention a fluid diet for 3 days. Pooling of data of this last subgroup was not possible because only one study was included in this systematic review. Nevertheless, the subgroup differences were not statistically noticeable ($I^2 = 0$; $\chi^2 = 0.70$; $p = 0.70$).

Discussion

Principal findings

The aim of our study was to update the current evidence on the effectiveness of preoperative MBP on CAL in patients undergoing colorectal surgery. Since 2010 eight new studies have been published, including 1065 participants and a total of 61 events (CAL). GRADE assessments showed a low-quality of evidence. There was no evidence found that MBP is associated with a lower odds ratio of CAL compared to no preparation, even in the subgroup analysis.

Strengths and limitations

This systematic review has both strengths and limitations. We performed an execution of the search string. Hence, there were probably no studies unintentionally left out of the systematic review. In addition, the data selection, synthesis and quality assessment were all conducted by two researchers, thus minimising subjectivity [33, 36].

Several limitations need to be taken into account when interpreting the results. The first limitation of this study is the low number of CAL incidences in the included studies.

In this connection, a possible explanation of the large confidence intervals is the small sample size and the relative low incidence of CAL in the included studies. Moreover, one study did not distinguish between open and laparoscopic surgery. In addition, other potentially modifying factors such as enhanced recovery after surgery (ERAS) programmes were not reported [51]. Furthermore, the number of types of surgery was also not similar across the studies. In addition, the low number of CAL had an influence on the calculation of the heterogeneity, although the Mantel–Haenszel test was used instead of the inverse variant; the former has shown to have better statistical properties when there are few events [52]. However, odds ratios were used, which are more sensitive to fewer events than risk ratios [33].

Another limitation was including the study by Kim et al. an observational study with a propensity matching analysis [45], which may have caused an overestimation of the effect size found in this study due to its design [53].

Unfortunately, two potentially relevant studies were excluded because of language constraints, which could potentially affect the pooled data. When these two studies were included in the meta-analysis, the funnel plot contained more than ten studies, according to which publication bias could emerge and be assessed.

The incidence of anastomotic dehiscence is increasing, as more anal anastomosis is performed. Therefore, bowel preparation might have different effects in the colon and rectum. Stratification between colonic and rectal surgery is important. Unfortunately, rectal surgery is a non-inclusion criterion in many studies.

In relation to other studies

The results are nevertheless comparable with the recent Cochrane review [54], which also found no significant difference between MBP and no preparation on the odds ratio of anastomotic leaks.

In addition, the results of this study were in line with two earlier systematic reviews and meta-analyses that produced an identical outcome. A fixed effect OR of fourteen trials was 1.08 [55] and a fixed-effects Peto OR of thirteen trials was 1.214 [56].

However, the results contradicted an earlier systematic review, which showed a higher rate of anastomotic leakage in the bowel preparation group [57]. Although researchers used Peto ORs, studies were included with less importance to allocation concealment, and two of the nine studies had high ORs in favour of MBP, probably affecting the pooled OR.

In contrast, three recent non-randomised studies all stated MBP in combination with AB prevents anastomose leaks, based on significantly lower ORs in the intervention group [58–61].

It is difficult to implement the outcome of this study directly in clinical practice. The odds ratios on anastomotic leaks are often difficult to interpret for clinical practice as compared to risk ratios [33]. Besides, possible factors such as the effect of MBP on surgical site infection, length of stay and patience adherence need to be taken into account [30, 55, 57]. In addition, inadequate MBP could lead to liquid bowel contents, which increases the rate of intraoperative spillage [51, 62]. This may increase the frequency of postoperative infectious complications.

Bowel preparation might decrease operating time by improving bowel handling during anastomosis, and might be helpful when intestinal palpation is necessary for identification of a lesion [62]. Additionally, the incidence of anastomotic dehiscence is increasing as more anal anastomosis is performed. Therefore, bowel preparation might have different effect in the colon and rectum. Stratification between colonic and rectal surgery is important. Unfortunately, rectal surgery was a non-inclusion criterion in many studies.

Finally, seven of the eight included studies were conducted in the Middle-East or Asia, and may be less applicable to a Western surgical department. In addition, most of the included surgeries were open procedures, in contrast to the more implemented ERAS guidelines, including laparoscopic colorectal surgery, carried out in the Netherlands and other European countries [51].

Conclusion

This update confirms that MBP for elective colorectal surgery does not lower the risk of CAL. These results should, however, be interpreted with caution, as most studies have a small sample size and poor quality. The usefulness of MBP in rectal surgery is not very clear, as rectal surgery is a non-inclusion criterion in many studies. Therefore, future research should focus more on high-quality, adequately powered RCTs in elective rectal surgery to determine possible effects of MBP.

Compliance with ethical standards

Conflict of interest The Authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not involve any studies with animals.

Informed consent For this type of study formal consent is not required.

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