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Usefulness of epinephrine-added injection solution to reduce procedure time for gastric endoscopic submucosal dissection

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ABSTRACT

Background and study aims Epinephrine-added submucosal injection solution is used to facilitate hemostasis of non-variceal upper gastrointestinal bleeding and to prevent delayed bleeding of large pedunculated colorectal lesions. However, its benefit in gastric endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is unclear. The effectiveness of epinephrine-added injection solution for outcomes of gastric ESD was examined using propensity score matching analysis.

Patients and methods A total of 1,599 patients with solitary EGC (83 with non-epinephrine-added solution and 1,516 with epinephrine-added solution) between 2011 and 2018 were enrolled. Propensity scores were calculated to balance the distribution of baseline characteristics: age, sex, tumor location, specimen size, presence of ulcer scar, tumor depth, histological tumor type, and operators' experience, and 1:3 matching was performed. En bloc resection rate, mean procedure time, delayed bleeding rate, and perforation rate were compared between the non-epinephrine (n = 79) and epinephrine (n = 237) groups.

Results Mean procedure time was significantly shorter in the epinephrine group than in the non-epinephrine group (60 vs. 78 min, $P < 0.001$). No significant difference was found in the rate of en bloc resection (both 99 %), incidence of delayed bleeding (both 6 %), or perforation (0 vs. 0.8 %) between the two groups. In multiple linear regression analysis, use of epinephrine-added solution was independently associated with short procedure time ($P < 0.001$) after adjustment for other covariates.

Conclusion The results suggest that epinephrine-added injection solution is useful for reduction of gastric ESD procedure time, warranting validation in a randomized controlled trial.

Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are established treatments for intramucosal (T1a) early gastric cancer (EGC) [1, 2]. ESD enables removal of lesions > 2 cm or those with ulcer scars that are unresectable by EMR in en bloc fashion [3–5]. However, ESD requires significant expertise and long procedure time, and is accompanied by a high incidence of adverse events (AEs) [6]. The main AEs associated with gastric ESD are bleeding and perforation, which develop in 0 % to 15.6 % and 1.2 % to 5.2 % of cases, respectively [7].

Vasoconstriction facilitates hemostasis; therefore, submucosal injection of epinephrine-added solution is used for treatment of non-variceal upper gastrointestinal bleeding, in combination with other hemostatic methods such as contact thermal, mechanical therapy, or injection of a sclerosing agent [8]. Submucosal injection of epinephrine-added solution is also recom-

mended for resection of pedunculated colorectal polyps with head ≥ 20 mm or stalk ≥ 10 mm in diameter [9]. This is because some observational studies [10, 11] and randomized controlled trials [12, 13] have indicated that epinephrine-added solution significantly reduces post-polypectomy bleeding compared with no injection of epinephrine-added solution. This potential advantage has resulted in epinephrine-added solution being routinely used for submucosal injection of gastric ESD [14]; however, its actual clinical effectiveness has not been fully investigated.

The aim of this study, therefore, was to clarify the benefit of injection of epinephrine-added solution into the submucosa during ESD for EGC.

Patients and methods

This was a retrospective observational study using propensity score matching analyses conducted in a single cancer referral center. All data were retrieved from medical records and endoscopic reports stored in a hospital computer server from June 2011 to June 2018.

The study protocol was approved by the Institutional Review Board of Osaka International Cancer Institute (No. 18176, Approved on January 4, 2019), and it was registered as UMIN000039326. Written informed consent for the gastric ESD procedure was obtained from all patients. Written informed consent for study participation was waived because only retrospective anonymous data were used.

Patients

Eligible patients underwent ESD for histologically confirmed EGC or adenoma in our hospital. Exclusion criteria were: (1) ESD for two or more lesions in a single session because it was not possible to identify in which lesion epinephrine was used; (2) regularly use of antiplatelet or anticoagulant agents; and (3) history of gastric resection or esophagectomy.

ESD procedure

ESD was performed with a videoendoscope (EVIS GIF-Q260J; Olympus Co. Ltd., Tokyo, Japan) that mounted a transparent cap (D-201-11804; Olympus) onto the tip. VIO 300 D (ERBE Elektromedizin, Tubingen, Germany) was used as an electrical surgical unit (Forced Coagulation mode: Effect 3, 20 W for marking; Endo Cut I mode: Effect 2, Duration 3, Interval 3 for mucosal incision; Swift Coagulation mode: Effect 3, 100 W for submucosal dissection; and Soft Coagulation mode: Effect 5, 80 W for haemostasis). An insulation-tipped knife 2 (KD-611L; Olympus) was mainly used as an ESD knife, otherwise a Flush-knife (DK2618JN12; Fujifilm Medical, Tokyo, Japan) was used for lesions with scars, or according to operator preference. After creation of marking dots around the lesion with the needle knife (KD-1L-1; Olympus), 0.4 % sodium hyaluronate (MucoUp; Boston Scientific Japan, Tokyo, Japan) with or without 0.001 % epinephrine (Bosmin; Daiichi Sankyo, Co. Ltd. Tokyo, Japan) was injected into the submucosa. Subsequently, circumferential mucosal incision and submucosal dissection were performed with the ESD knife; then, the lesion was removed. During the procedure, minor bleeding from a thin vessel was cauterized with the ESD knife, and major bleeding from a thick vessel was managed with hemostatic forceps (Radial Jaw Hot Biopsy Forceps; Boston Scientific Japan, or Coagrasper, FD-410LR; Olympus). After completion of ESD, the post-ESD ulcer was carefully examined and all active bleeding and visible vessels were cauterized with the hemostatic forceps. All patients received oral rabeprazole 40 mg from 1 day before ESD and it was continued for 8 weeks for treatment of post-ESD ulcer [15].

The ESD procedure was performed by an expert or non-expert endoscopist. The non-expert endoscopist always performed the procedure in the presence of an expert endoscopist.

Propensity score matching

To reduce the effect of selection bias and potential association with confounding factors between the epinephrine and non-epinephrine groups, a 1:3 match was created using propensity score analysis (caliper width = 0.0001). We evaluated the main outcome measures of gastric ESD, en bloc resection rate, procedure time, delayed bleeding rate, and perforation rate. Tumor location, presence of ulcer or scar, and histological type of tumor are reported to be associated with en bloc resection rate [16]. Tumor size, tumor location, presence of ulcer or scar in the tumor, and operator experience are reported to be associated with long procedure time for gastric ESD [15, 17, 18]. Male sex, tumor size, tumor location, and ulceration are reported to be significant risk factors for delayed bleeding [19]. Tumor location, tumor size, and presence of scar are risk factors for macroscopic perforation, and old age and tumor depth are risk factors for microperforation [20, 21]. Accordingly, we selected age, sex, tumor location, specimen size, presence of histological ulcer or scar, histological depth of tumor invasion, histological type of tumor, and operator experience as covariates to produce propensity scores. Tumor size was not included among the covariates for the following reasons: histological size was not measured in all patients; endoscopic size does not always accurately reflect histological tumor size; and actual outcome parameters of ESD procedure must be more closely associated with resected specimen size rather than the tumor size. Tumor macroscopic type and circumferential location were not used for propensity score generation because patient background was not well balanced with inclusion of these factors.

Definition of variables

As explanatory variables, tumor location (upper, middle, and lower third), specimen size, presence of histological ulceration or scar, histological depth of tumor invasion (T1a and T1b), histological type (differentiated type adenocarcinoma, undifferentiated type adenocarcinoma, and adenoma) were defined according to the Japanese Classification of Gastric Carcinoma [22]. Expert endoscopists were certified by the Japan Gastroenterological Endoscopy Society for over 10 years and had experience of gastric ESD in 100 cases or more.

Objective (outcome) variables included en bloc resection rate, procedure time, delayed bleeding rate, and perforation

rate. En bloc resection was defined as a single resection procedure performed for a single lesion [21]. Procedure time was measured from the end of marking until the completion of ESD. Delayed bleeding was defined as endoscopically confirmed active bleeding from the post-ESD ulcer or fresh blood in the stomach at emergency endoscopy. Emergency endoscopy was performed in case of suspicion of delayed bleeding such as hematemesis, melena, anemia, hypotension, or tachycardia. Perforation was defined as evidence of air or luminal contents outside the gastrointestinal tract by chest/abdominal radiography or computed tomography [23].

Statistical analysis

Categorical variables were expressed as numbers and proportion (percent). Continuous variables were expressed as median and interquartile range because they had skewed distribution. After matching, baseline characteristics and outcomes of the matched cohorts were compared. Age, specimen size, and procedure time were analyzed as continuous variables, while other variables were analyzed as categorical variables. Categorical variables were analyzed using the Mantel-Haenszel chi-square test or McNemar test (binary data), and continuous variables were analyzed using the Mann-Whitney U test or Wilcoxon signed rank test. Absolute standardized differences (ASDs) were used to evaluate matching effectiveness.

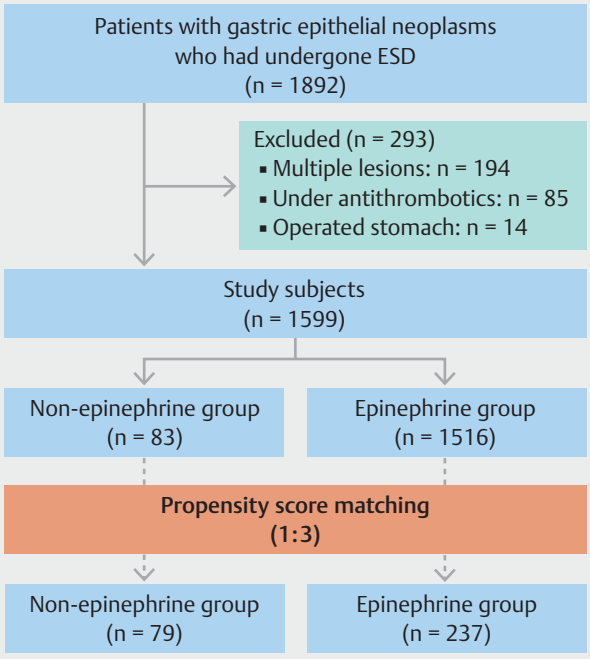
To identify other factors associated with ESD procedure time, and to confirm independence of association between administration of epinephrine-added injection solution and ESD procedure time, multivariate linear regression analysis was performed using logarithmic procedure time (min) as a dependent variable.

All statistical analyses were performed with R Statistical Software 3.5.1 (free download from http://www.r-project.org). $P<0.05$ was considered to be statistically significant.

Results

Participants

A total of 1892 patients with 2132 lesions were eligible for this study. We excluded 194 patients with multiple lesions (434 lesions), 85 patients taking antithrombotics, and 14 patients with a history of gastric resection or esophagectomy. This left 1599 patients (83 in the non-epinephrine group and 1516 in the epinephrine group) for propensity score matching. After propensity score matching, 79 patients in the non-epinephrine group and 237 in the Epinephrine group were selected for analysis (▶ **Fig. 1**).



▶ **Fig. 1** Flowchart of study subjects.

Baseline characteristics

Baseline characteristics of 1599 patients who underwent ESD for solitary EGC without administration of antithrombotic and history of gastroesophageal surgery are shown in ▶ **Supplementary Table S1**. Before propensity score matching, specimen size differed significantly between the two groups ($P=0.046$). Baseline characteristics of study subjects after 1:3 propensity score matching are listed in ▶ **Table 1**. ASDs < 0.1 or slightly over 0.1 suggested adequate variable balance after propensity matching.

Treatment outcomes after propensity score matching

Treatment outcomes are shown in ▶ **Table 2**. The mean (SD) procedure time in the epinephrine group was significantly shorter than that in the non-epinephrine group: 72 (54) versus 93 (62) min ($P<0.001$). There was no significant difference in the rate of en bloc resection, and incidence of delayed bleeding and perforation between the two groups.

In single regression analysis, injection solution, tumor location, specimen size, histological type, histological depth of tumor invasion, histological ulceration or scar, and operator experience were significantly associated with procedure time. However, multiple regression analysis revealed that only injection solution, tumor location, specimen size, histological ulceration or scar, and operator experience had an independent association with procedure time (▶ **Table 3**). Independent statistical association between use of epinephrine-added injection solution and procedure time was confirmed even after adjustment for other covariates.

Discussion

Although ESD is a standard treatment for patients with intramucosal gastric carcinoma in Japan, the technique still requires refinement. The present propensity score-matching analysis revealed that use of epinephrine-added injection solution reduced procedure time of gastric ESD by approximately 20 %.

▶ **Table 1** Baseline characteristics of epinephrine and the non-epinephrine groups after propensity matching.

	Non-Epinephrine group (n = 79)	Epinephrine group (n = 237)	*P* value	ASD
Median age, years (IQR)	72 (12)	70 (13)	0.189	0.094
Sex (%)			0.248	0.113
▪ Male	60 (76)	191 (81)		
▪ Female	19 (24)	46 (19)		
Tumor location (%)			0.486	0.111
▪ Upper third	13 (17)	48 (20)		
▪ Middle third	27 (34)	72 (30)		
▪ Lower third	39 (49)	117 (49)		
Median specimen size, mm (IQR)	35 (17)	40 (20)	0.299	0.037
Histological ulcer or scar (%)			0.230	0.120
▪ Absent	75 (95)	218 (92)		
▪ Present	4 (5.1)	19 (8.0)		
Histological depth of tumor invasion (%)			0.787	0.035
▪ pT1a	67 (85)	198 (84)		
▪ pT1b	12 (15)	39 (16)		
Histological type (%)			0.861	0.05
▪ Differentiated	69 (87)	207 (87)		
▪ Undifferentiated	7 (8.9)	19 (8.0)		
▪ Adenoma	3 (3.8)	11 (4.6)		
Operator experience (%)			0.073	0.159
▪ Non-expert	63 (80)	173 (73)		
▪ Expert	16 (20)	64 (27)		

ASD, absolute standardized difference; IQR, interquartile range.

Topically applied epinephrine causes contraction of the smooth muscle that lines most arterioles, via α1 receptor activation, and constricts blood vessels; therefore, it is used for control of hemorrhage from skin and mucous membranes. Gastric ESD is mainly divided into mucosal incision and submucosal dissection. In our previous investigation of the learning curve for gastric ESD, submucosal dissection took longer than mucosal incision, and difficulty with ESD was mainly related to uncontrollable hemorrhage during submucosal dissection [24]. The gastric submucosa is rich in blood vessels, thus, hemorrhage occurs frequently during submucosal dissection. Therefore, operators often spend a long time on hemostasis during submucosal dissection. Moreover, hemorrhage and clotting interfere with the visibility of the operating field, which causes operators to lose orientation, and deterioration of conduction of electric current of ESD devices [25]. We suspect that epinephrine reduced hemorrhage during ESD, avoided the above problems, and shortened the procedure time.

En bloc resection rates in the non-epinephrine and epinephrine groups were both 99 %. Although non-epinephrine solution might increase intraprocedural bleeding, the operators in this study managed it, and finally achieved en bloc resection of the lesions. The current study was conducted in a cancer referral center, therefore, less experienced endoscopists performed the ESD procedure with assistance from experienced endoscopists. In case of difficulty with hemostasis, an experienced endoscopist took over and completed the procedure. In a general clinical setting without a back-up expert endoscopist, use of epinephrine-added solution might contribute to completion of the ESD procedure and improvement of en bloc resection rate.

Some studies indicate that submucosal injection of epinephrine-added solution reduces post-procedural bleeding after colorectal polypectomy [12, 13]; therefore, we expected it would reduce delayed bleeding of gastric ESD. However, the delayed bleeding rate in the non-epinephrine and epinephrine groups was not significantly different (both 6 %). A recent meta-analysis of six randomized controlled trials showed that epinephrine injection significantly reduced the occurrence of early bleeding but not of delayed bleeding [26]. Epinephrine

▶ **Table 2** Treatment outcomes in the epinephrine and non-epinephrine groups after propensity score matching.

	Non-Epinephrine group (n = 79)	Epinephrine group (n = 237)	*P* value
En bloc resection (%)	78 (99)	234 (99)	1.000
Mean procedure time, min (SD)	93 (62)	72 (54)	<0.001
Delayed bleeding (%)	5 (6)	15 (6)	1.000
Perforation (%)	0 (0)	2 (0.8)	0.410

SD, standard deviation.

▶ **Table 3** Single and multiple linear regression analysis for factors associated with procedure time,

Variable		Single regression analysis		Multiple regression analysis	
		Coefficient for logarithmic ESD time (95 % CI)	*P* value	Coefficient for logarithmic ESD time (95 % CI)	*P* value
Injection solution	Non-Epinephrine Epinephrine	Reference −0.262 (−0.382, −0.142)	<0.001	Reference −0.320 (−0.418, −0.221)	<0.001
Age, years	≤60 >60	Reference 0.009 (−0.190, 0.209)	0.927	Reference −0.007 (−0.167, 0.154)	0.934
Sex	Male Female	Reference −0.046 (−0.194, 0.103)	0.544	Reference −0.123 (−0.247, 0.001)	0.051
Tumor location	Upper third Middle/lower third	Reference −0.428 (−0.581, −0.275)	<0.001	Reference −0.347 (−0.480, −0.214)	<0.001
Specimen size, mm	≤30 >30	Reference 0.697 (0.589, 0.805)	<0.001	Reference 0.643 (0.538, 0.748)	<0.001
Histological type	Differentiated/adenoma Undifferentiated	Reference 0.431 (0.214, 0.647)	<0.001	Reference 0.094 (−0.089, 0.278)	0.314
Histological depth of tumor invasion	pT1a pT1b	Reference 0.264 (0.098, 0.430)	0.002	Reference −0.057 (−0.201, 0.088)	0.442
Histological ulceration or scar	Absent Present	Reference 0.405 (0.160, 0.650)	0.001	Reference 0.253 (0.049, 0.457)	0.015
Operators' experience	Non-expert Expert	Reference 0.309 (0.168, 0.450)	<0.001	Reference 0.215 (0.095, 0.334)	<0.001

Adjusted for age, sex, tumor location, specimen size, depth of tumor invasion, presence of histological ulcer or scar, and operator experience. Adjusted R-square was 0.36.
CI, confidence interval; ESD, endoscopic submucosal dissection.

has a short duration of action of 5 to 10 minutes; therefore, we considered that epinephrine injection would not be effective for reduction of delayed bleeding of gastric ESD.

Incidence of perforation was not significantly different between the non-epinephrine and epinephrine groups (0 vs. 0.8 %). In case of bleeding, even after hemostasis, blood discolors the submucosal tissue, and degrades the endoscopic visualization of the dissection plane in the submucosa. Then, operators often lose orientation during submucosal dissection and may cut into the muscularis propria and cause perforation. We thought that epinephrine-added solution should avoid such a situation and decrease the incidence of perforation. However, the low incidence of perforation made it difficult to show a significant reduction in incidence.

Multivariate linear regression analysis showed that non-epinephrine submucosal injection, upper third tumor location, specimen size > 30 mm, presence of ulcer scar, and expert endoscopists were independently associated with long procedure time. One reason for the long procedure time of expert endoscopists was because they performed ESD for more difficult lesions than non-expert endoscopists did. All these factors were consistent with previous reports [15–17]. After adjustment for all these factors, a significant association remained between ESD procedure time and submucosal injection of epinephrine-added solution.

As this was retrospective study, control of bias for selecting epinephrine-added solution and non-epinephrine-added solution should be addressed if possible. In this study, 94.8 % of gas-

tric ESDs were performed with epinephrine-added injection solution. In fact, there were no definite criteria for use of epinephrine-added solution for gastric ESD in our endoscopy unit. For tumor characteristics such as location, size, presence of ulceration or scar, depth of tumor invasion, and histological type, there was no significant difference in proportion of epinephrine used procedure (▶ **Table S1**). We therefore thought those uncertainties resulted in operators not using epinephrine-added solution in some procedures. When we compared frequency of epinephrine-added injection solution among all endoscopists, we found that two endoscopists used non-epinephrine injection solution (13 % and 28 %, respectively) more frequently than others (5.0 %). In regard to year of procedures, we found that the frequency of non-epinephrine-used procedure was significantly higher in 2015 (11 %) than in other years (4 %). Because the prevalence of non-epinephrine injection procedure was only high in this year and there is no increasing or decreasing trend, we suspected this happened by chance. Even if we included "non-frequent epinephrine user" and "Year 2015" as covariables, multiple linear regression analysis showed independent statistical significance of epinephrine-added injection solution for short procedure times (Coefficient for logarithmic ESD time: –0.43 [–0.59, –0.27], $P < .001$).

This study had several limitations. First, although selection bias was reduced by the propensity score matching method, the study sample was derived from a single center. Our planned multicenter randomized trial should clarify whether the benefits of epinephrine-added solution in our study can be generalized. Second, because this was a retrospective analysis, we could not measure the time for mucosal incision and submucosal dissection separately. Moreover, time of forceps hemostasis and number of patients affected were not evaluated. If we had such data, we could evaluate further whether our speculation that epinephrine reduced bleeding during submucosal dissection and reduced ESD procedure time was appropriate. Third, as this was a retrospective study, all AEs, especially blood pressure and pulse rate during the procedure, were not completely recorded in all cases. Therefore, harm caused by epinephrine injection was not fully assessed. This information will be evaluated in a future prospective study. Fourth, we could not obtain information about time of delayed bleeding. Different characteristics and pathogenesis are suggested according to onset time (≤ 24 or > 24 hours) of delayed bleeding after gastric ESD [27, 28]. Submucosal epinephrine injection may be effective for certain types of delayed bleeding. Such detailed clinical information could be collected in a prospective study. Fifth, we categorized endoscopist experience according to certification by the Japan Gastroenterological Endoscopy Society for 10 years or experience with > 100 cases of gastric ESD. Procedures performed by non-expert endoscopists were often taken over by an assistant expert endoscopist, but such information was not included as a variable. Therefore, actual operator expertise may not be accurately reflected in the variable of operators' experience.

Despite these limitations, to the best of our knowledge, this was the first study to explore the usefulness of epinephrine-added submucosal injection solution in gastric ESD. The results suggest that injection of epinephrine-added solution into the submucosa shortens the procedure time of gastric ESD in patients with EGC, and a further randomized controlled trial is warranted to validate our results.

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Competing interests

The authors declare that they have no conflict of interest.

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▶ **Table S1** Baseline characteristics of epinephrine and non-epinephrine groups before propensity score matching.

	Non-epinephrine group (n = 83)	Epinephrine group (n = 1516)	*P* value
Median age, years (IQR)	71 (12)	71 (12)	0.506
Sex (%)			0.720
▪ Male	64 (77)	1143 (75)	
▪ Female	19 (23)	373 (25)	
Tumor location (%)			0.790
▪ Upper third	14 (17)	287 (19)	
▪ Middle third	30 (36)	497 (33)	
▪ Lower third	39 (47)	732 (48)	
Median specimen size, mm (IQR)	35 (13)	38 (18)	0.046
Histological ulceration or scar (%)			0.223
▪ Absent	79 (95)	1385 (91)	
▪ Present	4 (5)	132 (9)	
Histological depth of tumor invasion (%)			0.610
▪ pT1a	69 (83)	1291 (85)	
▪ pT1b	14 (17)	225 (15)	
Histological type (%)			0.260
▪ Differentiated	69 (83)	1343 (89)	
▪ Undifferentiated	11 (13)	123 (8)	
▪ Adenoma	3 (4)	49 (3)	
Operator experience (%)			0.330
▪ Non-expert	64 (77)	1234 (81)	
▪ Expert	19 (23)	282 (19)	

IQR, interquartile range.