L-Menthol for Gastrointestinal Endoscopy: A Systematic Review and Meta-Analysis

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INTRODUCTION: **In randomized controlled trials, L-menthol inhibits gastrointestinal peristalsis during endoscopy. Our goal was to quantitatively synthesize the available evidence to evaluate the efficacy and safety of L-menthol for gastrointestinal endoscopy.**

METHODS: **We comprehensively searched for relevant studies published up to January 2020 in PubMed, EMBASE, Web of Science, and Cochrane Library. The main outcomes consisted of the proportion of no peristalsis, proportion of no or mild peristalsis, adenoma detection rate, and adverse events.**

RESULTS: **Eight randomized controlled trials analyzing 1,366 subjects were included. According to the pooled data, L-menthol significantly improved the proportion of no peristalsis (odds ratio [OR] = 6.51, 95% confidence interval [CI] = 4.94–8.57, $P < 0.00001$), and the proportion of no or mild peristalsis (OR = 7.89, 95% CI = 5.03–12.39, $P < 0.00001$) compared with the placebo, whereas it was not associated with an improvement in the adenoma detection rate (OR = 1.03, 95% CI = 0.54–1.99, $P = 0.92$). Adverse events did not differ significantly between the 2 groups (OR = 1.40, 95% CI = 0.75–2.59, $P = 0.29$).**

DISCUSSION: **The findings of this study support the use of L-menthol to suppress gastrointestinal peristalsis during endoscopic procedure.**

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INTRODUCTION

Gastrointestinal cancers are serious life-threatening diseases. Although the number of deaths related to gastrointestinal cancers has been substantially reduced in the past 50 years because of remarkable progress in research on cancer prevention and treatment (1), 2.17 million deaths and 3.45 million new cases of this diseases were reported in 2018 worldwide, accounting for 22.7% of all cancer-related deaths and 19.1% of all cases of cancer, values that are far higher than other cancers (2). In fact, the great majority of gastrointestinal cancers are preventable and curable through early diagnostic and therapeutic gastrointestinal endoscopy, and early screening combined with the resection of precancerous lesions has been confirmed to be an effective method to reduce the incidence and mortality (3–5). Currently, gastrointestinal endoscopy, endoscopic submucosal dissection, and endoscopic mucosal resection have become important methods for the diagnosis and treatment of gastrointestinal cancers because of their comparable safety (6), superior diagnostic sensitivity (7), facility of excision of early neoplastic lesions (8), cost-effectiveness, and minimal invasion (9) compared with the conventional surgical operation. However, unclear surgical fields caused by peristalsis and miss rates of 5%–32% for polyps remain concerns (10). Hence, the suppression of gastrointestinal peristalsis facilitates the endoscopic examination and potentially improves the lesion detection rate (11,12).

Buscopan and glucagon are the 2 conventional antispasmodics used for endoscopic detection and are considered reliable treatments to facilitate endoscopy (13,14). Buscopan, a specific inhibitor of M-acetylcholine receptor, achieves antiperistaltic effects by selectively relieving gastrointestinal smooth muscle spasms (15,16). Although the use of this drug is safe in most cases, some serious adverse reactions, including fatal hypersensitivity (17,18), cardiac arrest (10), and even deaths, have been reported after intravenous administration (13,19), particularly in elderly patients with multiple comorbidities (20). Generally, glucagon was postulated to be safer than Buscopan (21,22). However, nausea, vomiting, allergy (23,24), and delayed hypoglycemia (25) have also been documented in clinical trials. In addition, these drugs are contraindicated in many patients, and intravenous injection access may not be easily obtained in many patients (e.g., intravenous drug users). Therefore, the availability of an efficacious topical antiperistaltic agent is important.

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L-menthol, the major and active constituent of peppermint oil extracted from *Mentha haplocalyx* Briq (26), is ubiquitous in our daily life and considered a safe additive in food, cosmetics, pharmaceuticals, and daily use chemicals (27–29). According to previous studies, L-menthol relaxes the gastrointestinal smooth muscle (30). Animal studies revealed that their muscle relaxation mechanisms of action were similar to dihydropyridine calcium antagonists and mediated by direct actions on smooth muscle, suppressing calcium influx and K^+ depolarization-induced Ca^{2+} uptake (31–33). Hence, L-menthol has also been applied in the clinic, even as a first-line drug (34), for the treatment of irritable bowel syndrome (35,36) and functional dyspepsia (37–39), and several meta-analyses have assessed and confirmed its effectiveness and safety (40–44). In recent years, accumulating clinical trials have shown that directly spraying L-menthol onto the gastrointestinal mucosa significantly improves spasms (45,46) and the adenoma detection rate (ADR) (47) during an endoscopic procedure. However, some of the conclusions were inconsistent. Thus, a rigorous meta-analysis is needed to evaluate the efficacy and safety of L-menthol for endoscopic procedure.

METHODS

Search strategy

PubMed (1900 till 2020), EMBASE (1966 till 2020), Web of Science (1900 till 2020), and Cochrane Library, were searched during January 2020. We used the following search terms: Menthol AND ("endoscope*" OR "endoscopy" OR "endoscopic" OR "colonoscopy" OR "gastroscope" OR "enteroscope" OR "duodenoscopes" OR "sigmoidoscopes" OR "esophagoscopes" OR "peristalsis" OR "antispasmodic" OR "antiperistaltic" OR "antipruritics"). A recursive and cross-checking search of the references and relevant review articles was also performed.

Article inclusion and data extraction

This meta-analysis was conducted based on the methodology recommended by the Cochrane Handbook for Systematic Reviews of Interventions Version 6 (48) and was reported according to the protocol outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (49). Studies eligible should meet the following criteria: (i) the experimental group was treated with the local administration of L-menthol sprayed onto the gastrointestinal mucosa, (ii) at least one of the 4 outcomes was reported, including proportion of no peristalsis (PNP), proportion of no or mild peristalsis (PNMP), ADR, and adverse events (AEs).

Two authors (X.C. and L.C.) independently selected the studies and extracted the data. When a discrepancy occurred, it was settled through discussion.

Quality assessment

The 2 aforementioned investigators independently evaluated the methodological quality of the trials. The risk of bias consisted of 7 domains, including selection bias, allocation concealment, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. Each item was classified into a low, high, and unclear risk of bias. Differences were resolved through discussion.

Data analysis

In this review, we calculated odds ratios (ORs) for dichotomous data, while the continuous data are presented as mean differences. The data were pooled using either the Mantel-Haenszel (fixed-effects model) (50) or DerSimonian-Laird (random-effects model) approach (51). Heterogeneity between studies was analyzed using the χ^2 test. We defined $P \geq 0.1$ and $I^2 < 50$ as an indication of good agreement between the results, and therefore the fixed-effects model was chosen. However, $I^2 > 50\%$ indicated significant heterogeneity among trials. Accordingly, a random-effects models was applied. Differences were determined to be statistically significant at $P < 0.05$.

RESULTS

Search results and study characteristics

The detailed process of study selection and characteristics are presented in Figure 1 and Table 1, respectively. One hundred ninety-nine relevant records were identified in the initial search: Web of Science (n = 41), Cochrane Library (n = 50), EMBASE (n = 76), and PubMed (n = 32). One hundred twelve abstracts remained after 87 duplicate records were removed. Of the 112 remaining records, 98 records were further excluded after the titles and abstract were reviewed. Finally, 8 studies (1 abstract (52) and 7 full-text articles) involving 1,366 patients published between 2011 and 2019 were included.

All but one (52) of the studies were conducted in Japan. Five of the 8 studies involved gastroscopes, while the patients in the other 3 studies (47,52,53) underwent a colonoscopy. The sample sizes varied from 24 to 611 patients, and the age of participants ranged from 22 to 94 years. Gastric peristalsis was evaluated using Niwa's Classification and classified into 5 grades (grade 1: no peristalsis, grade 2: mild peristalsis, grade 3: moderate peristalsis, grade 4: vigorous peristalsis, and grade 5: markedly vigorous peristalsis) (54), while colonic peristalsis was assessed using the method reported by Asao et al. in 2011, which classified colonic peristalsis into 4 grades (grade 1: no peristalsis, grade 2: mild peristalsis, grade 3: moderate peristalsis, and grade 4: severe peristalsis) (55). Three doses were used: 80, 160, and 320 mg. The interventions used in the control group included a placebo (n = 6), liquid simethicone (n = 1) (52) and CO_2/air (n = 1) (53).

Methodological quality assessment

A low risk of selection bias was observed for 6 studies (6/8) because they used a computer (11,45,56,57) and randomization table (47,53) to generate the randomization code. Regarding allocation concealment, the majority of studies (5/8) (11,45,46,56,57) were deemed as displaying a low risk of bias due to the use of opaque sealed envelopes. In terms of attrition bias and reporting bias, no incomplete outcome data and selective reporting were identified in any of the included studies. In addition, no other sources of bias were identified in the included studies. The overall quality of the included studies was rated as high because a large proportion displayed a low risk of bias (47/56). The major potential factor contributing to the risk of bias was attributed on 1 study (52) because it is an abstract that provides limited information for the risk assessment, as shown in Figure 2.

Primary outcomes

Effects of L-menthol on peristalsis. All but one of the included studies (56) used PNP and PNMP to evaluate gastrointestinal peristalsis. Five studies (11,47,52,53,57) reported the PNP, while 6 studies (11,45–47,53,57) described the PNMP. Because mild peristalsis was considered tolerable and had little effect on the operative visual field, PNMP was also employed to compare the effects of L-menthol and the control. According to the heterogeneity test, moderate heterogeneity existed in the

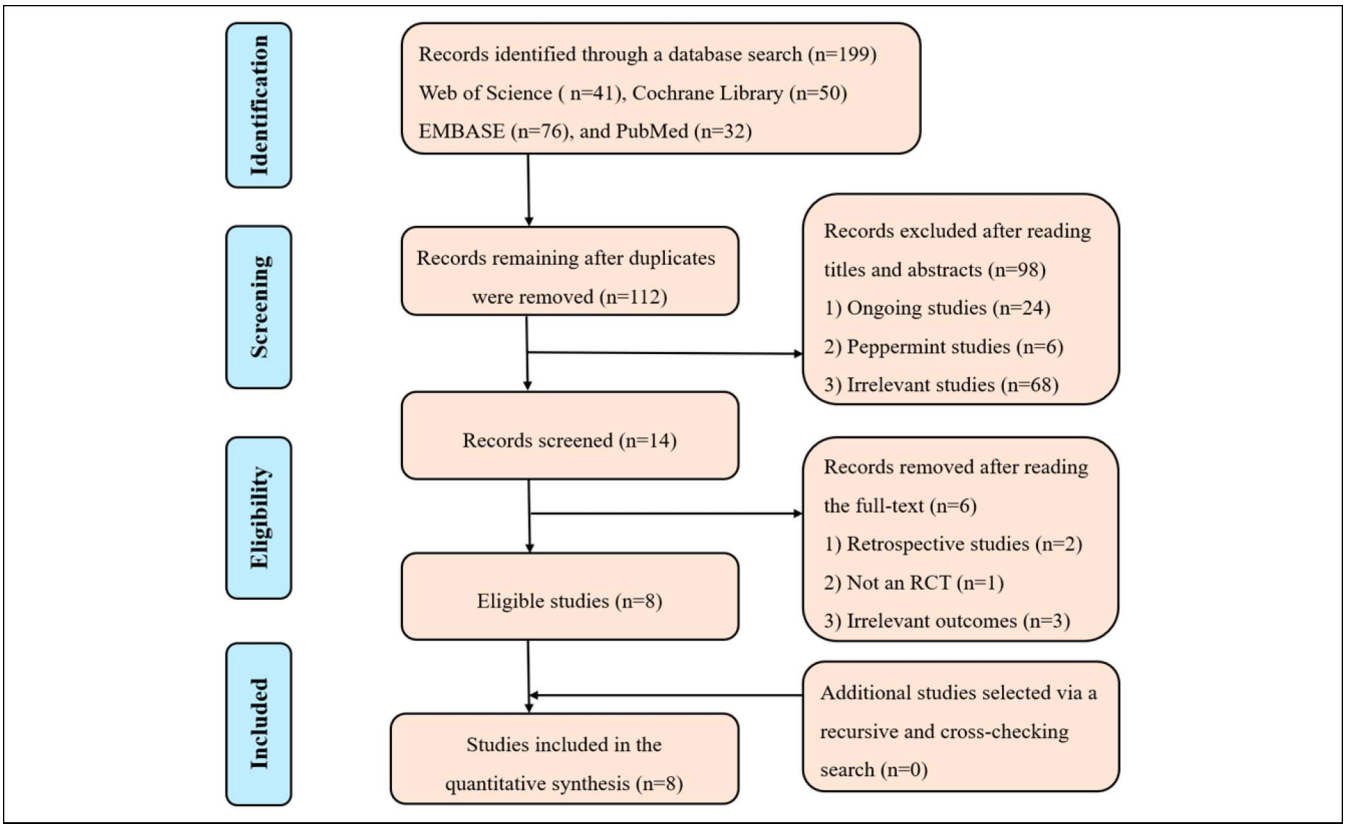

Figure 1. Flow chart of the study selection process. The study selection process mainly included 4 steps: Identification, Screening, Eligibility, and Included. RCT, randomized controlled trial.

PNP ($I^2 = 34\%$, $P = 0.20$) and PNMP ($I^2 = 27\%$, $P = 0.27$). Thus, a fixed-effect model was used to pool the data. Both the PNP (366/596, 61.4%, OR = 6.51, 95% confidence interval [CI] = 4.94–8.57, $P < 0.00001$) and PNMP (585/624, 93.8%; OR = 7.89, 95% CI = 5.03–12.39, $P < 0.00001$) of the L-menthol groups were higher than their control groups, as shown in Figure 3.

Secondary outcomes

Effects of L-menthol on ADR. ADR was provided by 3 colonoscopy studies (47,52,53). Of the 3 studies, 1 reported a significant improvement in the ADR of the L-menthol group compared with the control group (47), while the other 2 individual studies showed no significant differences. Given the striking heterogeneity ($I^2 = 79\%$, $P = 0.008$), a random-effects model was applied to calculate the OR. The result suggested that L-menthol did not significantly increase the ADR in patients undergoing colonoscopy (OR = 1.03, 95% CI = 0.54–1.99, $P = 0.92$), as shown in Figure 4.

Subgroup analysis

Subgroup analyses of the primary outcomes based on the dose and endoscope type were introduced. Three different doses (80, 160, and 320 mg) were investigated in 7 studies, one (57) of which employed a 3 × 1 dose-response design to simultaneously evaluate the 3 doses. Therefore, the placebo group of this study was compared with different doses. No significant difference was observed in PNP ($P = 0.26$, $I^2 = 25.8\%$) between the subgroups, while a significant difference was detected in PNMP ($P = 0.006$, $I^2 = 80.6\%$). Although, 80 mg of L-menthol did not significantly improve peristalsis compared to the placebo, it is too early to conclude that 80 mg of L-menthol was not effective because only 1 study was included in this subgroup. Therefore, additional studies employing a dose-response design are needed to confirm this finding. However, the analysis of both the PNP and PNMP in the 160 mg subgroup showed a higher OR effect size value and narrower CIs than the 80 mg and 320 mg subgroups. Overall, 160 mg of L-menthol was sufficiently effective and was currently recommend as the effective dosage to suppress gastrointestinal peristalsis.

Two endoscope types, gastroscopy and colonoscopy, were analyzed. The analysis of differences between subgroups did not reveal differences in PNP ($P = 0.89$, $I^2 = 0\%$) and PNMP ($P = 0.19$, $I^2 = 40.8\%$), as shown in Table 2.

Sensitivity analysis

Because moderate heterogeneity was observed in the pooled analysis of PNP ($I^2 = 34\%$, $P = 0.20$) and PNMP ($I^2 = 27\%$, $P = 0.27$), a sensitivity analysis was performed to identify the sources of heterogeneity. According to the sensitivity analysis plot, 1 study (53) had the largest off-center deviation compared to the other studies. Interestingly, the exclusion of this study resulted in the disappearance of heterogeneity in both PNP and PNMP. Hence, this study was the primary source of heterogeneity. The likely explanation was that this study employed a 2 × 2 factorial design to compare L-menthol + air with air and L-menthol + CO_2 with CO_2. Thus, the effects of the combination of L-menthol

Table 1. **The baseline characteristics of the 8 included studies**

Study	(1) Study design; (2) registration number; (3) endoscope type (details); (4) criteria used to evaluate peristalsis	Location	Age, yr, mean (range)/sample size (M/F)	Intervention/dosage (drug manufacturer)	Outcomes	Adverse events
Dhillon et al. (52)	(1) Randomized double-blind controlled trial; (2) unclear; (3) colonoscopy (colorectal cancer screening for healthy people); (4) unclear	Canada: University of Alberta Hospital	E: /61 (−/−); C: /61 (−/−)	E: L-menthol solution; C: Liquid simethicone (unclear)	PNP, ADR	No major side effects and no significant differences in abdominal distension or abdominal pain were observed between the 2 groups
Fujishiro et al. (45)	(1) 8 centers in randomized double-blind placebo-controlled trial (September to December 2011); (2) NCT01411176; (3) gastroscope (patients with EGC required EMR and ESD); (4) modified version of Niwa's Classification	Japan: (1) The University of Tokyo Hospital, (2) Toranomon Hospital, (3) National Cancer Center Hospital, (4) Cancer Institute Hospital of the Japanese Foundation for Cancer Research, (5) Kanto Medical Center at NTT East, (6) Kitasato University East Hospital, (7) Osaka Medical Center for Cancer and Cardiovascular Diseases, and (8) Wakayama Medical University Hospital	E: 70.4 (58–88)/42 (33/8); C: 69.6 (48–82)/41 (33/8)	E: L-menthol; 160 mg (0.8%, 20 mL); C: Placebo (Nihon Pharmaceutical, Tokyo, Japan)	PNMP, DSR, PS, PT	E: 15 (aspiration pneumonia, procedural pain, and postoperative bleeding); C: 12 (rash)
Hiki et al. 2011 (56)	(1) Randomized double-blind, placebo-controlled trial (May to August 2005); (2) unclear; (3) gastroscope (healthy male Japanese volunteers); (4) unclear	Japan: Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo	E: 47.3 (36–64)/18 (18/0); C: 51.2 (41–64)/6 (6/0)	E: L-menthol; 80 mg (0.8%, 10 mL) (n = 6); 160 mg (0.8%, 20 mL) (n = 6); 320 mg (0.8%, 40 mL) (n = 6); C: Placebo (Nihon Pharmaceutical, Tokyo, Japan)	OPRPM, PP	E: 10 (pharyngeal discomfort, upper abdominal pain, abdominal discomfort, abdominal distension, headache, choking sensation, ST-T change on an electrocardiogram, ventricular premature beats, increased blood amylase levels, and malaise); C: 2 (pharyngeal discomfort and diarrhea)
Hiki et al. 2011 (11)	(1) 6 centers in a randomized double-blind placebo-controlled trial (September 2008 to January 2009); (2) NCT00742599; (3) gastroscope (patients required treatment or follow-up for confirmed or suspected upper GI disease); (4) modified version of Niwa's Classification	Japan: (1) Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo; (2) Showa General Hospital (M.K.), Tokyo; (3) Kyoto Second Red Cross Hospital, Kyoto; (4) JR West Osaka General Hospital, Osaka; (5) Hiratsuka Gastroenterological Hospital (T.H.), Tokyo; (6)	E: 64.5 (28–85)/45 (27/18); C: 62.4 (28–84)/42 (27/15)	E: L-menthol; 160 mg (0.8%, 20 mL); C: Placebo (Nihon Pharmaceutical, Tokyo, Japan)	PNP, PNMP, PS, EIE	E: 4 (increased blood amylase levels, white blood cell counts, and urinary glucose levels); C:6 (increased blood amylase levels and positive urinary occult blood)

Table 1. (*continued*)

Study	(1) Study design; (2) registration number; (3) endoscope type (details); (4) criteria used to evaluate peristalsis	Location	Age, yr, mean (range)/sample size (M/F)	Intervention/dosage (drug manufacturer)	Outcomes	Adverse events
		Saiseikai Kawaguchi General Hospital, Saitama				
Hiki et al. (57)	(1) Multicenter randomized double-blind placebo-controlled trial (February to June 2007); (2) unclear; (3) gastroscope (patients required gastric endoscopy); (4) Niwa's Classification	Japan: not specified	E: 57.0 (22–77)/87 (53/34); C: 59.6 (22–82)/29 (18/11)	E: L-menthol; 80 mg (0.4%, 20 mL) (n = 30); 160 mg (0.8%, 20 mL) (n = 28); 320 mg (1.6%, 20 mL) (n = 29); C: Placebo (Nihon Pharmaceutical, Tokyo, Japan)	PNP, PNMP PS, EIE	E: (0.4%): 5 (supraventricular premature beats, diarrhea, and increased WBC counts); (0.8%): 3 (electrocardiogram ST-segment depression) (1.6%): 7 (premature ventricular contractions and headache); C:2 (premature ventricular contractions and supraventricular premature beats)
Inoue et al. (47)	(1) Randomized single-blind prospective placebo-controlled trial (April 2012 to February 2013); (2) UMIN000007972; (3) colonoscopy (patients required); (4) classification of colonic peristalsis	Japan: North Medical Center Kyoto Prefectural University of Medicine, Kyoto	E: 68 (33–87)/118 (65/53); C: 66 (27–90)/108 (54/54)	E: L-menthol; 320 mg (1.6%, 20 mL); C: Placebo (Kenei Pharmaceutica, Osaka, Japan)	PNP, PNMP ADR	No adverse events
Inoue et al. (53)	(1) Randomized single-blind prospective trial (September 2016 to September 2017); (2) UMIN 000023383; (3) colonoscopy (patients required); (4) classification of colonic peristalsis	Japan: Fukuchiyama City Hospital, Kyoto prefecture	E: 61 (23–89)/309 (148/161); C: 61 (23–92)/302 (146/156)	E: L-menthol + CO_2/air; 160 mg (0.8%, 20 mL); C: CO_2/air (MINCLEA; Nihon Seiyaku, Tokyo)	PNP, PNMP ADR	No adverse events
Mori et al. (46)	(1) Randomized prospective open-label placebo-controlled trial (June 4 to July 31, 2013); (2) UMIN000010859; (3) gastroscope (patients required); (4) modified version of Niwa's classification	Japan: Ichinomiya Nishi Hospital, Ichinomiya	E: 64 (25–94)/49 (23/26); C: 59 (26–82)/49 (29/20)	E: L-menthol; 160 mg (0.8%, 20 mL); C: Placebo (MINCLEA; Nihon Seiyaku, Tokyo)	PNMP, MCR	No serious adverse events

These characteristics included study design, registration number, endoscope type, criteria used to evaluate peristalsis, location, the age of participants, intervention dosage, outcomes, and information of adverse events.
ADR, adenoma detection rate; C, control group; E, experimental group; EGC, early gastric cancer; EIE, ease of the intragastric examination; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; MCR, mucosal change rate; OPRPM, occurrence of gastric peristalsis per min; PNMP, proportion of no or mild peristalsis; PNP, proportion of no peristalsis; PP, pharmacokinetic parameters; PS, peristalsis score; PT, procedure times; DSR, duration of sustained response.

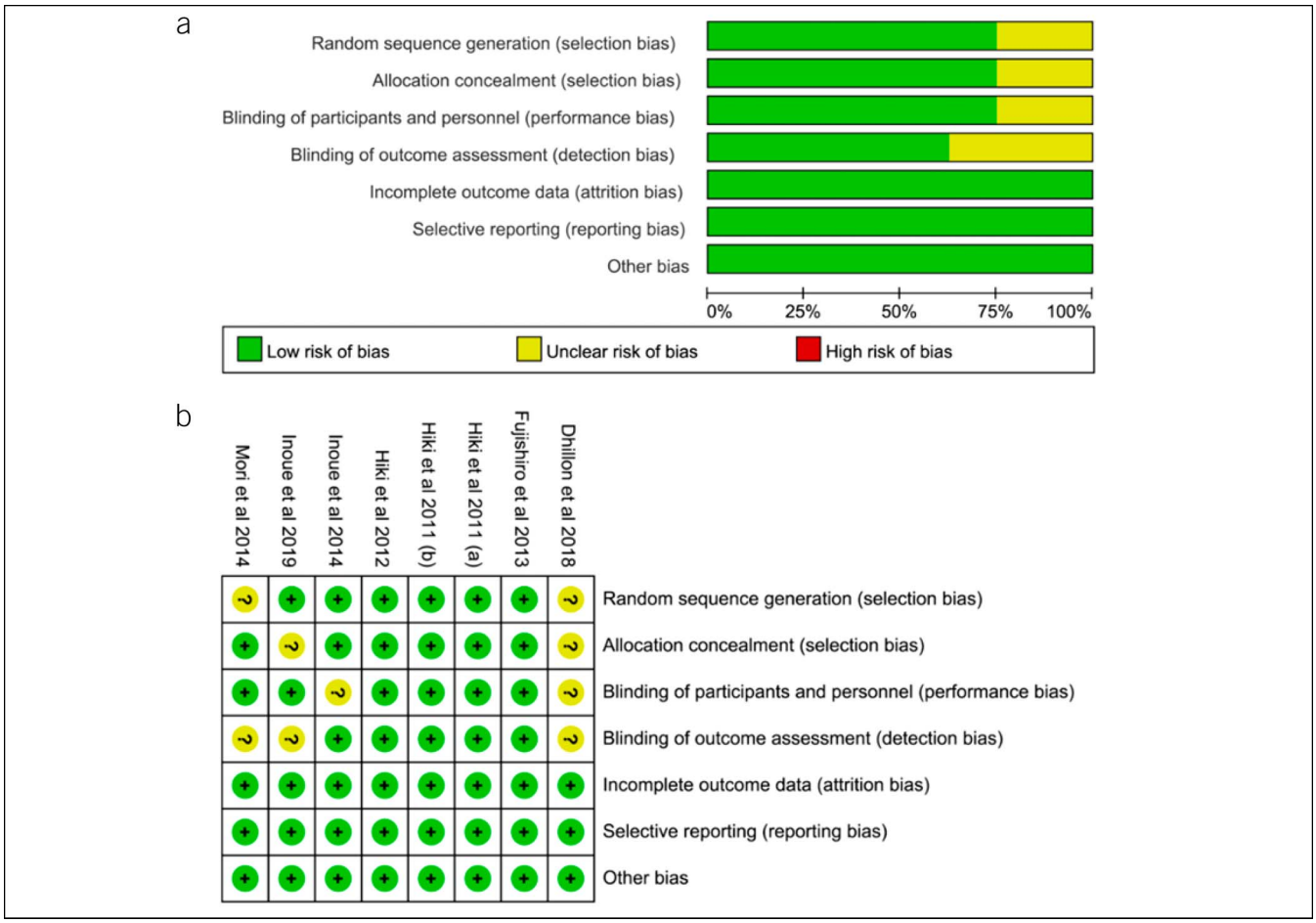

Figure 2. Risk of bias assessment of the included studies. (**a**) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (**b**) Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green (+), low risk of bias; yellow (?), unclear risk of bias; red (–), high risk of bias.

and air/CO_2 were significantly higher than the other studies using L-menthol alone. However, after excluding this study, the pooled results of PNP (OR = 6.51, 95% CI = 4.94–8.57, $P < 0.00001$ vs OR = 4.81, 95% CI = 3.18–7.27, $P < 0.00001$) and PNMP (OR = 7.89, 95% CI = 5.03–12.39, $P < 0.00001$ vs OR = 5.85, 95% CI = 3.57–9.60, $P < 0.00001$) before and after the intervention were consistent. Overall, the centralized small circles in the plots of the sensitivity analysis indicated a tolerable level of heterogeneity between studies, as shown in Figure 5.

Publication bias

Both Begg's and Egger's tests were applied to evaluate the possible publication bias in the PNP and PNMP. Begg's ($z = 0.24$, $Pr > |z| = 0.806$ and $z = 0.38$, $Pr > |z| = 0.707$) and Egger's tests ($t = -1.17$, 95% CI = −5.06 to 2.35, $P > |t| = 0.328$ and $t = 0.31$, 95% CI = −9.44 to 11.80, $P > |t| = 0.773$) did not reveal publication bias in PNP and PNMP, respectively. The results of the 2 detection methods were coincident.

Adverse events

All the included studies mentioned AEs. Two (46,52) only stated that no major side effects occurred, but the exact numbers were not reported. Hence, the remaining 6 studies reporting specific numbers were used for the quantitative synthesis, and 2 of the 6 studies (47,53) declared that no AEs occurred in their trial. These AEs mainly included procedural discomfort (pharyngeal discomfort, abdominal pain, abdominal distension, and a choking sensation) (45,56), cardiovascular disorders (ST-T change in an electrocardiogram and premature ventricular beats (56,57)) and rash, increased blood amylase levels, diarrhea, headache, changes in urinary glucose levels, positive urinary occult blood, etc. Although a severe AE (aspiration pneumonia) occurred and required further hospitalization of 1 patient in the L-menthol group in 1 study (45), it was considered unrelated to L-menthol. The pooled OR did not identify a significant difference between the 2 groups (OR = 1.40, 95% CI = 0.75–2.59, $P = 0.29$), as shown in Figure 6.

DISCUSSION

In this meta-analysis, 8 studies published from 2011 to 2019 were systematically evaluated, in which a total of 1,366 participants were randomly assigned to receive either L-menthol or placebo. The results indicated that L-menthol is a reliable anti-peristaltic agent for gastroscopy and colonoscopy. The anti-peristaltic effect of L-menthol is associated with a 61.4% and 93.8% success rate for the pooled PNP and PNMP, respectively.

Spasmolytics are routinely used in gastrointestinal endoscopic practice normally in the form of intravenous glucagon or parasympatholytic agents (Buscopan, Hyoscyamine sulphate and

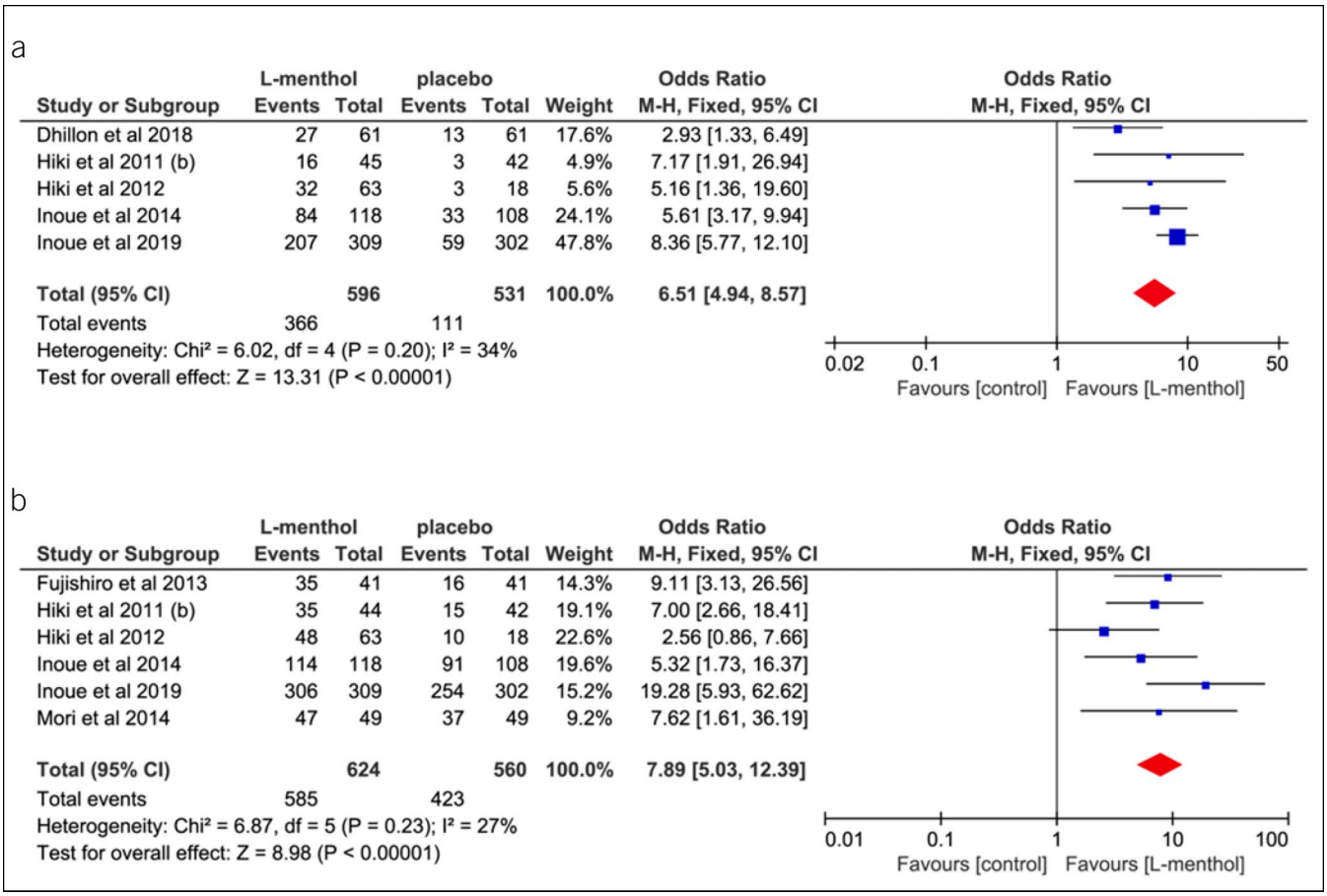

Figure 3. Forest plot and meta-analysis of (**a**) a proportion of no peristalsis (PNP) and (**b**) proportion of no or mild peristalsis (PNMP). The odds ratio for (**a**) PNP and (**b**) PNMP using fixed effects model was 6.51 (95% CI = 4.94–8.57) and 7.89 (95% CI = 5.03–12.39), respectively. CI, confidence interval.

Hyoscine). Several studies have compared their efficacy and safety. In an early prospective study (58), it was found that intravenous Buscopan 20 mg significantly increased the heart rate and decreased the systolic, diastolic, and mean arterial pressure, as compared to glucagon. In another study (25), a total of 240 consecutive patients over 40 years of age were recruited to compare the efficacy and safety of glucagon with Buscopan as upper gastrointestinal endoscopy premedication, and the result showed that the heart rates of patients treated with Buscopan 10 mg after premedication remained significantly higher than those of patients treated with glucagon. However, blood pressure, arterial oxygen saturation and number of retching episodes at this dose did not differ significantly between the 2 groups.

A subsequent study comparing peppermint oil and Buscopan also found that obvious side effects (dry mouth, blurred vision, and urinary retention, etc) occurred in Buscopan group, but not in peppermint oil group, and local peppermint oil displayed superior efficacy and fewer side effects than intravenous Buscopan (59). However, among the non-elderly patients (<70), the antispasmodic effect of peppermint oil was weaker than Buscopan, while among the elderly patients (≥70), its effect was comparable to Buscopan and was significantly more potent than glucagon (60).

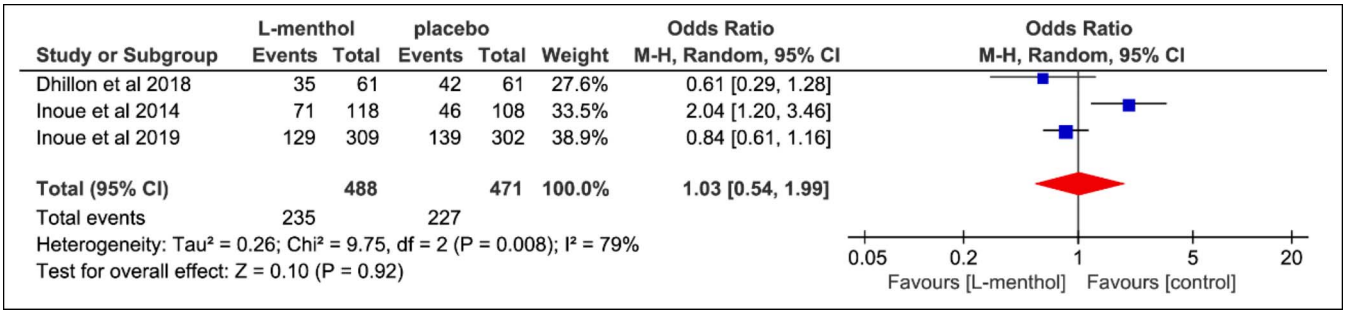

Figure 4. Forest plot and meta-analysis of adenoma detection rate. The odds ratio for adenoma detection rate using random effects model was 1.03 (95% CI = 0.54–1.99). CI, confidence interval.

Table 2. Main findings of this meta-analysis, including outcomes (PNP, PNMP, ADR, PS, and AE), and subgroup analysis results of PNP and PNMP, based on the dose (80 mg vs 160 mg vs 320 mg) and the endoscope type (colonoscopy vs gastroscope)

Outcomes	No. of trials	No. of participants (n_E/n_C)	Heterogeneity test				Effects model	Pooled effects (OR)	95% CI	*P* Value
			χ^2	*df*	I^2	*P* Value				
PNP	5	1,327 (596/531)	6.02	4	34%	0.20	Fixed	6.51	4.94–8.57	<0.00001
PNMP	6	1,184 (624/560)	6.87	5	27%	0.23	Fixed	7.89	5.03–12.39	<0.00001
ADR	3	959 (488/471)	9.75	2	79%	0.008	Random	1.03	0.54–1.99	0.92
AE	6	1,147 (619/528)	2.76	3	0%	0.43	Fixed	1.40	0.75–2.59	0.29
Subgroup analysis of PNP based on the dose (80 mg vs 160 mg vs 320 mg)										
80 mg	1	44 (26/18)	/	/	/	/	Fixed	2.65	0.60–11.62	0.2
160 mg	3	735 (373/362)	0.10	2	0%	0.95	Fixed	8.17	5.77–11.57	<0.00001
320 mg	2	262 (136/126)	0.45	1	0%	0.50	Fixed	6.02	3.52–10.28	<0.00001
Total	6	1,041 (535/506)	3.28	5	0%	0.66	Fixed	7.17	5.39–9.54	<0.00001
Test of differences between subgroups: $\chi^2 = 2.70$, $df = 2$ ($P = 0.26$), $I^2 = 25.8\%$										
Subgroup analysis of PNMP based on the dose (80 mg vs 160 mg vs 320 mg)										
80 mg	1	44 (26/18)	/	/	/	/	Random	1.09	0.32–3.67	0.89
160 mg	5	1,054 (536/518)	2.73	4	0%	0.60	Random	9.53	5.35–16.97	<0.00001
320 mg	1	36 (18/18)	/	/	/	/	Random	4.00	0.85–18.84	0.08
Total	7	1,136 (535/506)	13.27	6	55%	0.04	Random	6.13	2.88–13.06	<0.00001
Test of differences between subgroups: $\chi^2 = 10.32$, $df = 2$ ($P = 0.006$), $I^2 = 80.6\%$										
Subgroup analysis of PNP based on the endoscope type (colonoscopy vs gastroscope)										
Gastroscope	2	168 (108/60)	0.12	1	0%	0.73	Fixed	6.10	2.38–15.59	0.0002
Colonoscopy	3	959 (488/471)	5.88	2	66%	0.05	Fixed	6.55	4.91–8.74	<0.00001
Total	5	1,127 (596/531)	6.02	4	34%	0.20	Fixed	6.51	4.94–8.57	<0.00001
Test of differences between subgroups: $\chi^2 = 0.02$, $df = 1$ ($P = 0.89$), $I^2 = 0\%$										
Subgroup analysis of PNMP based on the endoscope type (colonoscopy vs gastroscope)										
Gastroscope	4	347 (197/150)	3.10	3	3%	0.38	Fixed	6.01	3.48–10.40	<0.00001
Colonoscopy	2	837 (427/410)	2.53	1	60%	0.11	Fixed	11.41	5.15–25.30	<0.00001
Total	6	1,184 (624/560)	6.87	5	27%	0.23	Fixed	7.89	5.03–12.39	<0.00001
Test of differences between subgroups: $\chi^2 = 1.69$, $df = 1$ ($P = 0.19$), $I^2 = 40.8\%$										

ADR, adenoma detection rate; AE, adverse event; CI, confidence interval; OR, odds ratio; PNMP, proportion of no or mild peristalsis; PNP, proportion of no peristalsis; PS, peristalsis score.

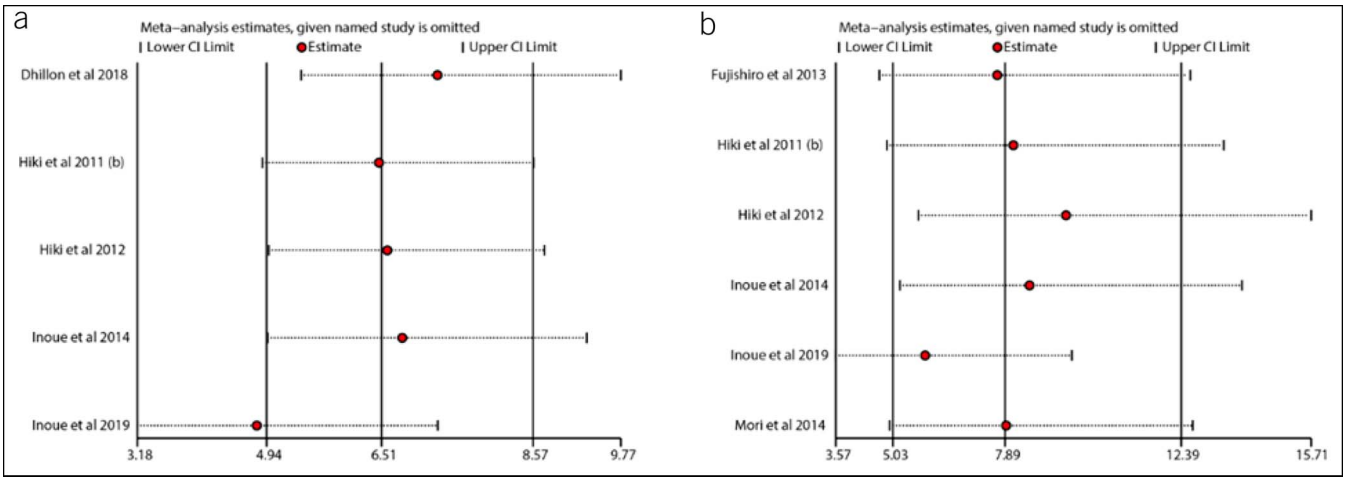

Figure 5. Plots of the sensitivity analysis of the primary outcomes. Dotted line: confidence interval. Little red circle: Value of odds ratio. (**a**) Five studies on the proportion of no peristalsis and (**b**) 6 studies on the proportion of no or mild peristalsis.

Two meta-analysis from 2014 (61,62) showed that intravenous Buscopan 20 mg did not significantly improve the polyps detection rate and/or ADR during colonoscopy, as compared to the same volume of saline solution. Although another meta-analysis revealed an improvement of polyps detection rate and ADR in the Buscopan group compared with the placebo group, it failed to reach statistical significance (63).

Overall, these antispasmodics ease the endoscopic procedure, but they do not offer significant benefit in lesion detection rate. Glucagon has a weaker effect on cardiopulmonary function during upper gastrointestinal endoscopy than Buscopan. Local peppermint oil has some potential advantages (as opposed to intravenous antispasmodics). However, the comparative studies on these antispasmodic drugs are limited. In addition, L-menthol, as another topical antispasmodic for endoscopy, has been rarely compared. Therefore, further 'head to head' studies and systematic reviews on these antispasmodics, are needed to systematically compare their efficacy and safety.

Because the gastric peristalsis was distinctly different from colorectal peristalsis, a subgroup analysis was conducted to differentiate the effects on the different types of peristalsis. Although there was no statistically significant difference between the 2 subgroups, the 2 colonoscopy studies (47,53) included in our meta-analysis showed a higher PNP and PNMP than the remaining 5 gastroscopy studies because the intestinal epithelial cells were the main absorption site for L-menthol (64) Similar result was found in a gastroscopy study which observed congestive more significant changes in the gastric mucosa of patients with atrophic gastritis after the administration of L-menthol than in patients without atrophy (46). A potential explanation for this finding is that atrophic gastritis is usually accompanied by intestinal metaplasia and contains some intestinal metaplasia cells that absorb L-menthol. In addition, hyperemia may have changed the permeability of the gastric mucosa, allowing L-menthol to readily penetrate the cell membrane. Consequently, the PNP and PNMP reported by Mori et al. were higher than that reported by other included gastroscopy studies. In another study (one of the excluded studies) (12), it was also shown that the anti-peristaltic effect of L-menthol on gastroscopy was more pronounced in patients with elevated levels of anti-*Helicobacter pylori* antibody and pepsinogen than patients without because *H. pylori* is considered a major culprit for the development of atrophic gastritis and intestinal metaplasia (65). Overall, after the intragastrointestinal spraying of L-menthol, patients undergoing colonoscopy benefited more than patients undergoing gastroscopy, and *H. pylori*-induced pathological changes in the gastric mucosa enhanced the anti-peristaltic effect of L-menthol.

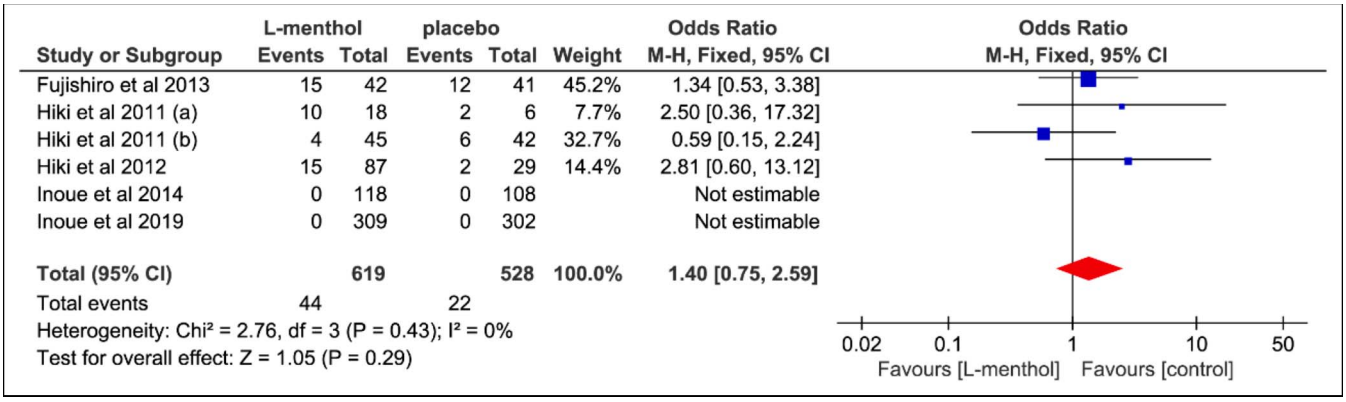

Figure 6. Forest plot and meta-analysis of adverse events. The odds ratio for adverse events using fixed effects model was 1.40 (95% CI = 0.75–2.59). CI, confidence interval.

In addition to assessing peristalsis using PNP and PNMP, a previous meta-analysis (66) assess the possible effects of peppermint oil on ADR. Unfortunately, despite the improvement in peristalsis, their pooled results suggested that the desired effect of peppermint oil on ADR was not significantly increased. However, a more recent meta-analysis (67) showed that peppermint oil was associated with a significant improvement of ADR. Therefore, their conclusions on the effect of peppermint oil on ADR were inconsistent. In our meta-analysis, the pooled result from the 3 colonoscopy studies suggested that ADR was not associated with L-menthol. The possible explanation is that peppermint oil is composed of 30%–50% L-menthol, 14%–32% L-menthone and small amounts of other chemical constituents, and therefore the anti-peristaltic effect of this preparation differs from monomeric L-menthol. More likely, significant heterogeneity existed in this outcome and only 2 studies evaluated this outcome in the previous 2 reviews. In addition, whether the endoscopies are performed by experienced endoscopists may be another factor that affects outcomes.

In this review, various outcomes have been reported, while most of the included studies used PNP and PNMP as the main endpoints. Although these studies appointed an independent agency to assess peristalsis through recorded endoscopic videos, the analysis is still somewhat subjective. A recent study (68) introduced optical imaging to identify the margin of early gastric cancer by comparing the color changes before and after spraying L-menthol using light imaging to minimize bias, and found that the proportion of patients displaying color changes in stomach mucosa was significant. Thus, this technique represents a more objective method to assess the effect of L-menthol. Despite the impersonal ADR reported in our meta-analysis, only 3 studies determine this outcome, and therefore additional clinical trials are needed to investigate this outcome. In addition, other objective and important outcomes, such as the time of the endoscopic submucosal dissection, endoscopic mucosal resection procedures and detection rates for other lesions (e.g., polyps, precancerous lesions, early cancer, and neoplasms) should also be evaluated in future studies.

Although previous animal studies indicated that the anti-peristaltic effect of L-menthol was associated with the transmembrane migration of calcium ions, only 1 included study (56) detailed pharmacokinetic parameters of L-menthol after administration. In addition, the interaction between the gastric mucosa and menthol may differ from the interaction with the colorectal mucosa. Thus, the precise mechanisms by which L-menthol relaxes the gastrointestinal smooth muscle warrant further investigation.

Strength and limitations

The main advantage of this study was that this meta-analysis provides systematic evidence for the clinical use of L-menthol to suppress gastrointestinal peristalsis during endoscopy. Compared with Buscopan and glucagon, it is easy to administer with an endoscope channel, even multiple doses, and does not produce severe adverse reactions. We also confirmed for the first time that a dose of 160 mg was sufficient based on the persistent effectiveness and limited AEs.

However, this meta-analysis had several limitations. First, we only searched the major English language electronic databases. Consequently, some studies that meet our inclusion criteria and are published in other languages or databases may be excluded, particularly clinical trials published in Japanese and included in Japanese local electronic databases, because L-menthol is mainly used in Japan. Second, almost all of the included studies were conducted in Japan. Thus, the general applicability of our findings was limited. Third, a certain degree of selective reporting bias may exist because 3 studies (52,56,57) were not registered.

Despite the above limitations, the findings of this study support the use of L-menthol to suppress gastrointestinal peristalsis during endoscopic procedure.

CONFLICTS OF INTEREST

Guarantor of the article: Youping Liu, PhD.
Specific author contributions: Qiang You, PhD and Lan Li, PhD, contributed equally to this work. Q.Y. and Y.L.: conception and design. Q.Y. and H.C.: literature search. L.L., X.C., L.C., and Q.Y.: data extraction, quality assessment, statistical analysis and interpretation of data. Q.Y.: drafting the manuscript. X.C. and Y.L.: manuscript revision.
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