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Postoperative bleeding after gastric endoscopic submucosal dissection in patients receiving antithrombotic therapy

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Abstract

Background and aims It is controversial whether antithrombotic therapy increases the risk of bleeding after endoscopic submucosal dissection (ESD). The aim of this study was to evaluate the effects of antithrombotic therapy on gastric ESD.

Methods Patients who underwent gastric ESD at Toranomon Hospital between April 2005 and July 2014 were enrolled. The risk of post-ESD bleeding was evaluated by multivariate logistic regression analysis.

Results Of 1781 patients enrolled, 253 were taking an antithrombotic; 186 discontinued taking a single antithrombotic ($n = 150$) or multiple antithrombotics ($n = 36$) before ESD, whereas 15 continued taking a single antiplatelet agent and another 52 switched to heparin alternative therapy during the peri-ESD period. Post-ESD bleeding occurred in 101 patients (5.7 %): 68 patients (3.8 %) who did not take an antithrombotic, 11 patients (7.3 %) who discontinued taking a single antithrombotic, six patients (16.7 %) who discontinued taking multiple antithrombotics, one patient (6.7 %) who continued taking a single antiplatelet agent, and 15 patients (28.8 %) who switched to heparin therapy. In multivariate analysis, heparin alternative therapy [odds ratio (OR) 10.04, 95 % confidence interval (CI) 4.35–23.16], discontinuation of the use of multiple antithrombotics before ESD (OR 5.44, 95 % CI 2.00–14.79), tumor location in the lower third of the stomach (OR 2.17, 95 % CI: 1.32–3.58), and a long procedure time (100 min or greater; OR 2.00, 95 % CI 1.25–3.20) were independent risk factors for post-ESD bleeding. Among 52 subjects who switched to heparin therapy, one developed acute renal infarction and one developed cerebral bleeding.

Conclusions Because heparin alternative therapy significantly increases the risk of post-ESD bleeding and may not decrease the risk of thromboembolic events, other options should be considered for patients receiving anticoagulation therapy.

Keywords Endoscopic submucosal dissection · Antithrombotic · Heparin · Gastric tumor

Introduction

Endoscopic submucosal dissection (ESD) is accepted as a highly curative resection for early gastric cancer without metastasis. Compared with endoscopic mucosal resection, ESD has curative advantages because of the high rate of R0 resection, even in patients with ulceration or difficult gastric location [1–5]. However, in contrast with its superior curability, ESD is associated with higher rates of procedure-related complications; this remains an important issue to be resolved.

The rate of post-ESD bleeding in the stomach has been reported to range between 0 and 15.6 % [6, 7], which is higher than the rate of post-ESD bleeding in the colon (1.5–6.6 %) [7–11] and esophagus (0–5.2 %) [7, 12, 13]. Previous studies have shown that tumor location, size, and noncoagulated vessels exposed on the ESD ulcer bed are significantly associated with a higher rate of post-ESD bleeding in the stomach [14–16]. However, there are conflicting reports as to the relationship between the use of antithrombotic agents and post-ESD bleeding. For

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example, Lim et al. [17] reported that there was no significant independent association between continuous administration of antiplatelet drugs and post-ESD bleeding; however, Koh et al. [18] reported that antithrombotic therapy was an independent risk factor for delayed bleeding. Moreover, there are no informative data on the relationship between post-ESD bleeding and anticoagulants such as warfarin and heparin, which, given their pharmacological action, would be thought likely to increase the rate of post-ESD bleeding. Therefore, endoscopists face the practical difficulty of deciding how best to manage patients taking anticoagulants during the gastric ESD perioperative period .

The aim of the present study was to evaluate the effects of different types of antithrombotic therapy on bleeding after gastric ESD, with particular emphasis on patients who were switched to heparin therapy as an alternative to anticoagulant therapy.

Methods

Subjects

Patients who underwent gastric ESD at Toranomon Hospital between April 2005 and July 2014 were enrolled in the present study, with the exception of patients with a history of upper gastrointestinal tract surgery, including esophagectomy or gastrectomy. Patients were also excluded from the study if ESD was performed simultaneously in two or more portions of the stomach. Indications for ESD were based on endoscopic and pathologic findings. To investigate potential risk factors for postoperative bleeding after ESD, the following variables were analyzed: age, sex, comorbidities that could affect bleeding (e.g., central neurological disease, pulmonary disease, cardiovascular disease, renal disease, hepatic disease, hypertension, and diabetes mellitus), the use of antithrombotic agents (continued use of antiplatelet agents, discontinuation of use of a single antithrombotic agent or multiple antithrombotic agents, heparin alternative therapy), the maximum diameter of the resected specimen (less than 20 mm or 20 mm or more), tumor location (upper, middle, or lower third of the stomach), pathologic factors (cancer or adenoma, histologic depth, ulcer presence), and operation time. The indications for ESD were determined on the basis of endoscopic findings, including chromoendoscopy with indigo carmine dye, and biopsy. The criteria for gastric ESD used at Toranomon Hospital are those published by the Japanese Gastric Cancer Association [19]. All patients provided written informed consent to undergo the proposed procedure. The study itself was approved by the hospital Ethics Committee.

ESD procedure

The ESD procedure was performed with a hook knife (KD-620LR; Olympus Medical Science, Tokyo, Japan), a flex knife (KD-630L; Olympus Medical Science), and a dual knife (KD-650Q; Olympus Medical Science) through a two-channel scope equipped with multibending and water jet functions (GIF-2TQ260 M; Olympus Medical Science) or a single-channel endoscope (Q260 J Olympus Medical Science). A soft transparent hood (D-201-13404; Olympus Medical Science) was attached to the tip of the endoscope to obtain good, direct endoscopic views of the submucosal layer. Marker dots were placed on the normal mucosa approximately 5 mm from the tumor margin to indicate the safety margins. After submucosal injection of glycerol solution (10 % glycerol and 5 % fructose; Chugai Pharmaceutical, Tokyo, Japan) containing a small amount of indigo carmine and epinephrine, a mucosal incision was made outside the marker dots. Hyaluronic acid solution was added to the glycerol solution being injected if mucosal elevation was insufficient because of ulceration of the lesion or massive fibrosis of the submucosal layer. After mucosal incision, the submucosal layer was dissected directly to obtain a perfect specimen, and complete en bloc resection was performed. Hemostatic forceps (HDB2422 W; Pentax, Tokyo, Japan) in soft coagulation mode were used to control bleeding during the procedure. In all cases, prophylactic coagulation of visible vessels on the mucosal defect was performed immediately after ESD with hemostatic forceps or with EZ Clips (HX-610-090/HX-610-090S/HX-610-135; Olympus Medical Systems).

ESD was usually performed in conscious patients sedated with a mixture of diazepam (5–20 mg) and pethidine hydrochloride (35–70). However, if the procedure was expected to take longer 2 h, general anesthesia was administered.

Patients started drinking water and a liquid diet the day after the ESD procedure if there were no signs of perforation or post-ESD bleeding. A proton pump inhibitor was administered to all patients on the day of ESD, and use was regularly continued for 60 days after ESD. In most cases, second-look endoscopy was performed on day 7 after ESD, and the decision to discharge the patient from the hospital was made if there was no stigma of bleeding (Forrest type I or type IIa) on the artificial ESD ulcer. In cases in which massive intraprocedural bleeding occurred or was considered as high risk for post-ESD bleeding, second-look endoscopy was performed on day 1 or day 2 after ESD. If a clinical episode of melena or hematemesis occurred during the post-ESD period, emergency endoscopy was performed, with therapeutic endoscopic hemostasis, if necessary, with use of hemostatic forceps or hemostatic clips. The method used to achieve hemostasis was selected on the

basis of the bleeding condition. Efforts to achieve hemostasis were continued until active bleeding had stopped for several seconds, including after flushing with water, or the visible vessels had disappeared.

Management of antithrombotic treatment

If patients were being treated with oral antithrombotic agents, such as low-dose aspirin, thienopyridine, or cilostazol, the prescribing physicians were consulted as to how best to manage antithrombotic therapy during the peri-ESD period. In most patients who were taking antithrombotics before ESD and who were assessed as having low risk of cardiovascular events, aspirin use was discontinued 3–5 days before ESD, thienopyridine use was discontinued 5–7 days before ESD, and warfarin use was discontinued 3–4 days before ESD, whereas patients at high risk of cardiovascular events were either treated with intravenously administered heparin as an alternative or continued receiving their antiplatelet agent therapy. Unfractionated heparin was used as the heparin alternative therapy, and continuous administration of heparin was initiated and controlled to keep the activated partial thromboplastin time at 1.5-fold to 2.5-fold that of the control. Heparin therapy was stopped 6 h before ESD. Antithrombotic treatment was restarted as soon as possible when hemostasis was confirmed by the absence of symptoms of gastrointestinal bleeding or no significant decrease in hemoglobin level. In patients taking warfarin, heparin therapy was discontinued when the prothrombin time international normalized ratio reached approximately 1.5–2.5. For patients who were restarted on antiplatelet agent therapy, heparin therapy was discontinued on the same day.

Definitions of post-ESD bleeding

Post-ESD bleeding was defined as an episode of hematemesis/melena or a decrease in hemoglobin levels (more than 2 g/dL). All patients meeting this criterion underwent emergency esophagogastroduodenoscopy, and endoscopic hemostatic procedures were performed when active bleeding (Forrest type I) or stigmata of potential bleeding (Forrest type IIa) were observed. Preventive hemostasis for visible vessels without the clinical criterion of bleeding on second-look endoscopy was not included in post-ESD bleeding.

Evaluation of resected specimens

Gastric neoplasms were categorized according to their location (i.e., upper, middle, or lower third of the stomach). Tumor size and ulceration were determined histopathologically, and the size of the resected specimen was measured at its maximum diameter.

Statistical analysis

Unless indicated otherwise, data are expressed as the mean ± standard deviation. Mean quantitative values among groups were compared statistically by analysis of variance followed by the t test.

These categorical variables were compared statistically by the chi-squared test or Fisher's exact test in univariate analysis. Those variables with $P < 0.05$ on univariate analysis were examined in multivariate logistic regression models. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated by logistic regression analysis to identify factors associated with postoperative bleeding. Two-tailed $P < 0.05$ was considered significant. All data analyses were conducted with Stata version 11 (StataCorp, College Station, TX, USA).

Results

In all, 1781 patients were enrolled in the study; clinicopathologic characteristics of the patients are shown in Tables 1 and 2. The mean patient age was 69.0 years. Many patients had comorbidities, including cardiovascular disease (13.5 %) and central neurological disease (7.8 %), which required antithrombotic therapy. Of the 1781 patients, 253 (14.2 %) were being treated with antithrombotic agents. During the peri-ESD period, 186 of these 253 patients discontinued taking antithrombotic agents: 150 discontinued taking a single agent and 36 discontinued taking multiple agents. Of the remaining patients who were receiving antithrombotic therapy, 15 continued taking a single antiplatelet agent and 52 were switched to heparin therapy. Table 3 provides details of the antithrombotic agents whose use was discontinued or continued in all 253 patients. Heparin alternative therapy was administered to 52 patients: 40 patients (76.9 %) who had been taking an anticoagulant agent with ($n = 17$) or without ($n = 23$) other antithrombotics, five patients (9.6 %) who had been taking multiple antiplatelet agents, and seven patients (13.5 %) who had been taking a single antiplatelet agent.

Post-ESD bleeding occurred in 101 patients (5.7 %) in total. Relationships between post-ESD bleeding and various clinicopathologic factors were examined by univariate analysis (Table 1). Significant relationships were identified between post-ESD bleeding and six factors: cardiovascular disease, antithrombotic use, tumor location (upper and lower third of the stomach), tumor size (20 mm or greater), the presence of an ulcer in the tumor, and operation time (100 min or longer). With regard to antithrombotic

Table 1 Clinicopathologic characteristics of the patients and univariate analysis of the relationship between post-endoscopic submucosal dissection (*ESD*) bleeding and various clinicopathologic factors

	All patients (n = 1781)	No bleeding (n = 1680)	Bleeding (n = 101)	Bleeding rate (%)	P
Males/females	1377/404	1298/382	79/22	5.7/5.4	0.824
Age (years)	69.0 ± 9.4	69.0 ± 9.4	67.7 ± 10.1		0.154
Comorbidities					
Central neurological disease	139	126	13	9.4	0.051
Pulmonary disease	130	118	12	9.2	0.068
Cardiovascular disease	240	218	22	9.2	0.012
Renal disease/dialysis	89/19	83/16	6/3	6.7/15.8	0.654
Hepatic disease/hepatic cirrhosis	130/47	119/44	11/3	8.5/6.4	0.165
Hypertension	663	624	39	5.9	0.766
Diabetes mellitus	343	325	18	5.2	0.706
Antithrombotic user	253	220	33	13.0	<0.001
Continued use of a single antiplatelet agent	15	14	1	6.7	0.585
Discontinued use of a single antithrombotic	150	139	11	7.3	0.358
Discontinued use of multiple antithrombotics	36	30	6	16.7	0.004
Heparin alternative therapy	52	37	15	28.8	<0.001
Tumor location					
Upper third of the stomach	323	313	10	3.1	0.027
Middle third of the stomach	550	525	25	4.5	0.170
Lower third of the stomach	908	842	66	7.3	0.003
Pathologic finding					
Carcinoma/adenoma	1566/215	1473/207	93/8	5.9/3.7	0.187
Tumor size (mm)	20.1 ± 15.6	19.9 ± 15.3	24.5 ± 19.0		0.004
Tumor size ≧20 mm	687	637	50	7.3	0.020
Tumor depth					
Intramucosal	1540	1450	90	5.8	0.424
Submucosal or deeper	241	230	11	4.6	
Presence of ulcer in tumor	265	243	22	8.3	0.045
Operation time (min)	88.2 ± 54.6	87.1 ± 53.7	107.6 ± 64.3		<0.001
No. with ESD <100 min/≧100 min	1183/598	1130/550	53/48	4.5/8.0	0.002

Unless indicated otherwise, the data are given as the mean ± standard deviation or as the number of patients in each group

therapy, heparin alternative therapy ($P < 0.001$) and discontinuation of the use of multiple antithrombotic agents ($P = 0.004$) were significantly related to post-ESD bleeding. Tumor location in the lower third of the stomach was significantly associated with a high rate of post-ESD bleeding, whereas tumor location in the upper third of the stomach was associated with a low rate of bleeding.

Multivariate analysis was then performed on these factors to determine which factors remained associated with post-ESD bleeding (Table 4). Heparin alternative therapy, discontinuation of the use of multiple antithrombotic agents, tumor location in the lower third of the stomach, and long operation time (100 min or longer) were

significantly related to post-ESD bleeding. Of these factors, the OR was higher for heparin alternative therapy (OR 10.04, 95 % CI 4.35–23.16) and discontinuation of the use of multiple antithrombotic agents (OR 5.44, 95 % CI 2.00–14.79).

Next, we examined relationships between clinical outcomes of ESD and subgroups on the basis of antithrombotic use (Table 2). If patients who were not using antithrombotic agents were set as the reference group, the ORs of post-ESD bleeding were significantly higher for patients receiving heparin alternative therapy (OR 8.70, 95 % CI 4.56–16.6) and those who discontinued use of multiple antithrombotic agents (OR 4.29, 95 % CI 1.73–10.66). Similarly, the ORs

Table 2 Clinical characteristics and outcomes of gastric endoscopic submucosal dissection (*ESD*) according to antithrombotic use

	All patients	No antithrombotic	Continued single antiplatlet agent use	Discontinued antithrombotic use		Heparin
				Single	Multiple	
Patients	1781	1528	15	150	36	52
Age (years)	69.0 ± 9.4	68.1 ± 9.4	73.9 ± 6.9	74.0 ± 7.8	73.9 ± 6.7	75.6 ± 6.9
Males/females	1377/404	1162/366	13/2	130/20	31/5	41/11
Absolute indication	934 (52.4 %)	805 (52.7 %)	13 (86.7 %)	72 (48.0 %)	21 (58.3 %)	23 (44.2 %)
Expanded indication	642 (36.0 %)	549 (35.9 %)	2 (13.3 %)	61 (40.7 %)	12 (33.3 %)	18 (34.6 %)
Outside of indication	205 (11.5 %)	174 (11.4 %)	0 (0 %)	17 (11.3 %)	3 (8.3 %)	11 (21.2 %)
Post-ESD bleeding	101 (5.7 %)	68 (4.5 %)	1 (6.7 %)	11 (7.3 %)	6 (16.7 %)	15 (28.8 %)
OR[a]		1.00	1.53 (0.19–11.8)	1.70 (0.88–3.29)	4.29 (1.73–10.7)	8.70 (4.56–16.6)
Median timing of post-ESD bleeding[b] (days)	3 (0–15)	2 (0–15)	6 (6–6)	3 (1–14)	4.5 (1–13)	7 (2–10)
CR[a]		1.00	2.47 (−5.07 to 10.01)	2.47 (0.04–4.90)	2.30 (−0.88 to 5.49)	3.00 (0.87–5.14)
Blood transfusion	18 (1.0 %)	9 (0.6 %)	0 (0.0 %)	3 (2.0 %)	2 (5.6 %)	4 (7.7 %)
OR[a]		1.00	Not evaluated	3.44 (0.92–12.9)	9.92 (2.06–47.7)	14.06 (4.18–47.3)
Perforation	39 (2.2 %)	34 (2.22 %)	0 (0 %)	4 (2.7 %)	0 (0 %)	1 (1.9 %)
OR[a]		1.00	Not evaluated	1.17 (0.41–3.34)	Not evaluated	0.90 (0.12–6.72)
Hospital stay (days)	10.7 ± 7.6	10.1 ± 5.8	13.2 ± 8.6	12.3 ± 14.7	13.4 ± 7.9	21.5 ± 13.8
CR[a]		1.00	3.13 (−0.69 to 6.88)	2.25 (1.01–3.48)	3.32 (0.89–5.75)	11.45 (9.42–13.5)
Thromboembolism after ESD	1 (0.06 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (1.9 %)

Unless indicated otherwise, data are given as the mean ± standard deviation or as the number of patients in each group

CI confidence interval, *CR* coefficient of regression, *OR* odds ratio

[a] The 95 % confidence interval is given in *parentheses*

[b] The range is given in *parentheses*

of blood transfusion were significantly higher for patients receiving heparin alternative therapy (OR 14.06, 95 % CI 4.18–47.3) and those who discontinued use of multiple antithrombotic agents (OR 9.92, 95 % CI 2.06–47.7). Furthermore, the timing of post-ESD bleeding tended to be later in patients receiving heparin alternative therapy compared with patients who were not taking any antithrombotic agent (median day 7 vs day 2 after ESD; coefficient of regression 3.00, 95 % CI 0.87–5.14 if patients not taking antithrombotic agents were set as the reference group). The length of hospital stay was almost doubled in patients receiving heparin alternative therapy compared with patients not taking any antithrombotic agent (21.5 ± 13.8 days vs 10.1 ± 5.8 days, respectively).

Perforation occurred in 39 patients (2.2 %). All perforations were cured without surgery by conservative treatment with intravenous administration of antibiotics, a proton pump inhibitor, and by withholding oral intake for a few days.

Thromboembolism during the peri-ESD period was observed in one patient who was switched to heparin therapy; left renal infarction occurred on day 7 after ESD when heparin alternative therapy and warfarin were administered simultaneously. One major hemorrhage other than gastrointestinal bleeding occurred in one patient receiving heparin alternative therapy in whom heparin therapy was not restarted; specifically, this patient experienced cerebral bleeding in an old cerebral infarction in the left hemisphere 12 h after completion of ESD. Thromboembolism and major bleeding other than gastrointestinal bleeding did not occur during the peri-ESD period in any patients who were not receiving heparin alternative therapy.

Discussion

The present study provides detailed information regarding the relationship between bleeding after gastric ESD and antithrombotic therapy in a large cohort of 1781 patients, including 253 patients (14.1 %) who were being treated with antithrombotic agents. Regardless of discontinuation or continuation of use of the drug, taking a single antiplatelet agent did not significantly alter the postoperative bleeding risk. In contrast, multivariate analysis identified that heparin alternative therapy and discontinuation of use of multiple antithrombotic agents significantly increased the risk of post-ESD bleeding. A possible explanation for this is that the antithrombotic effect of heparin alternative therapy and multiple antithrombotics is stronger than that of a single antithrombotic, and some antithrombotic effect

Table 3 Details of the antithrombotic agents used in 253 patients

Antithrombotic type	All patients (n = 253)	Continued single antiplatelet agent use (n = 15)	Discontinued antithrombotic use		Heparin (n = 52)
			Single (n = 150)	Multiple (n = 36)	
Aspirin	100 (39.5 %)	6 (40.0 %)	90 (60.0 %)	–	4 (7.7 %)
Thienopyridine	23 (9.1 %)	4 (26.7 %)	17 (11.3 %)	–	2 (3.8 %)
Cilostazol	17 (6.7 %)	1 (6.7 %)	15 (10.0 %)	–	1 (1.9 %)
Warfarin	45 (17.8 %)	–	24 (16.0 %)	–	21 (40.4 %)
NOAC	6 (2.4 %)	–	4 (2.7 %)	–	2 (3.8 %)
Aspirin + thienopyridine[a]	24 (9.5 %)	4 (26.7 %)	–	16 (44.4 %)	4 (7.7 %)
Aspirin + cilostazol	13 (5.1 %)	0 (0 %)	–	12 (33.3 %)	1 (1.9 %)
Aspirin + warfarin	17 (7.1 %)	0 (0 %)	–	6 (16.7 %)	11 (21.2 %)
Aspirin + NOAC	1 (0.4 %)	0 (0 %)	–	0 (0 %)	1 (1.9 %)
Thienopyridine + cilostazol	2 (0.8 %)	0 (0 %)	–	2 (5.6 %)	0 (0 %)
Thienopyridine + warfarin	2 (0.8 %)	0 (0 %)	–	0 (0 %)	2 (3.8 %)
Cilostazol + warfarin	1 (0.4 %)	0 (0 %)	–	0 (0 %)	1 (1.9 %)
Aspirin + thienopyridine + warfarin	1 (0.4 %)	0 (0 %)	–	0 (0 %)	1 (1.9 %)
Aspirin + cilostazol + warfarin	1 (0.4 %)	0 (0 %)	–	0 (0 %)	1 (1.9 %)

Data show the number of patients in each group, with percentages in *parentheses*

NOAC novel oral anticoagulant

[a] Continued use of aspirin and discontinued use of thienopyridine during the peri-endoscopic submucosal dissection period

Table 4 Multivariate analysis of factors related to post-endoscopic submucosal dissection bleeding

	OR	95 % CI	P
Heparin alternative therapy	10.04	4.35–23.16	<0.001
Discontinued use of multiple antithrombotics	5.44	2.00–14.79	0.001
Lower third of the stomach	2.17	1.32–3.58	0.002
Operation time $\geqq$ 100 min	2.00	1.25–3.20	0.004
Presence of ulcer in tumor	1.54	0.91–2.59	0.108
Tumor size $\geqq$ 20 mm	1.27	0.81–1.99	0.303
Cardiovascular disease	0.91	0.46–1.79	0.781
Upper third of the stomach	0.56	0.26–1.21	0.138

CI confidence interval, *OR* odds ratio

may remain in the peri-ESD period in cases of discontinued use of multiple antithrombotics and cause post-ESD bleeding at a higher rate even if the use of antithrombotics is discontinued.

Compared with patients who were not receiving antithrombotic therapy, hemorrhage occurred later (on around day 7 after ESD) in patients receiving heparin alternative therapy. During the switch from heparin to warfarin, a certain degree of overlapping action of these two drugs might cause a stronger antithrombotic effect in a later period and consequently caused delayed bleeding.

One of the patients receiving bridging heparin therapy experienced a renal infarction during the period of heparin treatment. Thromboembolic events or major hemorrhage other than gastrointestinal bleeding was not observed in any patients in any other groups who were not receiving

heparin alternative therapy. These data lead us to question whether heparin alternative therapy is truly appropriate for perioperative management of patients taking anticoagulants who are at high risk of thromboembolic events.

The American Society for Gastrointestinal Endoscopy [20] and the Japan Gastroenterological Endoscopy Society [21] guidelines recommend heparin alternative therapy in patients receiving warfarin during endoscopic procedures. However, a recent large randomized prospective trial [22] that enrolled 681 patients reported that heparin bridging therapy during implantation of cardiovascular implantable electronic devices was associated with a significantly higher rate of device-pocket hematoma compared with uninterrupted warfarin therapy (16.0 % vs 3.5 %, respectively) and no difference in the rate of thromboembolic events. Also, two meta-analyses [23, 24]

supported this result. These findings suggest that one option in the perioperative management of gastric ESD is uninterrupted warfarin therapy rather than substitution of heparin for warfarin.

Another option may be the use of novel oral anticoagulants (NOACs) with or without short-term interruption. All NOACs are rapid-acting agents, and so the anticoagulation-off window could be shorter, even in the case of interrupted use. Although the number of patients was limited in the present study, post-ESD bleeding did not occur in the five patients taking NOACs with short-term discontinuation. However, further data are necessary before the use of NOACs can be considered as an appropriate alternative for patients taking warfarin.

The present study showed that a single antiplatelet agent did not significantly affect the postoperative bleeding risk, regardless of whether its use was discontinued or continued. These findings are compatible with those of Sanomura et al. [25] and Lim et al. [17]. So, in patients at moderate to high risk of thromboembolism, gastric ESD with uninterrupted single antiplatelet treatment during the perioperative period could be an acceptable management option [26, 27].

There are several limitations in this study. Firstly, this study is of a retrospective design from a single high-volume center of endoscopy, and thus the results obtained need to be confirmed by further studies of prospective type. The management of antithrombotic agents for treatment of gastric ESD patients was not established previously because of the chronological trend and introduction of guidelines. Antithrombotic therapy is so diverse because of the many different drugs and many combinations of them as shown in Table 3 that the categorization of antithrombotic therapy was complicated. To avoid excessive subdivision of antithrombotic users, we tentatively classified them into four categories: continued use of a single antiplatelet agent, discontinued use of a single antithrombotic, discontinued use of multiple antithrombotics, and heparin alternative therapy. As a result, each category was not uniform but included users taking different drugs or different combinations of antithrombotics (Table 3). The validity of the categorization of antithromotic users should be verified by further studies. Another limitation is that we could not evaluate the relationship between post-ESD bleeding and the time at which antithrombotic use was restarted. The restarting times were too broad to set a clear threshold or criterion for the restarting time for assessment if it influenced the risk of post-ESD bleeding.

In conclusion, perioperative management of anticoagulation is a challenging clinical issue that requires balancing the risk of acute thromboemobolism against the risk of perioperative bleeding. Gastric ESD may be performed in patients taking a single antiplatelet agent regardless of whether use of the drug is continued or discontinued.

Because heparin alternative therapy significantly increases post-ESD bleeding risk and may not decrease the risk of thromboembolic and cardiovascular events, other options should be considered, including warfarin use or the use of NOACs.

Compliance with ethical standards

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for their being included in the study.

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