





ORIGINAL ARTICLE

# Effect of spraying L-menthol on peristalsis resumption during endoscopic submucosal dissection of gastric tumors

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## Key words

endoscopic submucosal dissection, gastric motility, gastric relaxation, gastric tumor, L-menthol.

Accepted for publication 7 April 2021.

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**Declaration of conflict of interest:** The authors have no financial conflicts of interest to disclose concerning the study.

## Abstract

**Background and Aim:** L-Menthol has smooth muscle-relaxing and antiperistaltic effects. We examined its effectiveness against peristalsis resumption during endoscopic submucosal dissection (ESD) of gastric tumors.

**Methods:** We retrospectively examined clinical data of 485 patients (501 lesions) who underwent ESD for upper gastrointestinal tumors in 2017. We included 119 patients (127 lesions) in whom peristaltic movement resumed during ESD and L-menthol was applied; 366 patients (374 lesions) without L-menthol application were used as controls. Video recordings were reviewed to determine whether L-menthol suppressed peristalsis resumption.

**Results:** In cases with L-menthol application, 2 (2.9%), 36 (14.3%), and 89 (71.2%) lesions were found in the upper (U), middle (M), and lower (L) regions, respectively. In the control group, the corresponding values were 66 (17.6%), 215 (57.5%), and 93 (24.9%), respectively. L-Menthol efficacy was observed in 116 of the 127 treated lesions (91.3%), over 90% of which were in the posterior wall of the U region, anterior wall and greater curvature of the M region, and anterior wall and lesser curvature of the L region. The most and least effective areas for L-menthol application were the anterior wall of gastric antrum and posterior wall of the M region, respectively. The mean time from application to peristalsis inhibition was 8.7 s. No adverse effects were observed; perforation and secondary hemorrhage were not significantly different between the groups.

**Conclusion:** Direct L-menthol application to the submucosal layer during mucosal resection affects smooth muscles and rapidly inhibits peristalsis resumption. Clinically, L-Menthol can be used to suppress peristalsis recurrence during ESD, without adverse effects.

## Introduction

The effect of peppermint oil on gastrointestinal peristalsis has been reported by Hiki et al.<sup>1</sup> The active compound of the oil is L-menthol, which has been commercialized and reported for its utility in upper gastrointestinal endoscopy and treatment.<sup>2–5</sup> The use of menthol is associated with only a few adverse effects, and the compound has been shown to be safer than other antiperistaltic or anticholinergic agents and glucagon, which are commonly used to treat gastrointestinal problems. Almost no adverse effects were observed in phase I–III trials,<sup>3–5</sup> and the compound has been found to be beneficial in upper gastrointestinal endoscopic examinations.

In Japan, the use of L-menthol is accepted during upper gastrointestinal endoscopy and endoscopic submucosal dissection (ESD). The use of L-menthol during ESD for upper gastrointestinal tumors has been reported by Fujishiro et al.,<sup>6</sup> and the compound is known to exert its antiperistaltic effect by reacting with calcium channels in the smooth muscle to cause muscle relaxation.<sup>7,8</sup> However, peristaltic activity may resume during ESD, making it difficult to complete the

operation. During our clinical practice, we have noticed that when peristalsis resumes during ESD, the application of L-menthol to the lesion immediately suppresses peristalsis. Our experience suggests that this effect is immediate because the drug acts directly on the smooth muscle at the incision site. Based on this experience, in the present study, we aimed to evaluate the efficacy of applying L-menthol to suppress peristalsis resumption during ESD by examining cases in our hospital.

## Methods

**Study population.** We recruited all patients with gastrointestinal lesions who underwent ESD in our hospital in 2017. From patient records in our hospital, we selected patients in whom L-menthol was applied during ESD for gastric tumors. Control cases, which are those without L-menthol application during ESD in the same period, were also selected. The exclusion criteria were a lack of resumption of peristalsis during ESD

**Table 1** Clinicopathological characteristics of the study population

	Added L-menthol 127 lesions, 119 cases		Without L-menthol 374 lesions, 366 cases		P value
M:F	344:138	84:32	260:106		0.775
Years		70.5 (43–84)	66.7 (36–89)		0.541
Lesion's size	15.8	14.4 (4–38)	16.6		0.792
Histology					
Intestinal	399	106	293		0.457
Diffuse	86	18	68		
Adenoma	16	3	13		
Depth					
M	440	119	321		0.019
SM	61	8	53		
Macroscopy					
0-I	13	8	5		0.15
0-IIa	118	35	83		
0-II c	273	68	205		
0-IIa + IIc	42	6	36		
Others	55	10	45		
U:M:L	68:251:182	2 (0.8%):36 (28.8%):89 (71.2%)	66 (17.6%):215 (57.4%):93 (24.8%)		

M:F, male:female; M, mucosa; SM, submucosa; U:M:L, upper:middle:lower.

**Table 2** Locations of lesions in cases where L-menthol was added during endoscopic submucosal dissection

	Anterior Wall	Lesser Curvature	Posterior wall	Great curvature	P-value
U	2/68 (2.9)	0/13 (0)	2/42(4.8)	0/0(0)	0.059 2.22e-16 1.26e-13
M	36/251(14.3)	8/49 (16.3)	7/46 (15.2)	10/56 (17.9)	
L	89/182 (48.9)	31/44 (70.4)	13/36 (33.3)	14/41 (34.1)	
Total	127/501(25.3)	39 /106 (36.8)	42/171 (24.6)	27/127 (21.3)	24/97 (24.7)

**Table 3** Percentage of cases in which suppression of peristalsis resumption was observed after the application of L-menthol

	Anterior wall	Lesser curvature	Posterior wall	Great curvature
Upper 2/2 (100)	0/0(0)	0/0(0)	2/2 (100)	0/0(0)
Middle 32/36 (88.9)	8/8(100)	9/11 (81.8)	5/7 (71.4)	10/10 (100)
Lower 83/89 (93.3)	30/31 (96.8)	30/31 (96.8)	11/13 (84.6)	12/14 (85.7)
Total 117/127(91.5)	38/39 (97.4)	39/42 (92.9)	18/22 (81.8)	22/24 (91.7)

**Table 4** Time from application until observation of the antiperistaltic effect(s)

	Anterior wall	Lesser curvature	Posterior wall	Great curvature	Mean time	P value
Upper 2			10.5		10.5	
Middle 32	8.3	9.2	5.3	7.5	7.56	
Lower 83	5.3	6.8	9.6	5.7	7.05	
117	7.5	8.9	9.8	6.5		0.70

**Table 5** Adverse events

	L-menthol	Without L-menthol	<i>P</i> value
Perforation	0	2 (2.7)	0.409
Bleeding	5 (3.9)	16 (4.3)	0.868
Others (fever and arthritis)	2 (1.5)	5 (1.3)	0.844
Total	7/127 (5.6)	23/374 (6.1)	0.793

or disagreement between specialists with regard to the suppression of peristalsis (see Section 2.4). All the cases were not used L-menthol at the start of ESD.

ESD was performed using the Q260J system (Olympus, Tokyo, Japan). After marking the lesion (Olympus ESG100; Olympus, and VAIO200, ERBE) and administering a local injection of hyaluronic acid, a precut was made with a needle knife, and incision and detachment were performed using ITknife2 (Olympus) for resection. After resection, the ulcer margin and exposed blood vessels were treated with Coagrasper hemostatic forceps (Olympus) and hemoclips to prevent bleeding after ESD.

The procedure was recorded on video from marking to completion, and the videos of all cases were stored.

**Data collection.** We performed a retrospective examination by reviewing the videos of ESD. In addition, the case number and times of drug administration during ESD were recorded. In cases where peristalsis resumed and L-menthol was applied, we assessed the efficacy when there was apparent suppression of peristalsis following application and the time from application to suppression of peristalsis.

**Surgical procedure.** Anesthesia during ESD was performed by sedation and analgesia with pethidine hydrochloride and midazolam. The procedure was performed by five specialists from our hospital, and they are accredited by the Japanese Gastroenterological Endoscopy Society (JF, TH, TY, AI, and YH). During ESD, when peristalsis was an obstacle to the procedure, L-menthol was sprayed directly to the propria muscle (shown in Video S1).

**Evaluation of the efficacy of L-menthol.** In cases where L-menthol was used, we reviewed and categorized the outcome as follows: suppression of peristalsis as (+) or no change in peristalsis (−) after application. The videos were reviewed by three specialists (JF, AI, and YH), and cases in which the assessments of the three specialists agreed were included in the subsequent analysis. Based on the videos, peristalsis of over grade 3 was identified in all cases in which L-menthol was applied (grade 1: no peristalsis, grade 2: mild, grade 3: moderate, grade 4: vigorous, grade 5: markedly vigorous).<sup>4</sup> After the application of L-menthol, peristalsis (−) was identified as grade 1.<sup>4</sup> Adverse events included perforation, bleeding, pneumonia, and arthritis. The criteria of adverse events were as follows. Perforation was determined from free air by computed tomography, or via our observation during ESD. Bleeding was indicated by clinical events such as hematemesis, tarry stool, and decreased hemoglobin of over 2 mg/dL. Pneumonia was determined via chest X-ray.

**Statistical analysis.** Fisher's exact probability test was performed to compare the two groups. The mean values were analyzed using *t*-test, *F*-test, and Ryan's procedure. When equal variances were not assumed, Mann–Whitney *U* test was performed. A *P* value <0.05 was considered to indicate a significant difference. SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

**Ethical statement.** The protocol of this study was approved by the Cancer Institute Hospital (IRB No. 2019-1129). Informed consent for ESD was obtained from all patients.

**Study design.** Retrospective single-center study.

## Results

In this study, we recruited 482 patients, accounting for 501 gastrointestinal lesions. All cases were analyzed; after applying the exclusion criteria, we finally enrolled 116 patients in whom L-menthol was used during ESD, accounting for 127 lesions. As a control group, 366 patients (374 lesions) where L-menthol was not applied were selected. All lesions were cases of gastric tumors (gastric cancer or gastric adenoma). Table 1 details the clinicopathological data of the study population. There were no significant differences in age, sex, or macroscopic type and size of lesions between the treated and control groups. With regards to location, L-menthol was more frequently applied to L-region lesions, and there was a significant difference in lesion location between the treated and control cases (Table 2).

Evaluation of the lesion site revealed that L-menthol was most frequently applied to L-region lesions (35–50%), whereas its application was less frequent in the M region. We also examined differences among the anterior wall, posterior wall, greater curvature, and lesser curvature. Table 3 shows the data of lesion sites in cases where L-menthol was applied.

The video review indicated that L-menthol was effective in 117/127 lesions (91.5%). Efficacy of at least 90% was observed for all areas except the posterior wall. Specifically, efficacy of ≥90% was observed in the U region, M region of the anterior wall and greater curvature, and L region of the anterior wall and lesser curvature.

The mean time from application to peristalsis suppression was 8.7 s. There is no significant difference for each position and location. However, the mean time at each position was within 10 s (Table 4). In terms of complications, perforation occurred in two cases of the control group. The incidence of secondary hemorrhage within or after 1 week was not significantly different between the treatment and control groups (Table 5).

## Discussion

The procedure of ESD for gastric tumors was developed in Japan,<sup>9,10</sup> and it has become a widely used therapeutic technique in China and Korea, where the incidence of gastric cancer is high.<sup>11,12</sup> With *Helicobacter pylori* infection rates declining in Japan, the morbidity of gastric cancer is primarily observed in older people.<sup>13</sup> ESD procedure is a minimally invasive therapeutic technique that contributes to patients' quality of life by sparing the stomach even after gastric tumor resection. Lesions that

were subjected to total gastrectomy before the development of ESD are now frequently removed via ESD, and as there is a shift in the prevalence of gastric cancer toward older people, the increased numbers of gastric cancers that are being treated with ESD is unsurprising. With more elderly people being treated, ESD will be performed on patients with more systemic complications such as heart diseases and benign prostatic hyperplasia. Drugs with antiperistaltic effects include anticholinergic agents and glucagon; however, these drugs are associated with adverse effects and may be contraindicated in elderly people with conditions such as heart diseases, prostate diseases, and eye lesions. Fujishiro *et al.* reported the effectiveness and lack of adverse effects of L-menthol.<sup>6</sup> In their study, L-menthol was applied before ESD, and ESD proceeded smoothly with peristalsis suppression for 15 min. Peristalsis was suppressed to a greater extent than that with the placebo, for an additional 25 min. The procedure of ESD is time-consuming; therefore, it is crucial to create optimal conditions.

The present study reveals that L-menthol is useful when peristalsis resumes during ESD. It has been reported that L-menthol acts directly on calcium channels and has a relaxing effect on smooth muscle.<sup>7,8</sup> We found that the most effective relaxing effect is achieved by the direct spraying of L-menthol to the muscularis propria during submucosal dissection. We also found the majority of lesions in the treatment group to be in the L region, whereas the majority of lesions in the control group were in the M region. The region from the ventricular angle to the gastric antrum is considered key in the initiation of peristalsis,<sup>1</sup> and the M–U region seems to be minimally affected by peristalsis during ESD therapy. This explains the high rate of L-region lesions in the group that included patients treated with L-menthol.

Fujishiro *et al.*<sup>6</sup> report the proportion of patients with no or mild peristalsis to be significantly higher in the treated group (85.4%) than in the placebo group (39.0%). The duration of effectiveness of L-menthol was confirmed as 30 min in 90% *vs* 39.6% of cases, respectively, and until completion of resection in 79.9% *vs* 35.7% of cases, respectively. Fujishiro *et al.* applied L-menthol at the start of the procedure to observe its effect on peristalsis and found no significant difference in the number of adverse events between the treatment and placebo groups. The present retrospective examination of the direct application of L-menthol to the muscularis propria shows that the effectiveness of this approach is high and the time to effect is short. These features are advantageous as treatment can be resumed quickly. A key difference between the present study and the study of Fujishiro *et al.* is the application site. In the latter, the site was covered by the mucous membrane, while we exposed the submucosal layer and applied L-menthol directly to the smooth muscle. Because we enrolled patients in whom peristalsis had resumed during ESD and submucosal incisions were made to expose the muscularis propria, we can conclude that the direct action of L-menthol on the muscularis propria resulted in the high efficacy observed.

We did not observe adverse events in any subject. As the mean age of patients undergoing ESD was fairly high, completing the procedure without adverse effects was highly important.

In addition to its utility in upper gastrointestinal endoscopy,<sup>14,15</sup> L-menthol has been shown to be useful during

colonoscopy examination and in prospective studies focusing on polyp detection.<sup>16,17</sup> The present study highlights the advantages of L-menthol over other antiperistaltic agents, such as glucagon and buscopan, indicating its utility in future gastroscopic therapies. The drug could be particularly beneficial in the treatment of conditions in the L region, which is easily affected by peristalsis. Our study was a single-center, retrospective study. This point is the limitation. In conclusion, we also demonstrate the specific benefits for ESD sprayed to submucosa directly, as the effect of L-menthol in terms of suppressing the resumption of peristalsis is immediate.

## Acknowledgments

We would like to thank Editage ([www.editage.com](http://www.editage.com)) for English language editing.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Video S1** Methods of spraying L-menthol.