Association Between Antispasmodics and Detection of Lesions By Screening Esophagogastroduodenoscopy

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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 of this retrospective study comprised consecutive cases who had undergone screening EGDS 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 31484 participants (0.23%), 18260 and 13224 of whom had received and not received pre-procedure antispasmodic agents, 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 ($P = 0.12$).

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 ^{4,5 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, 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 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

This retrospective study was conducted at a general hospital in Japan. Consecutive individuals who had undergone screening EGDS 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 database. 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. Participant 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 antispasmodic of choice was scopolamine (initially 5 mg), followed by glucagon (initially 0.5 mg) when scopolamine was contraindicated. L-menthol was used when no intravenous line was available or both scopolamine and glucagon were contraindicated.

Outcome and Definitions

The main outcome was 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). 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 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).

Results

The study cohort comprised 31484 participants, 72 of whom (0.23%) were found to have targeted lesions. Antispasmodics were administered to 18260 (58.0%) participants, namely scopolamine, glucagon and L-menthol in 15405, 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.

Table 1
Participants' characteristics and outcomes according to antispasmodic status

	Antispasmodic group 18260 cases	Non-antispasmodic group 13224 cases	P value
Age	53 (18-89)	54 (20-90)	< 0.01
Sex			
Male	8745 (48)	7844 (59)	< 0.01
Female	9515 (52)	5380 (41)	
Sedation			
Yes	15404 (84.4)	1272 (9.6)	< 0.01
No	2856 (15.6)	11952 (90.4)	
Endoscopists' experiences			
1-5 years	10080 (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
Data are presented as median (range) or n (%).			

Multiple logistic regression analysis showed no association between use of antispasmodics and rate of detection of lesions (Table 2). The Hosmer–Lemeshow test yielded $P = 0.37$, the highest variance inflation factor being 2.25.

Table 2
Factors associated with rate of detection of lesions

		Multiple logistic regression analysis	
		Odds ratio (95% CI)	P value
Age		1.07 (1.04-1.09)	< 0.01
Sex	Male/ Female (reference)	2.45 (1.41-4.25)	< 0.01
Antispasmodics	Yes/ No (reference)	1.67 (0.88-3.19)	0.12
Sedation	Yes/ No (reference)	0.51 (0.27-0.99)	0.05
Endoscopists' experience		0.85 (0.69-1.05)	0.13

Table 3 shows no significant differences in lesion size, location, macroscopic type or pathological type between the two study groups.

Table 3
Clinicopathological characteristics of detected lesions

			Antispasmodic group 38 cases	Non-antispasmodic group 34 cases	P value
Number of lesions	Esophagus		5 (13)	2 (6)	0.64
	Stomach		26 (68)	26 (76)	
	Duodenum		7 (19)	6 (18)	
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*	Ce	0	0	0.29
		Ut	0	1 (50)	
		Mt	1 (20)	0	
		Lt	1 (20)	1 (50)	
		Ae	3 (60)	0	
	Stomach**	U	2 (8)	7 (27)	0.25
		M	14 (54)	11 (42)	
		L	10 (39)	8 (31)	
	Duodenum	1st	0	0	1
		2nd	7 (100)	6 (100)	

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

* Ae, abdominal esophagus; Ce, cervical esophagus; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; Ut, upper thoracic esophagus.

** L, lower third of stomach; M, middle third of stomach; U, upper third of stomach

† SCC, squamous cell carcinoma; por1, poorly-differentiated adenocarcinoma solid type; por2, poorly-differentiated adenocarcinoma non-solid type; sig, signet-ring cell carcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately-differentiated tubular adenocarcinoma

			Antispasmodic group 38 cases	Non- antispasmodic group 34 cases	P value
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 (8)	1 (4)	0.86
		0-IIa	7 (27)	9 (35)	
		0-IIb	1 (4)	0	
		0-IIc	15 (58)	16 (62)	
		Type 3	1 (4)	0	
	Duodenum	0-I	1 (14)	1 (17)	0.11
		0-IIa	5 (71)	1 (17)	
		0-IIb	0	0	
		0-IIc	1 (14)	4 (67)	
Pathological type [†]	Esophagus	SCC	2 (40)	2 (100)	0.62
		tub 1	1 (20)	0	
		tub 2	2 (40)	0	

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

* Ae, abdominal esophagus; Ce, cervical esophagus; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; Ut, upper thoracic esophagus.

** L, lower third of stomach; M, middle third of stomach; U, upper third of stomach

[†] SCC, squamous cell carcinoma; por1, poorly-differentiated adenocarcinoma solid type; por2, poorly-differentiated adenocarcinoma non-solid type; sig, signet-ring cell carcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately-differentiated tubular adenocarcinoma

			Antispasmodic group 38 cases	Non-antispasmodic group 34 cases	P value
	Stomach	Adenoma	8 (31)	10 (39)	0.66
		tub1	8 (31)	10 (39)	
		tub2	3 (12)	3 (12)	
		por1	3 (12)	0	
		por2	1 (4)	1 (4)	
		sig	3 (12)	2 (8)	
	Duodenum	Adenoma	6 (86)	5 (83)	1
	Adenocarcinoma	1 (14)	1 (17)		
Data are presented as median (range) or n (%).					
* Ae, abdominal esophagus; Ce, cervical esophagus; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; Ut, upper thoracic esophagus.					
** L, lower third of stomach; M, middle third of stomach; U, upper third of stomach					
† SCC, squamous cell carcinoma; por1, poorly-differentiated adenocarcinoma solid type; por2, poorly-differentiated adenocarcinoma non-solid type; sig, signet-ring cell carcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately-differentiated tubular adenocarcinoma					

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 4).

Table 4
Rates of detection of lesions according to type of antispasmodic

	Scopolamine group 15404 cases*	L-menthol group 2833 cases*	P value
Detected lesions	28 (0.18)	10 (0.35)	0.07
Data are presented as n (%).			
*One participant who received both scopolamine and L-menthol was excluded.			

Discussion

In this study, we found no association between 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 minutes 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 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 22,23}. 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 43228 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.

Abbreviations

EGDS, esophagogastroduodenoscopy

Declarations

Author contributions

Conception and design, H.I.; provision of study materials or participants, H.I., T.S., N.J., S.N., M.W., S.U., T.K., H.M., Y.N., T.A., S.U., Y.U., and Y.Y.; analysis and interpretation of the data, H.I. and T.S.; drafting of the article, H.I. critical revision of the article for important intellectual content T.N.; All authors approved the final version of the article.

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Statement of Ethics

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 12 October 2020 (No. 806) and the study was performed in accordance with the Declaration of Helsinki.

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