Original Article

Antiperistaltic effect and safety of \(\text{L-}
\text{menthol oral solution}
\) on gastric mucosa for upper gastrointestinal endoscopy in Chinese patients: Phase III, multicenter, randomized, double-blind, placebo-controlled study

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**Objective:** The topical antispasmodic agent \(\text{L-}
\text{menthol is commonly used for gastric peristalsis suppression during}
\) diagnostic upper gastrointestinal (GI) endoscopy. We evaluated the efficacy and safety of a single dose \(\text{L-}
\text{menthol solution in suppressing gastric peristalsis during upper GI}
\) endoscopy in Chinese patients.

**Methods:** In this phase III, multicenter, randomized, double-blind, placebo-controlled study (ClinicalTrials.gov: NCT03263910), 220 patients scheduled to undergo upper GI endoscopy at five Chinese referral centers received a single dose of either 160 mg of \(\text{L-}
\text{menthol (n = 109) or placebo (n = 111). Both treatments were sprayed endoscopically on the}
\) gastric mucosa. An independent committee evaluated the degree of gastric peristalsis (peristaltic score: grade 1–5).

**Results:** At baseline, the proportion of patients with grade 1 peristalsis (no peristalsis) did not differ between the groups. The proportion of patients with grade 1 peristalsis post-treatment was significantly higher in the \(\text{L-}
\text{menthol group (40.37%, 44/109) versus the placebo group (16.22%, 18/111;}
\) \(P < 0.001\)); the difference between the groups was 24.15% (95% confidence interval: 12.67%–35.63%; \(P < 0.001\)). In the \(\text{L-}
\text{menthol group, 61.47% of patients had grade 1 peristalsis after}
\) endoscopy versus 24.55% in the placebo group (\(P < 0.001\)). The ease of intragastric examination correlated significantly with the grade of peristalsis. The incidence of adverse events was comparable between the groups (\(P = 0.340\)).

**Conclusions:** During upper GI endoscopy, a single dose of \(\text{L-}
\text{menthol solution (160 mg) sprayed on the gastric mucosa significantly attenuated gastric peristalsis versus placebo, thereby}
\) improving the visual stability without any safety concerns.

**Key words:** Chinese, gastric peristalsis, \(\text{L-}
\text{menthol, upper gastrointestinal endoscopy}

INTRODUCTION

Upper gastrointestinal (GI) endoscopy is indicated for several GI conditions such as *Helicobacter pylori* and other GI infections, and early gastric cancer.\(^1\,^2\) Gastric motility or peristalsis plays a significant role in directing the ingested food to the definitive positions in the digestive tract and has attracted considerable interest from the researchers.\(^1\,^3\,^4\) However, excessive peristalsis may obstruct mucosal visual clarity during endoscopy.\(^5\) Although anticholinergic drugs, antispasmodic agents (hyoscine-N-butyl bromide), and glucagon could suppress gastric peristalsis, the associated side effects such as severe heart disease, glaucoma, delayed hypoglycemia, and prostatic hypertrophy limited their clinical application.\(^1\,^4\,^6\,^7\)
L-menthol is a new topical antispasmodic drug, an active extract from peppermint oil. With high clarity and stable chemical properties, L-menthol is more effective than the intramuscular injection of butyl scopolamine bromide. L-menthol had a dose-dependent effect in suppressing gastric peristalsis and a positive correlation with the ease of observation in a phase III placebo-controlled study. Antiperistaltic and antispasmodic effects of peppermint oil or L-menthol have been studied in several trials. Japanese researchers have confirmed that L-menthol could improve the stability of the visual field both in endoscopic diagnosis and treatment, including gastric endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). thereby making it a useful antispasmodic drug for upper GI endoscopy.

Although evidence on the safety and efficacy of L-menthol during upper GI endoscopy is available from several countries, its effectiveness remains unexplored in the Chinese population. We investigated the safety and efficacy of using L-menthol on gastric motility as an inhibitor of peristalsis for the first time in Chinese patients who needed gastroscopy.

**METHODS**

**Study design and patients**

This phase III (ClinicalTrials.gov: NCT03263910), multicenter, double-blind, placebo-controlled study was conducted at five centers in China (August 2017—August 2018). The patients (N = 220) were randomized (1:1) to receive a single dose of 160 mg L-menthol (n = 109) or placebo (n = 111), sprayed endoscopically on the gastric mucosa.

Eligible patients were 18–80 years old and advised for upper endoscopy examination or follow-up for confirmed or suspected upper GI disease. Patients with previous surgery involving the upper GI tract, severe gastric stenosis or deformation, reflux esophagitis (Los Angeles classification B, C, or D), active gastric or duodenal ulcer (A1, A2), and those receiving chemotherapy or radiotherapy for cancer were excluded. Patients with reduced cardiac function (New York Heart Association cardiac function classification grade III/higher), upper GI bleeding requiring hemostasis, a history of shock, hypersensitivity to L-menthol or peppermint oil, and pregnant women were also excluded.

Written informed consent from patients was obtained before enrolment. The study was approved by the institutional review board of each participating center (main institutional review board approval number: 2017-P1-Drug 016-02) and performed following Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. Neither the methods nor the outcomes were changed after trial commencement.

**Study outcomes**

The primary outcome was the proportion of patients with no peristalsis (grade 1 peristalsis) after treatment and at the end of endoscopy. Secondary outcomes included the proportion of patients with grade 1 peristalsis for each period (before and after treatment, and at the end of endoscopy) in both groups, the proportion of patients based on the peristaltic grade for each period in each group, the proportion of patients evaluated for the ease of intragastric examination by using a 4-grade scale (very easy, easy, slightly difficult and difficult) based on whether gastric peristalsis after treatment interfered with the endoscopic examination (Table 1), and the correlation between the time interval from the completion of the drug spraying to the end of endoscopy and peristaltic grade. Safety data (laboratory findings, clinical symptoms, and physical findings), adverse events (AEs), and adverse drug reactions (ADRs) were evaluated throughout the study (by observing patients for 7 + 3 days post-endoscopy).

**Endoscopic procedures**

After confirming patient eligibility by endoscopy, L-menthol or placebo were administered according to the randomization number. The randomization code was computer-generated by independent staff members at each referral center, and any potential bias was strictly avoided. The treatment assignments were contained in opaque, sealed envelopes to ensure blinding. Since L-menthol could be distinguished from the placebo by its odor, the endoscopy room was pre-filled with the fragrance of peppermint oil. Additionally, investigators were required to wear gloves and masks impregnated with the aroma of peppermint oil.

All patients were administered an oral mucolytic agent and an anti-foaming agent before endoscopy. Lidocaine hydrochloride mucilage was used for pharyngeal anesthesia. Sedation was not used. Investigators checked the stomach and duodenum first to ensure patient eligibility. Solution of 0.8% L-menthol (160 mg) or placebo pre-filled in a 20 mL syringe was directly sprayed on the antrum via the endoscopic biopsy channel. The residual liquid was pushed out by air.

All investigators were well-trained. The procedural video was recorded as reported by Hiki et al. Endoscopic images of the pyloric ring and the area around the gastric angle were
recorded for 45 s each before treatment, after treatment (from 90 to 135 s post-treatment), and at the end of endoscopy.

To ensure the objective evaluation, gastric peristalsis was scored by an independent Endoscopic Video Evaluation Committee (Table 1), consisting of three board-certified endoscopists not involved in the endoscopy examination. Each committee member independently evaluated peristalsis on the videotapes of images. If the peristalsis grades differed among members, images were reviewed again to reach a consensus.

**Statistical analysis**

Based on the results of a phase III clinical study, with the expected response rates of 35% in the L-menthol group and 7% in the placebo group, and using Fisher’s exact test to assess the between-groups difference at two-tailed significance level of 5% and power of 90%, the target sample size of 39 per group was estimated. However, as per the Provisions for Drug Registration (Order No. 28, valid until July 2020) that recommended inclusion of ≥100 patients per group and considering 8–9% expected patient dropout rate, we expanded the sample size to 110 per group. We expected that a large trial would likely result in sufficient number of patients in other peristaltic grades for our secondary and exploratory analyses.

No interim analyses were performed. Quantitative data were summarized as mean (standard deviation [SD]). A Kendall rank correlation coefficient was calculated for all three observers combined. The primary outcome, ease of intragastric examination, and stratified analyses were assessed by the Cochran–Mantel–Haenszel test. The two-tailed significance level was 5%. The change in proportion of patients by peristaltic grades in each period was analyzed using the McNemar test. In an exploratory analysis of a subgroup of patients with grade 1 peristalsis before treatment, the proportion of those who remained in grade 1 after treatment was compared in the L-menthol group versus the placebo group. Also, the correlations between the peristaltic grade (5-grade scale) and ease of intragastric observation (4-grade scale) for each period after treatment and at the end of endoscopy were analyzed using the Spearman rank correlation coefficients. The incidences of AEs and ADRs were

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**Table 1** Evaluation of gastric peristalsis

| Ease of intragastric observation | Classification of gastric peristalsis† |
|----------------------------------|----------------------------------------|
| Very easy: No peristalsis was noted and no interference with observation | Grade 1: No peristalsis |
| Easy: Mild peristalsis was noted, but observation was performed without interference | Grade 2: Mild peristalsis |
| Slightly difficult: Peristalsis was noted and interfered with observation slightly | Grade 3: Moderate peristalsis |
| Difficult: Marked peristalsis was noted and made observation difficult | Grade 4: Vigorous peristalsis |

†This classification was partially modified from the Niwa et al. classification method.11
analyzed by using the Fisher exact test. All analyses were performed using SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population

Of 254 screened patients, 34 did not undergo treatment because of either consent withdrawal (n = 7) or meeting the exclusion criteria (n = 27). The remaining 220 patients underwent endoscopic examination and treatment according to the study protocol. There were negligible dropouts; 105/109 patients in the L-menthol group and 109/111 patients in the placebo group completed the study. The details for patient disposition are provided in Figure 1.

The endoscopic findings identified gastritis in 82.6% versus 78.4% of patients in the L-menthol and the placebo groups, respectively. Overall, the demographic and baseline characteristics were comparable between the groups (Table 2) with no significant differences. The Kendall rank correlation showed that the interobserver agreement of gastric peristalsis by the Endoscopic Video Evaluation Committee was 0.906 before treatment, 0.902 after treatment, and 0.902 at the end of endoscopy (all P < 0.001), with overall interobserver agreement considered acceptable.

Grade 1 peristalsis

The proportion of patients with no (grade 1) gastric peristalsis after treatment was significantly higher in the L-menthol group (40.37%; 44/109) versus the placebo group (16.22%; 18/111), between-group difference, 24.15% (95% confidence interval [CI] 12.67%–35.63%, P < 0.001; Fig. 2). Also, the proportion of patients with grade 1 peristalsis for each period in the L-menthol group was 38.53% (42/109) before treatment, 52.29% (57/109) after treatment, and 61.47% (67/109) at the end of endoscopy (Fig. 3). In the L-menthol group, the proportion of patients with grade 1 peristalsis was significantly different in before and after treatment periods (P = 0.011) and also between before treatment and the end of endoscopy (P < 0.001; Fig. 3). However, there was no significant difference between the corresponding time points in the placebo group (P = 0.117 and P = 0.144, respectively). The corresponding proportion of patients with grade 1 peristalsis in the placebo group were 32.43% (36/111), 25.23% (28/111), and 24.55% (27/110), respectively (Fig. 3). Compared with placebo, the L-menthol group had higher proportions of patients with grade 1 peristalsis after treatment as well as at the end of endoscopy (both P < 0.001; Fig. 3). In the subgroup analysis of patients who had grade 1 peristalsis before treatment, the proportion of patients who maintained grade 1 peristalsis after treatment was significantly higher in the L-menthol group versus the placebo group (P < 0.05, Fig. 4).

The proportion of patients according to peristaltic grades at different periods in each group

The proportions of patients by the peristaltic grades for each period in each group are presented in Figure 5. No patient had grade 5 peristalsis at any period in either group. In the L-menthol group, the proportions of patients in different
peristaltic grades were significantly different at the end of endoscopy versus before treatment ($P = 0.002$). However, the difference in peristalsis grades after treatment was not statistically significant ($P = 0.069$). In the placebo group, there were no significant changes in peristalsis grades both after treatment ($P = 0.210$) and at the end of the endoscopy ($P = 0.648$) compared with those before treatment. Overall, compared with the placebo group, the L-menthol group had higher proportions of patients with lower peristaltic grades after treatment and at the end of endoscopy ($P < 0.001$). Thus, the proportion of patients with no peristalsis seemed to be increasing in the L-menthol group but decreasing in the placebo group.

### Ease of intragastric examination

The proportion of patients reporting ease of intragastric examination as very easy or easy was 88.07% (96/109) in the L-menthol group and 79.28% (88/111) in the placebo group ($P = 0.078$). No patient evaluated the process as ‘difficult’ at any period in either group. Thus, in the L-menthol group patients with no or mild peristalsis (grade 1 or 2) at the end of endoscopy (87/109), the intragastric examination was very easy or easy (88.07%).
Correlation between the peristaltic grade and ease of intragastric examination

A significant correlation was observed between the ease of intragastric examination and the peristaltic grade after treatment ($r = 0.221$, $P = 0.001$) and at the end of endoscopy ($r = 0.294$, $P < 0.001$) (Table 3). No significant correlation was observed between the peristaltic grade (grades 1 to 4) and the time taken from the treatment to the end of endoscopy in the l-menthol group and the placebo group (Table 4).

Safety

The incidence of AEs or ADRs did not differ significantly between the groups: AEs were reported in 11.93% (13/109) of patients in the l-menthol group and 17.12% (19/111) in the placebo group ($P = 0.340$; Table 5); ADRs were reported in 2.75% (3/109) of patients in the l-menthol group and 6.31% (7/111) in the placebo group ($P = 0.333$) (Table 6). No serious AEs and deaths were reported.

DISCUSSION

THE CURRENT STUDY demonstrated that topical spray with l-menthol significantly suppressed gastric peristalsis during endoscopy compared to placebo. This is the first clinical trial evaluating the efficacy of l-menthol as an antiperistaltic drug to facilitate gastric endoscopy in the Chinese population. Additionally, no safety concern associated with the use of l-menthol during gastric endoscopy was observed in this population. This study expands on the earlier findings observed in a similar phase III study conducted in Japan.10

In the current study, a significant increase in grade 1 peristalsis, both after the treatment and at the end of endoscopy, was observed in the l-menthol group versus the placebo group. A distinct pattern of more grade 1 peristalsis was found in the l-menthol group during the endoscopic examination though a similar pattern was not observed in the placebo group. The new endoscopic classification system reported by Hiki et al.10 was more objective and provided reliable, accurate results. The proportion of complete suppression of gastric peristaltic in the l-menthol group in the current study is consistent with that in previous studies (35%–50%).10,12,14 The proportions of patients based on the peristaltic grades for each period also appear to be consistent with these studies.10,12,14 The validated methodology12 exploiting video recording of endoscopic images was used in the present study to minimize expected biases. The independent evaluation of recorded images was performed by experienced professional endoscopists, excluding the influence and effects induced by the investigator and the factors concerning hospitals.12 Here, the emphasis has been on the interobserver variability of the scale exploited in the grading of peristalsis.12 Thus, the primary outcome of the absolute status (presence/absence of
gastric peristalsis) after administration and at the end of endoscopy was consistent with previous studies.\textsuperscript{1,10,12,14}

Additionally, we assessed the effect of intervention in patients who had grade 1 peristalsis before treatment. In this subgroup, the proportion of patients who remained in the grade 1 peristalsis group after treatment was significantly higher ($P < 0.05$) in the L-menthol group (64.29\%) than the placebo group (33.33\%). Gastric peristalsis originates from gag reflex or any physical stimulus while conducting upper GI endoscopy. Our results suggest that spraying L-menthol not only weakens the degree of peristalsis but also suppresses its development. Thus, even for patients without any peristalsis before, L-menthol spraying may suppress the onset of peristalsis while undergoing endoscopy, especially useful for more complicated procedures (eg, magnifying endoscopy, EMR, ESD). Our study also showed that the suppression of gastric peristalsis correlated with the ease of intragastric examination. However, there was no significant correlation between the peristaltic grade (grades 1 to 4) and the procedural time. The investigation time was similar in both groups since this study was designed based on routine endoscopy examination and was performed by experienced, board-certified endoscopists. Further studies are required to demonstrate whether peristalsis suppression during a more complicated endoscopic procedure such as therapeutic endoscopy and magnifying endoscopy can improve therapeutic and diagnostic efficacy or reduce the procedure duration. Overall, the efficacy findings in our study were

![Figure 5](image)

**Figure 5** Proportion of patients according to peristaltic grade for each period in the L-menthol and placebo group. Numbers shown on the stacked columns indicate the number of patients in each subgroup.

| Peristaltic grades | Ease of intragastric examination, n (%) | Spearman rank value | $P$-value |
|--------------------|----------------------------------------|---------------------|-----------|
|                    | Very easy | Easy | Slightly difficult |
| After treatment    |           |     |                    |
| 1 (n = 85)         | 13 (15.29) | 62 (72.94) | 10 (11.76) | 0.221 | 0.001 |
| 2 (n = 41)         | 7 (17.07) | 33 (80.49) | 1 (2.44) |          |       |
| 3 (n = 70)         | 4 (5.71) | 48 (68.57) | 18 (25.71) |          |       |
| 4 (n = 24)         | 1 (4.17) | 16 (66.67) | 7 (29.17) |          |       |
| At the end endoscopy |          |     |                    |
| 1 (n = 94)         | 16 (17.02) | 72 (76.60) | 6 (6.38) | 0.294 | <0.001 |
| 2 (n = 47)         | 4 (8.51) | 37 (78.72) | 6 (12.77) |          |       |
| 3 (n = 57)         | 4 (7.02) | 38 (66.77) | 15 (26.32) |          |       |
| 4 (n = 21)         | 1 (4.76) | 12 (57.14) | 8 (38.10) |          |       |

Values shown for ease of intragastric examination are percentages; 1–4 = grades of peristalsis.
### Table 4  Correlation between the grade of peristalsis and the endoscopic examination time

| Group       | Endoscopic examination time, s, Mean (SD) | Spearman rank value | P-value |
|-------------|-----------------------------------------|---------------------|---------|
|             | Peristalsis grades                      |                     |         |
|             | 1           | 2                      | 3         | 4         |
| L-Menthol   | 7.10 (2.36) | 6.92 (2.43)            | 6.02 (1.53)| 5.24 (0.76)| –0.21               | 0.028 |
|             | n = 67     | n = 20                 | n = 17     | n = 5     |
| Placebo     | 6.71 (2.36) | 6.60 (1.82)            | 6.71 (2.18)| 6.65 (2.57)| 0.001               | 0.993 |
|             | n = 27     | n = 27                 | n = 40     | n = 16    |

1–4 = grades of peristalsis; SD = standard deviation.

### Table 5  Frequency of adverse events

| Adverse event                                      | L-Menthol (N = 109) | Placebo (N = 111) | P-value |
|----------------------------------------------------|---------------------|-------------------|---------|
|                                                    | N Patients (%)      | N Patients (%)    |         |
| Total                                              | 16 13 (11.93)       | 20 19 (17.12)     | 0.340   |
| Metabolic and nutritional disorders                | 0 0 (0.00)          | 2 2 (1.80)        |         |
| Hypertriglyceridemia                               | 0 0 (0.00)          | 2 2 (1.80)        |         |
| Infectious diseases                                | 4 4 (3.67)          | 5 5 (4.50)        |         |
| Urinary tract infection                            | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Upper respiratory tract infection                  | 2 2 (1.83)          | 5 5 (4.50)        |         |
| Bronchitis                                         | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Abnormal laboratory examination                    | 6 6 (5.50)          | 7 6 (5.41)        |         |
| Increased white blood cell count                   | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Urinary leukocyte esterase positive                 | 1 1 (0.92)          | 3 3 (2.70)        |         |
| Urine protein positive                             | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Urine sugar positive                               | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Positive urine occult blood                       | 1 1 (0.92)          | 2 2 (1.80)        |         |
| Urine bacteria positive                            | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Elevated blood triglycerides                       | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Increased blood creatine phosphokinase             | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Nervous system disease                             | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Dizziness                                          | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Respiratory system, chest and mediastinal diseases | 2 1 (0.92)          | 0 0 (0.00)        |         |
| Epistaxis                                          | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Oropharyngeal pain                                 | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Skin and subcutaneous tissue diseases              | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Eczema                                             | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Systemic diseases and various reactions at the site | 1 1 (0.92)          | 0 0 (0.00)        |         |
| of administration                                  | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Fever                                              | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Kidney and urinary system diseases                 | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Hematuria                                          | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Gastrointestinal diseases                          | 1 1 (0.92)          | 4 4 (3.60)        |         |
| Abdominal pain                                     | 0 0 (0.00)          | 1 1 (0.90)        |         |
| Diarrhea                                           | 1 1 (0.92)          | 3 3 (2.70)        |         |
| Heart disease                                      | 1 1 (0.92)          | 0 0 (0.00)        |         |
| Palpitations                                       | 1 1 (0.92)          | 0 0 (0.00)        |         |
similar to those observed previously suggesting potential generalizability. Nevertheless, one should interpret the findings with caution, considering differences in study design, population, study parameters, endpoints, and overall settings.

Regarding safety, L-menthol was associated with a low risk of life-threatening conditions and adverse effects. In our study, the ADRs in the L-menthol group included diarrhea, fever, and leukocyte elevation in one (0.92%) patient each. In the placebo group, there were three (2.70%) patients with diarrhea, two (1.80%) with positive occult blood in urine, and one (0.90%) patient each with abdominal pain and creatine phosphokinase elevation. Thus, our study did not demonstrate any significant ADRs or AEs. One of the potential features reported L-menthol-induced edematous change of gastric mucosa, which subsequently clarified the margin of various gastric lesions, including erosion, ulcer, and early cancer.

Comparable baseline characteristics and determination of other peristaltic grades at defined time points in both study groups were the strengths of this study. The relatively large sample size versus other studies and the estimated sample size may be considered as a limitation. Large sample size trials may lead to statistically significant results with smaller effect sizes; however, our results were significant both statistically and clinically. Other limitations were not investigating the dose-response effects of L-menthol on gastric motility and not determining whether suppression of peristalsis contributed to improved detection and diagnosis of early cancer and other small lesions.

To date, very less-resourced and limited information exists on the usefulness and impact of L-menthol on the diagnosis of gastric cancer. In this study, the endoscopic finding did not differ in both groups, and only one patient in the L-menthol group had gastric cancer diagnosed by biopsy. Further study is needed to clarify whether the peristaltic suppression is more effective in the detection of lesions during endoscopy screening.

In conclusion, in upper GI endoscopy, L-menthol sprayed on the gastric mucosa significantly suppressed gastric peristalsis with minor ADRs versus placebo in the Chinese population, complementing the findings of Japanese study findings by Hiki et al. and other studies. Our findings could direct future clinical trials on efficacy and safety of L-menthol for gastric endoscopy in global and Asian populations.

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflicts of interest for this article.

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REFERENCES

1 Hiki N, Kaminishi M, Hasunuma T et al. A phase I study evaluating tolerability, pharmacokinetics, and preliminary efficacy of L-menthol in upper gastrointestinal endoscopy. Clin Pharmacol Ther 2011; 90: 221–8.
2. Leung WK, Wu MS, Kakugawa Y et al. Screening for gastric cancer in Asia: Current evidence and practice. *Lancet Oncol* 2008; 9: 279–87.

3. Park S, Chun HJ, Kim ES et al. The effect of peppermint oil on peristalsis during gastroscopy [in Korean with English abstract]. *Clin Endosc* 2009; 39: 199–204.

4. Hashimoto T, Adachi K, Ishimura N et al. Safety and efficacy of glucagon as a premedication for upper gastrointestinal endoscopy—a comparative study with butyl scopolamine bromide. *Aliment Pharmacol Ther* 2002; 16: 111–8.

5. Katoh K, Nomura M, Iga A et al. Comparison of gastric peristalsis inhibition by scopolamine butylbromide and glucagon: evaluation by electrogastrography and analysis of heart rate variability. *J Gastroenterol* 2003; 38: 629–35.

6. Saito N, Seshimo A, Kameoka S. Underlying—disease risk for antispasmodic premedication in older patients undergoing investigations of the gastrointestinal tract. *Clin Med Gastroenterol* 2008; 1: 27–31.

7. Umegaki E, Abe S, Tokioka S et al. Risk management for gastrointestinal endoscopy in elderly patients: Questionnaire for patients undergoing gastrointestinal endoscopy. *J Clin Biochem Nutr* 2010; 46: 73–80.

8. Hawthorn M, Ferrante J, Luchowski E et al. The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. *Aliment Pharmacol Ther* 1988; 2: 101–18.

9. Chiu PWY, Ueda N, Singh R et al. An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. *Gut* 2019; 68: 186–97.

10. Hiki N, Kaminishi M, Yasuda K et al. Antiperistaltic effect and safety of L-menthol sprayed on the gastric mucosa for upper GI endoscopy: A phase III, multicenter, randomized, double-blind, placebo-controlled study. *Gastrointest Endosc* 2011; 73: 932–41.

11. Hiki N, Kurosaka H, Tatsutomi Y et al. Peppermint oil reduces gastric spasm during upper endoscopy: A randomized, double-blind, double-dummy controlled trial. *Gastrointest Endosc* 2003; 57: 475–82.

12. Hiki N, Kaminishi M, Yasuda K et al. Multicenter phase II randomized study evaluating dose-response of antiperistaltic effect of L-menthol sprayed onto the gastric mucosa for upper gastrointestinal endoscopy. *Dig Endosc* 2012; 24: 79–86.

13. Imagawa A, Hata H, Nakatsu M et al. Peppermint oil solution is useful as an antispasmodic drug for esophagogastroduodenoscopy, especially for elderly patients. *Dig Dis Sci* 2012; 57: 2379–84.

14. Fujishiro M, Kaminishi M, Hiki N et al. Efficacy of spraying L-menthol solution during endoscopic treatment of early gastric cancer: A phase III, multicenter, randomized, double-blind, placebo-controlled study. *J Gastroenterol* 2014; 49: 446–54.

15. Kikuchi H, Hikichi T, Takagi T et al. Clinical application of l-menthol in the upper gastrointestinal endoscopic procedure. *Fukushima J Med Sci* 2015; 61: 160–6.

16. Ono S, Ono Y, Sakamoto N. Spraying L-menthol enhances gastric intestinal metaplasia in linked color imaging. *Dig Endosc* 2019; 31: e70–1.

17. Zhu WL, Shan YD, Guo JX et al. Double-blind, multicenter, active-controlled, randomized clinical trial to assess the safety and efficacy of orally administered nicorandil in patients with stable angina pectoris in China. *Circ J* 2007; 71: 826–33.

18. Hikichi T, Irisawa A, Sato M et al. Utility of peppermint oil for endoscopic diagnosis of gastric tumors. *Fukushima J Med Sci* 2011; 57: 60–5.

19. Imagawa A, Takeuchi K, Yoshida Y et al. The evaluation of effectiveness and safety of peppermint oil solution as antispasmodic agent during endoscopic submucosal dissection [in Japanese with English abstract]. *Gastroenterol Endosc* 2012; 54: 3783–9.