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A meta-analysis of randomized controlled trials of the addition of lubiprostone to bowel preparation before colonoscopy

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Abstract

Aim: Adequate bowel preparation is essential to the quality of colonoscopy. We performed a meta-analysis to determine the efficacy and safety of the addition of lubiprostone to the bowel preparation process prior to colonoscopy.

Methods: Online databases, namely, PubMed, MEDLINE and Cochrane Library, were searched for randomized controlled trials that assessed the additive effect of lubiprostone on the quality of colon preparation in patients undergoing colonoscopy. Each included study was evaluated by the Jadad score to assess the quality of the study. The primary outcome was bowel preparation efficacy, defined as the proportion of patients with an excellent or poor preparation. The secondary outcomes included the length of the colonoscopy, polyp detection, and any adverse effects.

Results: In total, 5 articles published between 2008 and 2016 fulfilled the selection criteria. The addition of lubiprostone to the bowel cleansing process significantly increased the proportion of patients with an excellent preparation (risk ratio [RR] = 1.68, 95% confidence interval (CI): 1.40–2.02, $P < .00001$) but did not decrease the procedural time or increase the polyp detection rate (mean difference = -0.52, 95% CI: -3.74–2.69, $P = .75$; RR = 1.16, 95% CI: 0.96–1.42, $P = .13$, respectively). There was no significant difference in the proportion of patients with any adverse events.

Conclusion: The addition of lubiprostone to the bowel preparation regimen prior to colonoscopy is effective and safe.

Abbreviations: CI = confidence interval, PEG-E = polyethylene glycol-electrolyte, RR = risk ratio.

Keywords: bowel preparation, colonoscopy, lubiprostone, meta-analysis, polyethylene glycol

1. Introduction

Colonoscopy remains the preferred procedure for colorectal cancer screening and surveillance, and adequate bowel preparation is essential for optimal visualization of mucosal lesions.[1] Poor bowel preparation results in incomplete colonoscopy, increased procedure time, lower rates of adenoma detection, and potentially adverse events, in addition to patient discomfort.[2–4]

Since its introduction in 1980, osmotically balanced polyethylene glycol-electrolyte (PEG-E) bowel lavage solution has become the most commonly used laxative for colonic cleansing.[5] The PEG-E solution has been confirmed as being safe and efficacious for bowel preparation.[6] However, the generally poor tolerance of the large volume necessary influences patient compliance. Therefore, adjunct therapies and split-dose regimens have been used to improve the quality of colonoscopy.[7]

Lubiprostone is a newly approved medication for the treatment of chronic idiopathic constipation that selectively activates type 2 chloride channels in the gastrointestinal tract to enhance intestinal fluid secretion and increase intestinal transit.[8] Lubiprostone also seems to improve the quality of bowel preparation.[9] We conducted a meta-analysis to evaluate the efficacy and safety of the addition of lubiprostone to the bowel preparation regimen prior to colonoscopy.

2. Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement and guidelines were consulted as our reference to promote this meta-analysis.[10]

2.1. Eligibility criteria

Studies were included in the meta-analysis if

(1) they were randomized controlled trials published in English up to April 2018, the full text of which could be acquired,
(2) they assessed the additive effect of lubiprostone on the quality of colon preparation in patients undergoing colonoscopy, and

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Ethical approval was not necessary for this meta-analysis of published studies.

The authors have no conflicts of interest to disclose.

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(3) they reported bowel preparation efficacy as the main outcome.

Studies were excluded if they were

(1) nonrandomized and noncomparative studies,
(2) case reports,
(3) letters to the editor, or
(4) review articles.

2.2. Search strategy

Two authors independently searched four online databases, namely, PubMed, Web of Science, EMBASE, and the Cochrane Library, with the following terms: "lubiprostone," "colonoscopy," "bowel preparation," "bowel cleansing," "colon preparation," and "colon cleansing." After the initial search, we independently scanned the titles and abstracts of the articles and retrieved the full texts for further scrutiny. Finally, all of the eligible studies were included in the meta-analysis and systematic review.

2.3. Validity assessment

Two investigators assessed the eligibility of the articles, and discrepancies were resolved by an independent reviewer. Each study was evaluated by the Jadad score to assess the quality.[11] All data abstraction and entries were validated independently by 2 authors.

2.4. Data extraction

Two authors independently extracted the following data from each included article: patient characteristics (age, sex); diet before preparation; time of colonoscopy; use of cathartics (type, dose, and preparation regimen); scale used to evaluate colon cleansing; degree of colon cleansing (excellent, poor); adverse events; and study quality indicators included in the Jadad score. The corresponding authors of the papers were contacted by e-mail for further information or missing data.

2.5. Outcomes

The primary outcome was bowel preparation efficacy, defined as the proportion of patients with an excellent or poor preparation. Secondary outcomes included procedural duration, polyp detection, adverse effects, or complications, which were empirically grouped according to hierarchal symptoms for clarity as follows: nausea, abdominal cramps/pain and abdominal bloating.

2.6. Statistical analyses

We used the Review Manager software (ver. 5.2; The Cochrane Collaboration, Oxford, England) to perform the meta-analysis. Dichotomous data were entered as numbers of events, while continuous data were entered as the means and standard deviations. The presence of heterogeneity was explored using a χ^2 test, with significance set at $P = .1$, and the degree of heterogeneity was measured using the I^2 value. A random effects model was used when significant heterogeneity was identified ($P < .1$; $I^2 > 50\%$); otherwise, a fixed effects model was used ($P > .1$; $I^2 < 50\%$). Sensitivity or subgroup analyses were performed if there was significant heterogeneity among studies. The risk ratio (RR) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes and mean differences and 95% CIs were calculated for continuous outcomes. Funnel plots were constructed to assess the risk of publication bias across series for the primary outcome.

3. Results

3.1. Literature search and study characteristics

The literature search initially yielded 52 references according to the search strategy described above. After applying our eligibility criteria, 40 references were excluded on the basis of their titles and abstracts or because they were duplicates. Ultimately, we identified 5 prospective randomized controlled trials with a total of 998 patients to include in our meta-analysis after reading the full texts of the remaining 12 references[12–16] (Fig. 1).

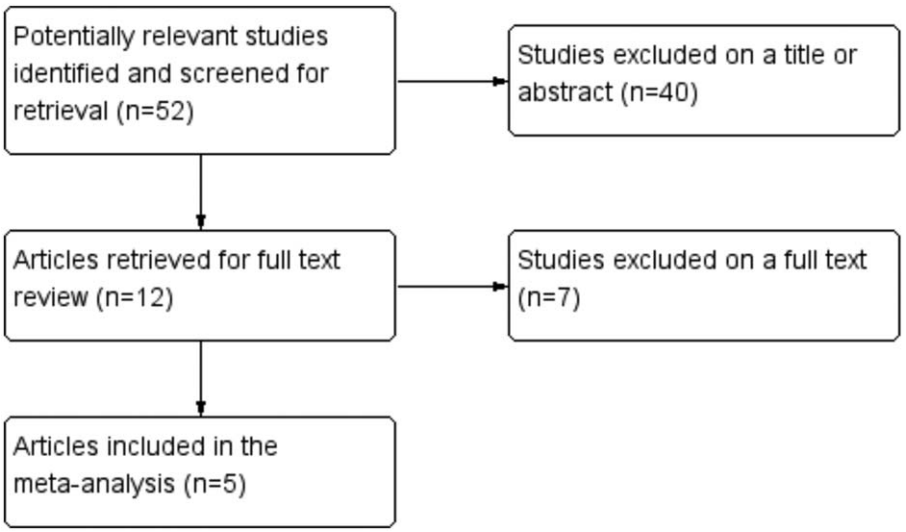

Figure 1. Flow diagram for studies included and excluded.

Table 1

Characteristics of included studies.

Study	Country	Participants	Bowel preparation regimen	Adjunct regimen		Bowel preparation scale	Sedation	Dietary instructions	Modified Jadad score
				Lubiprostone	Control				
Banerjee 2016	India	Outpatient colonoscopy, 18–75 y, March to July 2011	2 L PEG-E, Single dose	24 mcg lubiprostone 1h before PEG-E	Placebo	Boston bowel preparation scale	Propofol	Standardized diet	5
Grigg 2010	United States	Outpatient screening colonoscopy with AODM, ≥50 y, July, 2008 to March, 2010	4 L PEG-E Single dose	24 mcg lubiprostone 2h before PEG-E and 2 h after PEG-E	No placebo	Aronchick scale	Fentanyl and midazolam, or diprivan	Only a clear liquid diet	1
Hjelkrem 2011	United States	Outpatient screening colonoscopy, ≥18 y, July 1, 2009 to July 1, 2010	255 g PEG without electrolytes mixed with 64 oz Gatorade, Split dose	24 mcg lubiprostone at noon the day before colonoscopy	No placebo	Ottawa bowel preparation scale	Fentanyl and midazolam	Only a clear liquid diet	2
Sofi 2015	United States	Screening, surveillance or diagnostic colonoscopy, ≥18 y	4L PEG-E, Split dose	24 mcg lubiprostone at 2 nights before colonoscopy, subsequent 24 mcg lubiprostone at breakfast, lunch, and dinner on the day before colonoscopy	Placebo	Ottawa bowel preparation scale	Not available	Only a clear liquid diet	5
Stengel 2008	United States	Outpatient screening colonoscopy, ≥18 y, October 5, 2007 to December 4, 2007	4L PEG-E, Split dose	24 mcg lubiprostone at noon the day before colonoscopy	Placebo	Ottawa bowel preparation scale	Fentanyl or meperidine and midazolam	standardized diet until 4 pm and subsequently only a clear liquid diet	5

AODM = adult-onset diabetic mellitus, PEG-E = polyethylene glycol-electrolyte.

Table 2

Characteristics of patients from included studies.

Study	Total number		Average age, yr		Male (%)	
	Lubiprostone	Control	Lubiprostone	Control	Lubiprostone	Control
Banerjee 2016	221	221	45.9 ± 15.2	45.8 ± 14.7	72.4	69.7
Grigg 2010	17	24	Not available	Not available	Not available	Not available
Hjelkrem 2011	101	100	55.4 ± 5.7	54.1 ± 5.3	48	49
Sofi 2015	57	66	56.1 ± 9.4	55.8 ± 9.1	38.2	39.5
Stengel 2008	95	96	55.4 ± 5.2	55.9 ± 4.8	49	54

The study and patient characteristics are provided in Tables 1 and 2. One study was performed in India,[12] and the others were conducted in the United States.[13–16] The study populations in 4 of the 5 studies were composed of subjects older than 18 years who underwent colonoscopy.[12,14–16] Another study enrolled outpatients who were at least 50 years of age with adult-onset diabetic mellitus.[13] Bowel preparation regimens varied among the studies, most of which used PEG for colon cleansing.[12,13,15,16] Participants from one study received PEG without electrolytes mixed with a sports drink (MiraLAX/Gatorade 64-oz).[14] Regarding the evaluation of bowel preparation, the Ottawa scale was used in three studies,[14–16] the Boston scale was used in one study,[12] and the Aronchick scale was used in the final study.[13] The quality of 3 studies was high,[12,15,16] but the quality of the other 2 studies was low.[13,14]

3.2. Primary outcomes

Three of the included studies reported the proportion of patients with an excellent preparation.[12–14] We used a fixed effects model to combine the 3 studies because no significant heterogeneity was observed ($P = .58$, $I^2 = 0\%$). The pooled RR was 1.68 (95% CI, 1.40–2.02; $P < .00001$), indicating that lubiprostone pretreatment significantly increased the proportion of patients with an excellent preparation (Fig. 2).

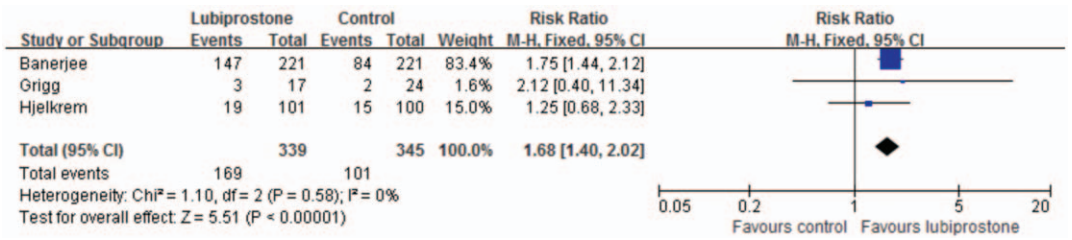

Figure 2. Forest plot concerning patients with an excellent preparation.

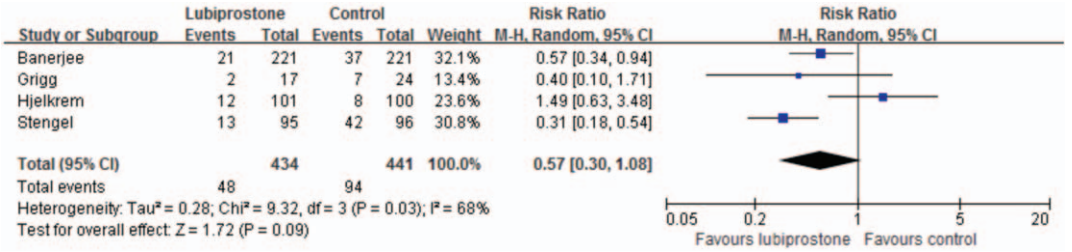

Figure 3. Forest plot concerning patients with a poor preparation.

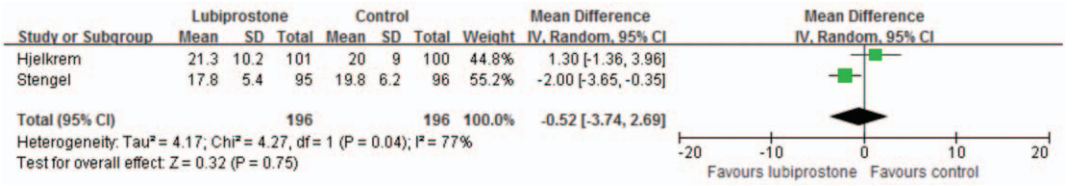

Figure 4. Forest plot concerning procedure duration of colonoscopy.

A random effects model was used in the meta-analysis of 4 studies reporting the proportion of patients with a poor preparation because of significant heterogeneity among the studies ($P=.03$, $I^2=68\%$).[12–14,16] The pooled RR of the 4 studies was 0.57, the 95% CI was 0.30–1.08, and the P value was $P=.09$ (Fig. 3). Although the analysis was not significant, there was a trend towards a decreased proportion of patients with poor preparation in the lubiprostone arm.

3.3. Secondary outcomes

The addition of lubiprostone to the colon preparation regimen did not significantly shorten the procedure duration or improve the polyp detection rate (Figs. 4 and 5). There was no significant difference in the proportions of patients with adverse events, nausea, abdominal pain, or bloating (Figs. 6–9). There was no statistically significant heterogeneity for any secondary outcomes except procedure duration.

3.4. Publication bias

There was no significant publication bias detected for the primary outcome of excellent bowel preparation efficacy in the funnel plot analysis (Fig. 10).

4. Discussion

This is the first reported meta-analysis of randomized controlled trials on the addition of lubiprostone to bowel preparation before colonoscopy. The primary outcome of the meta-analysis was bowel preparation efficacy, defined as the proportion of patients

Figure 5. Forest plot concerning polyp detection rate.

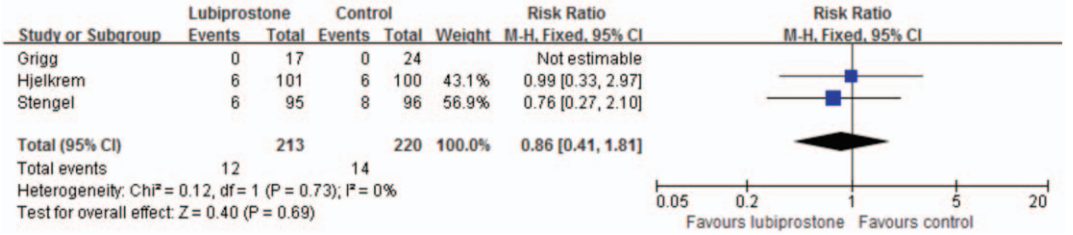

Figure 6. Forest plot concerning patients with adverse events.

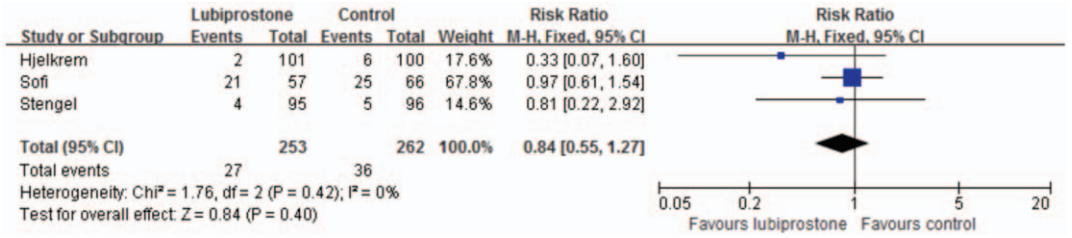

Figure 7. Forest plot concerning patients with nausea.

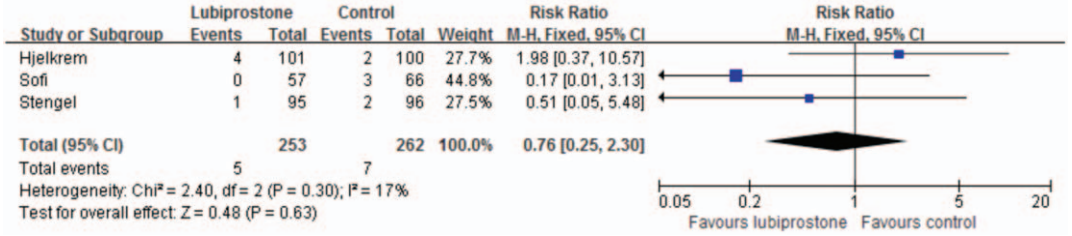

Figure 8. Forest plot concerning patients with abdominal pain.

with an excellent or poor preparation. The pooled RR for the proportion of patients with an excellent preparation was 1.68 (95% CI, 1.40–2.02; $P < .00001$), indicating that lubiprostone pretreatment significantly increased the proportion of patients with an excellent preparation. The P value for the primary outcome was $P < .00001$, with statistical significance. However, the P value for the proportion of patients with a poor preparation was $P = .09$, which was not statistically significant but a trend. As a result, the addition of lubiprostone to bowel cleansing significantly increased the proportion of patients with an excellent preparation and improved the quality of colon preparation. Besides, there were no significant differences in the procedure time, the polyp detection rate or the proportions of patients with any adverse events.

It is widely accepted that the quality of the bowel preparation plays an important role in the diagnostic accuracy and therapeutic safety of colonoscopy.[2,17] If the bowel preparation is unsatisfactory, the possibilities of missed lesions, prolonged procedure times, and increased patient discomfort increase, significantly impacted patients and healthcare costs.[18] Despite the high efficiency of PEG for colon cleansing, up to 20% to 25% of all colonoscopies are performed after an inadequate bowel preparation.[3] Therefore, several studies have evaluated various combinations of 2 agents to improve compliance and reduce adverse events.[19–21] Prokinetics stimulate colonic peristalsis and may be used as an adjuvant agent in bowel preparation. Mishima et al showed that administration of mosapride citrate or itopride hydrochloride prior to the use of oral lavage solution did not significantly improve bowel cleansing quality but decreased the incidence of uncomfortable abdominal symptoms.[22] Tajika et al showed that a regimen consisting of 2 L of PEG plus 15 mg of mosapride citrate resulted in significantly more optimal bowel cleansing in the left-sided colon than 2 L of PEG plus a placebo.[23]

Lubiprostone is a prostaglandin-derived bicyclic fatty acid approved for the long-term treatment of constipation by FDA.[24] Lubiprostone works by selectively stimulating type 2 chloride channels and increasing intraluminal chloride ion secretion, which leads to a passive influx of water and sodium, resulting in increased intestinal peristalsis and increased intestinal transit.[25] Our meta-analysis showed that the addition of lubiprostone to the bowel cleansing regimen significantly increased the proportion of patients with an excellent preparation, and there was a trend towards a decreased proportion of patients with poor preparation in the lubiprostone arm. This suggested that lubiprostone provided an additional laxative effect, leading to better preparation. The accelerated small intestinal and colonic

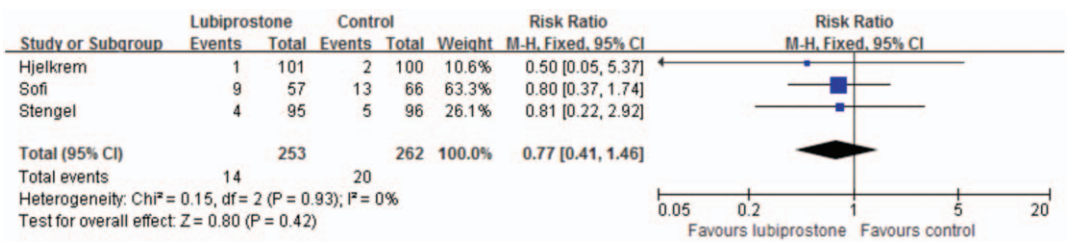

Figure 9. Forest plot concerning patients with abdominal bloating.

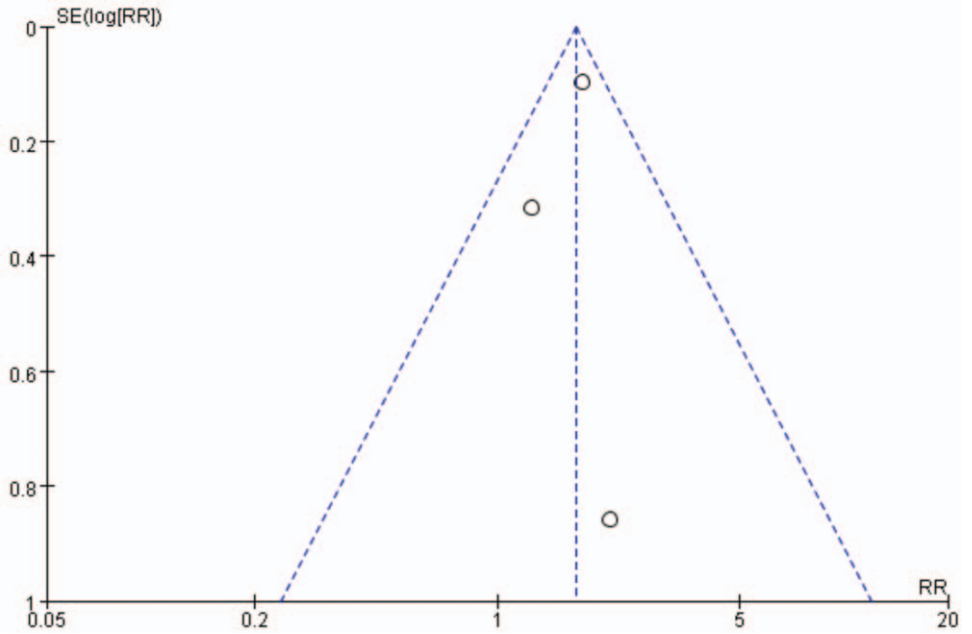

Figure 10. Funnel plot examining for potential publication bias among studies about patients with an excellent preparation.

transit times with lubiprostone and the consequent increased bowel movement frequency could have contributed to the increased efficacy. Lubiprostone is a new type of prokinetic because it has also been proven to be effective at increasing bowel movement frequency and will produce a spontaneous bowel movement in 44% to 63% of patients within 24 hours of the first dose.[26]

Suboptimal bowel preparation is associated with a prolonged procedural time, a reduced adenoma detection rate, and an increased risk of complications.[17,27] Compared to a low quality preparation, a high quality and an intermediate quality preparation have odds ratios of polyp detection of 1.46 and 1.73, respectively.[3] A systematic review and meta-analysis showed that poor bowel preparation (versus fair to good) resulted in a significantly longer cecal intubation time.[28] However, the procedure durations and polyp detection rates were not found to be different between the lubiprostone arm and control arm in our meta-analysis. In addition, there was no significant difference in the proportion of patients who experienced adverse events, nausea, abdominal pain, or bloating. Patient tolerability and adverse events are strongly affected by bowel preparation regimens. Poor tolerability is, in turn, associated with lower quality bowel preparations.[29]

There were certain limitations in our meta-analysis. Only a limited number of studies were available to be included in the analysis; however, these were all of the studies to date on the subject. The addition of future trials with better methodologies might affect certain conclusions. Second, there was no standardization of the bowel preparation evaluation scale. Unfortunately, there were too few studies that used the same bowel preparation evaluation scale to conduct subgroup analyses. In addition, variations in bowel preparation regimens, dietary instructions, differences in quantity of lubiprostone and also the time before colonoscopy might have contributed to the heterogeneity among trials.

5. Conclusion

To the best of our knowledge, this is the first reported meta-analysis of the addition of lubiprostone to the bowel preparation regimen prior to colonoscopy. The addition of lubiprostone to bowel cleansing improved the quality of colon preparation but did not decrease the procedure time or increase the polyp detection rate. There were no significant differences in the proportions of patients with any adverse events. We conclude that the combination of lubiprostone and the standard bowel cleansing pretreatment is an effective, safe, and well-tolerated bowel cleansing regimen prior to colonoscopy.

Author contributions

Conceptualization: Peng Li, Jing Du.
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Supervision: Jing Du.
Writing–original draft: Peng Li.
Writing–review and editing: Jing Du.
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