JGH Open An open access journal of gastroenterology and hepatology JGHF

doi:10.1002/jgh3.12828

ORIGINAL ARTICLE

Association between antispasmodics and detection of lesions by screening esophagogastroduodenoscopy

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Key words
antispasmodics, detection, gastrointestinal neoplasm, menthol, scopolamine.

Accepted for publication 26 September 2022.

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Declaration of conflict of interest: All authors declare that they have no conflicts of interest.
Author contributions: Conception and design: Hiroyoshi Iwagami; provision of study materials or patients: Hiroyoshi Iwagami, Takeshi Seta, Shogo Nakano, Midori Wakita, Takafumi Konishi, Hisakazu Matsumoto, Yasuki Nakatani, Takuji Akamatsu, Shunji Urai, Yoshito Uenoyama, and Yukitaka Yamashita; departmental management: Yukitaka Yamashita; analysis and interpretation of the data: Hiroyoshi Iwagami and Takeshi Seta; drafting of the article: Hiroyoshi Iwagami; critical revision of the article for important intellectual content: Takeo Nakayama. All authors approved the final version of the article.
Financial support: None.

Abstract

Background and Aim: Whether administration of antispasmodics as a component of premedication contributes to detection of lesions by screening esophagogastroduodenoscopy (EGDS) remains unclear. Our primary aim was to investigate this possibility.
Methods: The cohort in this retrospective study comprised consecutive asymptomatic individuals who had undergone screening EGDS as part of a health check-up at the Japanese Red Cross Wakayama Medical Center from October 2015 to September 2020. The investigated lesions comprised esophageal squamous cell carcinoma or adenocarcinoma, gastric adenoma or adenocarcinoma, and duodenal adenoma or adenocarcinoma.
Results: Targeted lesions were detected in 72 of 31 484 participants (0.23%), 18 260 and 13 224 of whom had received and not received pre-procedure antispasmodics, respectively. The rates of detection of lesions in these groups were 0.21% (38/18260) and 0.26% (34/13224), respectively ($P = 0.40$). Multivariate logistic regression analysis showed no association between administration of antispasmodics and rates of detection of targeted lesions [$P = 0.24$, Odds ratio (95% CI): 1.46 (0.78–2.75)].
Conclusions: Antispasmodics, which were administered to more than half of the study cohort, did not improve the rate of detection of targeted lesions.

Introduction

Esophageal and gastric cancers remain some of the most common cancers worldwide.[1] Additionally, the widespread use of endoscopy has resulted in duodenal neoplasms being increasingly detected.[2,3] Previous studies from Asian countries have found that screening of asymptomatic adults by esophagogastroduodenoscopy (EGDS) can reduce the mortality of digestive tract cancers,[4–6] and that increasing numbers of screening EGDS are being performed.

Antispasmodics, such as scopolamine, glucagon, and L-menthol, have often been used to inhibit peristalsis.[7,8] A randomized controlled trial[9] and a meta-analysis[10] have found that antispasmodics, including scopolamine, do not improve the rate of polyp detection by colonoscopy. However, few reports have investigated the association between antispasmodics and detection of lesions during screening EGDS.[11] A recent observational study in a single hospital in Japan reported that the rate of detection of lesions during screening EGDS did not differ significantly between the three-quarters of approximately 40 000 participants who received scopolamine and those who did not.[12] However, to the best of our knowledge, the association between rate of detection of lesions and use of any antispasmodic,

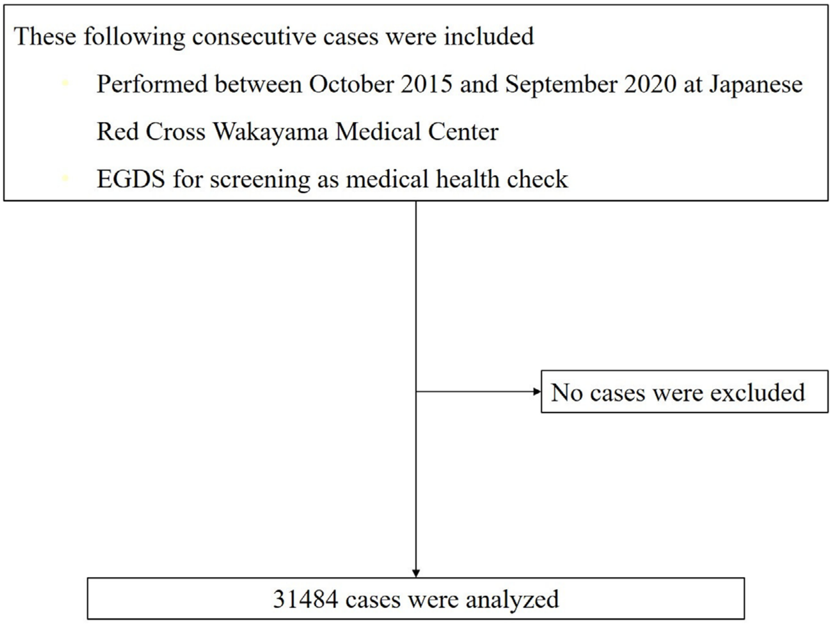

Figure 1 Flow chart showing enrollment of participants

including scopolamine, glucagon, and L-menthol, has not yet been investigated. Furthermore, differences in clinicopathological characteristics of detected lesions according to the status of antispasmodic use and differences in detection rate according to the type of antispasmodic have not yet been established. Investigation of these factors in real-world practice would strengthen the body of evidence on this issue and is needed to enable the development of appropriate recommendations.

We conducted this study in a real-world setting with the primary aim of investigating the association between antispasmodic use and rate of detection of lesions during screening EGDS. Our secondary aim was to determine the clinicopathological characteristics of detected lesions and differences in detection rates between different antispasmodics.

Participants and methods

Study design and participants. Consecutive individuals who had undergone screening EGDS as part of a health check-up at the Japanese Red Cross Wakayama Medical Center from October 2015 to September 2020 were enrolled based on data obtained from their medical records and our pathological

Table 1 Participants' characteristics and outcomes according to antispasmodic status before propensity score matching

	Antispasmodic group 18 260 cases	Non-antispasmodic group 13 224 cases	*P* value
Age	53 (18–89)	54 (20–90)	<0.01
Sex			
Male	8745 (47.9)	7844 (59.3)	<0.01
Female	9515 (52.1)	5380 (40.7)	
Sedation			
Yes	15 404 (84.4)	1272 (9.6)	<0.01
No	2856 (15.6)	11 952 (90.4)	
Endoscopists' experiences			
1–5 years	10 080 (55.2)	7299 (55.2)	<0.01
6–10 years	3241 (17.7)	3427 (25.9)	
11–15 years	626 (3.4)	1008 (7.6)	
16–20 years	3045 (16.7)	771 (5.8)	
21–25 years	1212 (6.6)	646 (4.9)	
More than 26 years	56 (0.3)	73 (0.6)	
Biopsies	1312 (7.2)	987 (7.5)	0.36
Detected lesions	38 (0.21)	34 (0.26)	0.40

Note: Data are presented as median (range) or *n* (%).

Table 2 Participants' characteristics according to antispasmodic status after propensity score matching

	Antispasmodic group 3916 cases	Non-antispasmodic group 3916 cases	*P* value
Age	55 (24–89)	54 (20–87)	0.07
Sex			
Male	2184 (55.8)	2175 (55.5)	0.86
Female	1732 (44.2)	1741 (44.5)	
Sedation			
Yes	1271 (32.5)	1226 (31.3)	0.29
No	2645 (67.5)	2690 (68.7)	
Endoscopists' experiences			
1–5 years	1586 (40.5)	1220 (31.2)	<0.01
6–10 years	501 (12.8)	848 (21.7)	
11–15 years	191 (4.9)	664 (17.0)	
16–20 years	1270 (32.4)	767 (19.6)	
21–25 years	349 (8.9)	409 (10.4)	
More than 26 years	19 (0.5)	8 (0.2)	

database. All participants were asymptomatic. The study protocol was approved by the Institutional Review Board of Japanese Red Cross Wakayama Medical Center (No. 806).

Details of screening EGDS. The endoscopic procedures were performed with the following equipment: GIF-EZ1500, GIF-H290Z, GIF-HQ290, GIF-H260Z, GIF-XP290N, GIF-H260 or GIF-H290 (Olympus, Tokyo, Japan), and EG-L580NW7 or EG-L600ZW7 (Fujifilm, Tokyo, Japan). The following video processors were used: EVIS LUCERA CV-260/CLV-260 or EVIS LUCERA ELITE CV-290/CLV-290SL (Olympus). The video endoscopic system used was LASEREO (Fujifilm). White light or narrow band imaging/blue light imaging was routinely used to assist detection of lesions that were suspicious of esophageal, gastric, or duodenal neoplasms. In some cases, magnifying endoscopy with narrow band imaging/blue light imaging was subsequently performed to differentiate detected lesions by evaluating the vascular and mucosal architecture. A biopsy was then performed if there was suspicion of neoplasia. Participants who requested that the endoscopic examination be performed under anesthesia received sedation, mainly with midazolam 0.04–0.05 mg/kg. Antispasmodics were injected intravenously when an intravenous line was available, otherwise, intramuscularly. The first-choice antispasmodic was scopolamine (initially 5 mg), followed by glucagon (initially 0.5 mg) if scopolamine was contraindicated (e.g., if the patient had glaucoma, coronary artery disease, or benign prostatic hyperplasia). L-menthol was used if no intravenous line was available or if both scopolamine and glucagon were contraindicated (e.g., if the patient had diabetes).

Outcome and definitions. The main outcome was the detection of any of the following: esophageal squamous cell carcinoma or adenocarcinoma, gastric adenoma or adenocarcinoma, or duodenal adenoma or adenocarcinoma. All lesions were confirmed histopathologically by one of nine independent pathologists at our hospital. The endoscopists' experiences were categorized as follows: 1–5 years, 6–10 years, 11–15 years, 16–20 years, 21–25 years, and more than 26 years. Furthermore, we analyzed the clinicopathological characteristics of the lesions by organ (i.e., esophagus, stomach, and duodenum) and differences in detection rates according to the type of antispasmodic administered.

Statistical analysis. The participants' characteristics were analyzed using descriptive statistics and univariate analyses. Results of χ^2 tests on categorical variables are presented as percentages and of Mann–Whitney's U test on quantitative data as median (range). We performed propensity score matching (PSM) to control and reduce the selection bias. Possible confounders were chosen based on our clinical knowledge and experience. The matching covariates were age, sex, sedation, and endoscopists' experience. We calculated propensity scores using logistic regression analysis and created a propensity score-matched cohort by matching patients with and without antispasmodics (1:1 match). A caliper width of 0.2 of the standard deviation for the logit of the propensity score was used. The matched cohorts were then compared.

Multiple logistic regression analysis was performed with the participant's age, sex, sedation, and endoscopist's experience as covariates to examine associations between antispasmodic use and detection of the specified lesions. The variance inflation factor was calculated to examine the multicollinearity of variables and the goodness-of-fit of the model was evaluated with the Hosmer–Lemeshow test. All tests were two-tailed, $P < 0.05$ being considered to denote statistical significance. The analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[13] a graphical user interface for R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Table 3 Outcomes according to antispasmodic status after propensity score matching

	Antispasmodic group 3916 cases	Non-antispasmodic group 3916 cases	*P* value
Biopsies	314 (8.0)	291 (7.4)	0.35
Detected lesions	13 (0.3)	9 (0.2)	0.52

Table 4 Factors associated with rate of lesion detection

		Multiple logistic regression analysis	
		Odds ratio (95% CI)	*P* value
Age	≧53 years/≦52 years	5.96 (2.96–12.0)	<0.01
Sex	Male/Female	2.54 (1.46–4.40)	<0.01
Antispasmodics	Yes/No	1.46 (0.78–2.75)	0.24
Sedation	Yes/No	0.55 (0.29–1.06)	0.07
Endoscopists' experience	≧6 years/≦5 years	0.84 (0.52–1.35)	0.48

Table 5 Clinicopathological characteristics of detected lesions according to the presence or absence of antispasmodic status

			Antispasmodic group 38 cases	Non-antispasmodic group 34 cases	*P* value
Number of lesions	Esophagus		5 (13.2)	2 (5.9)	0.64
	Stomach		26 (68.4)	26 (76.5)	
	Duodenum		7 (18.4)	6 (17.6)	
Lesion size, median (range)	Esophagus		15 (10–50)	6.5 (3–10)	0.12
	Stomach		10 (4–35)	8 (3–50)	0.12
	Duodenum		10 (4–50)	12 (5–20)	0.72
Tumor location	Esophagus	Ut	0	1 (50)	0.29
		Mt	1 (20)	0	
		Lt	1 (20)	1 (50)	
		Ae	3 (60)	0	
	Stomach	U	2 (7.7)	7 (26.9)	0.25
		M	14 (53.8)	11 (42.3)	
		L	10 (38.5)	8 (30.8)	
	Duodenum	Second	7 (100)	6 (100)	1
Macroscopic type	Esophagus	0-I	1 (20)	0	0.71
		0-IIa	1 (20)	0	
		0-IIb	0	1 (50)	
		0-IIc	3 (60)	1 (50)	
	Stomach	0-I	2 (7.7)	1 (3.8)	0.86
		0-IIa	7 (26.9)	9 (34.6)	
		0-IIb	1 (3.8)	0	
		0-IIc	15 (57.7)	16 (61.5)	
		Type 3	1 (3.8)	0	
	Duodenum	0-I	1 (14.3)	1 (16.7)	0.11
		0-IIa	5 (71.4)	1 (16.7)	
		0-IIc	1 (14.3)	4 (66.7)	
Pathological type	Esophagus	SCC	2 (40)	2 (100)	0.62
		tub 1	1 (20)	0	
		tub 2	2 (40)	0	
	Stomach	Adenoma	8 (30.8)	10 (38.5)	0.66
		tub1	8 (30.8)	10 (38.5)	
		tub2	3 (11.5)	3 (11.5)	
		por1	3 (11.5)	0	
		por2	1 (3.8)	1 (3.8)	
		sig	3 (11.5)	2 (7.7)	
	Duodenum	Adenoma	6 (85.7)	5 (83.3)	1
		Adenocarcinoma	1 (14.3)	1 (16.7)	

Note: Data are presented as median (range) or *n* (%).
Abbreviations: Ae, abdominal esophagus; Ce, cervical esophagus; L, lower third of stomach; Lt, lower thoracic esophagus; M, middle third of stomach; Mt., middle thoracic esophagus; por1, poorly-differentiated adenocarcinoma solid type; por2, poorly-differentiated adenocarcinoma non-solid type; SCC, squamous cell carcinoma; sig, signet-ring cell carcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately-differentiated tubular adenocarcinoma; U, upper third of stomach; Ut, upper thoracic esophagus.

Table 6 Rates of lesion detection and clinicopathological characteristics of detected lesions according to type of antispasmodic

			Scopolamine group 15 404 cases†	L-menthol group 2833 cases†	*P* value
Detected lesions			28 (0.18)	10 (0.35)	0.07
Number of lesions	Esophagus		4 (14.3)	1 (10)	0.54
	Stomach		20 (71.4)	6 (60)	
	Duodenum		4 (14.3)	3 (30)	
Lesion size, median (range)	Esophagus		15 (12–50)	10	0.28
	Stomach		11 (5–35)	9 (4–20)	0.39
	Duodenum		22.5 (5–50)	5 (4.4–10)	0.21
Tumor location	Esophagus	Mt	1 (25)	0	0.29
		Lt	1 (25)	0	
		Ae	2 (50)	1 (100)	
	Stomach	U	2 (10)	0	1
		M	10 (50)	4 (67)	
		L	8 (40)	2 (33)	
	Duodenum	Second	4 (100)	3 (100)	1
Macroscopic type	Esophagus	0-I	1 (25)	0	0.4
		0-IIa	0	1	
		0-IIc	3 (75)	0	
	Stomach	0-I	2 (10)	0	0.55
		0-IIa	6 (30)	1 (17)	
		0-IIb	0	1 (17)	
		0-IIc	11 (55)	4 (66)	
		Type 3	1 (5)	0	
	Duodenum	0-I	1 (25)	0	1
		0-IIa	3 (75)	2 (67)	
		0-IIc	0	1 (33)	
Pathological type	Esophagus	SCC	2 (50)	0	1
		tub 1	1 (25)	0	
		tub 2	1 (25)	1 (100)	
	Stomach	Adenoma	7 (35)	1 (17)	0.15
		tub1	7 (35)	1 (17)	
		tub2	1 (5)	2 (33)	
		por1	3 (15)	0	
		por2	1 (5)	0	
		sig	1 (5)	2 (33)	
	Duodenum	Adenoma	3 (75)	3 (100)	1
		Adenocarcinoma	1 (25)	0	

Note: Data are presented as median (range) or *n* (%).

Abbreviations: Ae, abdominal esophagus; L, lower third of stomach; Lt, lower thoracic esophagus; M, middle third of stomach; Mt., middle thoracic esophagus; por1, poorly-differentiated adenocarcinoma solid type; por2, poorly-differentiated adenocarcinoma non-solid type; SCC, squamous cell carcinoma; sig, signet-ring cell carcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately-differentiated tubular adenocarcinoma; U, upper third of stomach.

†One participant who received both scopolamine and L-menthol was excluded.

Results

The study cohort comprised 31 484 participants (Fig. 1), 72 of whom (0.23%) were found to have targeted lesions. Antispasmodics were administered to 18 260 (58.0%) participants, namely scopolamine, glucagon, and L-menthol in 15 405, 22, and 2834 cases, respectively. One individual received both scopolamine and L-menthol.

Table 1 shows relevant participant characteristics according to antispasmodic use status. The median age (range) was 53 (18–89) and 54 (20–90) years ($P < 0.01$); women comprised 52% and 41% of all participants ($P < 0.01$); and sedatives were administered to 84.4% and 9.6% of participants ($P < 0.01$) in the antispasmodic and non-antispasmodic groups, respectively. Table 1 also shows that targeted lesions were detected in 0.21% and 0.26% ($P = 0.40$) of the antispasmodic and non-antispasmodic groups, respectively, and that the rates of biopsy of suspicious lesions were 7.2% and 7.5% ($P = 0.36$), respectively.

Participants' characteristics according to antispasmodic status after PSM are shown in Table 2. There was still a significant difference in endoscopists' experience between the two groups after matching. The outcomes of the matched participants are shown in Table 3. Targeted lesions were detected in 0.3% and 0.2% ($P = 0.52$) of the antispasmodic and non-antispasmodic groups, respectively, and the rates of suspicious-lesion biopsy were 8.0% and 7.4% ($P = 0.35$), respectively.

Multiple logistic regression analysis showed no association between the use of antispasmodics and rate of detection of lesions (Table 4). The Hosmer–Lemeshow test yielded $P = 0.37$, with the highest variance inflation factor of 1.87.

Table 5 shows no significant differences in lesion size, location, macroscopic type, or pathological type between the two study groups.

The rates of detection of targeted lesions were 0.18% and 0.35% in the scopolamine and L-menthol groups, respectively ($P = 0.07$) (Table 6). There were no significant differences in the clinicopathological characteristics of the detected lesions between the two groups.

Discussion

In this study, we found no association between the use of antispasmodics and rates of detection of targeted lesions by screening endoscopy. Examining the usefulness of antispasmodics in EGDS is important because they can have adverse events,[14,15] and most screening EGDS take less than 10 min.[7] In the present study, we found that using antispasmodics conferred no benefits regarding detection of suspicious lesions.

Few studies have been published on factors associated with detection of lesions by screening EGDS. Omata *et al.* reported finding no statistically significant differences in rates of detection of upper gastrointestinal neoplasia according to the experience of the endoscopist.[12] As shown in Table 2 shows, we also found no association between detection rate and endoscopists' experience. Indeed, we did not identify any clinical factors that significantly impacted the rate of detection of lesions by screening EGDS.

Peristalsis is visible in the upper gastrointestinal tract, especially the esophagus, gastric antrum, and second part of the duodenum, making examination of these regions so difficult that lesions can be missed. However, our subgroup analysis (Table 3) showed no significant differences between the antispasmodic and non-antispasmodic groups in the location of tumors detected in the esophagus, stomach, or duodenum. These findings suggest that antispasmodic use confers no advantages regarding detection of lesions, not even affecting the rate of missing lesions in regions with active peristalsis.

The Handbook for screening EGDS published by the Japan Gastroenterological Endoscopy Society[16] does not recommend routine use of scopolamine or glucagon because there is no good evidence that these agents confer any benefit regarding detection of lesions and they can have adverse events.[7,17–23] However, L-menthol is reportedly safe.[8] Furthermore, our subgroup analysis (Table 4) showed a slightly higher, but not statistically significant ($P = 0.07$), rate of detection in the L-menthol than in the scopolamine group. These findings suggest that L-menthol may be a better option than scopolamine when suppression of peristalsis is required.

The expected advantages of not using antispasmodics are as follows. First, this would eliminate the risk of associated adverse events. Scopolamine is associated with cardiovascular events[7,17] and tachycardia and can also adversely affect the ocular, urinary, and salivary systems.[7] Additionally, it can cause allergic reactions,[18,19] including potentially fatal anaphylactic shock.[20] Glucagon can lead to delayed hypoglycemia[7,17] and induce nausea, vomiting, and anaphylactic and other allergic reactions.[21–23] Second, not using antispasmodics would eliminate their cost. One ampoule of scopolamine, glucagon, and L-menthol costs 12.7, 30, and 7 USD, respectively. From October 2015 to September 2020, our hospital spent a mean of 43 228 USD per year on antispasmodics. Third, participants would not be subjected to the pain of an intramuscular injection of scopolamine or glucagon. Fourth, not using antispasmodics would mean one less task for nurses. Eliminating the need for nurses to open an ampoule and inject an antispasmodic would free them up to attend to their many other tasks, such as monitoring participants, recording, and preparing other agents. Moreover, it would reduce their exposure to the risk of needle-stick injury.

Our study had several limitations. First, it was an observational study. Undetected differences in the characteristics of the antispasmodic and non-antispasmodic groups may have caused biases despite the use of multivariate analysis. Second, the generalizability of our findings is limited because this was a single hospital study. Third, there were too few participants to analyze our findings by organ. Fourth, we did not evaluate several subjective factors, namely the stress for endoscopists on encountering peristalsis in the upper gastrointestinal tract and the participants' tolerance of the EGDS procedure.

In conclusion, premedication with antispasmodics (scopolamine, glucagon, and L-menthol) does not improve the rate of detection of lesions by screening EGDS.

Acknowledgments

The authors are deeply grateful to the nurses and medical staff in the endoscopic examination rooms who assisted us every day. The authors also thank Dr. Trish Reynolds, MBBS, FRACP, from Edanz Group (https://jp.edanz.com/ac) for editing the draft of this manuscript.

Ethics statement

All study participants provided informed consent for undergoing EGDS. The study protocol was approved by the Institutional Review Board of Japanese Red Cross Wakayama Medical Center on October 12, 2020 (No. 806) and the study was performed in accordance with the Declaration of Helsinki.

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