

## Retrospective Cohort Study

**Postoperative bleeding in patients on antithrombotic therapy after gastric endoscopic submucosal dissection**

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**Abstract****AIM**

To investigate the relationship between postoperative bleeding following gastric endoscopic submucosal dissection (ESD) and individual antithrombotic agents.

**METHODS**

A total of 2488 gastric neoplasms in 2148 consecutive patients treated between May 2001 and June 2016 were studied. The antithrombotic agents were categorized into antiplatelet agents, anticoagulants, and other antithrombotic agents, and we included combination therapies [e.g., dual antiplatelet therapy (DAPT)]. The risk factors associated with post-ESD bleeding, namely, antithrombotic agents overall, individual antithrombotic agents, withdrawal or continuation of antithrombotic agents, and bleeding onset period (during the first six days or thereafter), were analyzed using univariate and multivariate analyses.

## RESULTS

The en bloc resection and complete curative resection rates were 99.2% and 91.9%, respectively. Postoperative bleeding occurred in 5.1% cases. Bleeding occurred in 10.3% of the patients administered antithrombotic agents. Being male ( $P = 0.007$ ), specimen size ( $P < 0.001$ ), and antithrombotic agent used ( $P < 0.001$ ) were independent risk factors for postoperative bleeding. Heparin bridging therapy (HBT) ( $P = 0.002$ ) and DAPT/multidrug combinations ( $P < 0.001$ ) were independent risk factors associated with postoperative bleeding. The bleeding rate of the antithrombotic agent continuation group was significantly higher than that of the withdrawal group ( $P < 0.01$ ). Bleeding within postoperative day (POD) 6 was significantly higher in warfarin ( $P = 0.015$ ), and bleeding after POD 7 was significantly higher in DAPT/multidrug combinations ( $P = 0.007$ ). No thromboembolic events were reported.

## CONCLUSION

We must closely monitor patients administered HBT and DAPT/multidrug combinations after gastric ESD, particularly those administered multidrug combinations after discharge.

**Key words:** Gastric cancer; Endoscopic submucosal dissection; Postoperative hemorrhages; Antithrombotic agent; Heparin

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**Core tip:** The major complication of gastric endoscopic submucosal dissection (ESD) is postoperative bleeding. Previous studies reported the relationship between postoperative bleeding and antithrombotic agents. We aimed to investigate postoperative bleeding following gastric ESD in relation to specific antithrombotic agents. We showed that antithrombotic agents, in particular heparin bridging therapy and dual antiplatelet therapy/multidrug combination, were independent risk factors for delayed bleeding. Furthermore, bleeding in the early period was significantly higher for warfarin, and bleeding in the late period was significantly higher for multidrug combination. We must strictly observe multidrug combination users especially after discharge.

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## INTRODUCTION

Endoscopic submucosal dissection (ESD) for early gastric cancer is routinely performed worldwide,

because it is minimally invasive and effective<sup>[1-3]</sup>. The most common complication associated with gastric ESD is postoperative bleeding, which has a frequency of 3.1%-6.5%<sup>[4-6]</sup>.

The number of individuals administered antithrombotic agents has increased over recent years. The Japan Gastrointestinal Endoscopy Society (JGES) guidelines indicate that withdrawal or continuation of antithrombotic agents depends on whether the patient is at a high or low risk of thromboembolism during ESD<sup>[7]</sup>. The risk of postoperative bleeding increases when gastric ESD is performed on patients on antithrombotic agent therapy<sup>[8-10]</sup>, and antithrombotic agent therapy is an independent risk factor for postoperative bleeding<sup>[11]</sup>. Heparin bridging therapy (HBT) is recommended for patients who are on anticoagulant therapy and are at a high risk of thromboembolism<sup>[7]</sup>, and postoperative bleeding associated with gastric ESD worsens with HBT<sup>[12-14]</sup>. Furthermore, the preventive effect of HBT on thromboembolism is low<sup>[15]</sup>. By contrast, the risk of thromboembolism following antithrombotic agent withdrawal is 0.6%-4.2%<sup>[16-18]</sup>. Thus, caution is required when deciding whether to withdraw or continue antithrombotic agents in preparation for endoscopic treatment.

Few studies have investigated the incidence of thromboembolism following gastric ESD in relation to the different types of antithrombotic agent. Moreover, the safety and validity of HBT remain controversial. This study aimed to evaluate postoperative bleeding, the washout periods, and the thromboembolism incidence in relation to different antithrombotic agents following gastric ESD performed on patients administered antithrombotic agents.

## MATERIALS AND METHODS

Between May 2001 and June 2016, ESD was performed on 2148 patients and 2488 early gastric cancer lesions. Of these patients, 50 with cancer in their remnant stomachs and four with gastric tubes were excluded; thus, 2094 patients and 2434 lesions were evaluated. Multiple lesions resected en bloc were included in this study, and since the analysis was based on ESD-induced ulcers, 2094 patients and 2378 ulcers were investigated. We retrospectively reviewed the clinical records of all patients after obtaining approval from the institutional review board.

ESD is indicated for differentiated mucosal cancer lesions without ulcers (UL[-]), regardless of size, differentiated mucosal cancer lesions  $\leq 3$  cm with ulcers (UL[+]), UL[-] undifferentiated mucosal cancer  $\leq 2$  cm in size<sup>[19-21]</sup>, and for lymph node metastasis-free and distant metastasis-free lesions that have been confirmed by preoperative computed tomography.

The antithrombotic agents were categorized into antiplatelet agents (low-dose aspirin and thienopyridine), anticoagulants [warfarin and direct oral anticoagulants (DOAC)], and other antithrombotic

agents, and we included combination therapies, for example, dual antiplatelet therapy (DAPT). Of the patients who received HBT, 94.9% were switched from warfarin; therefore, the warfarin group was called the non-HBT warfarin monotherapy group and it was analyzed separately from the group administered HBT.

The risk factors associated with postoperative bleeding were investigated in relation to age, sex, the size of the specimen, the tumor's morphology, the tumor's depth, the presence or absence of ulcerative findings, antithrombotic agent use, and the treatment outcomes. The postoperative bleeding risk was investigated in relation to the aforementioned drug categories. The time to bleeding with respect to each drug was separated into an early period, that is, before postoperative day (POD) 6, and a late period, that is, after POD 7. The withdrawal and continuation of the antithrombotic agents, including HBT, were investigated.

### **Management and procedure**

If a patient was taking an oral antithrombotic agent, we consulted the attending physician before the procedure began and determined the feasibility of treatment withdrawal and the duration of the withdrawal period using the JGES guidelines. If patients were taking DAPT or multiple antithrombotic agents, we changed their treatment to low-dose aspirin monotherapy following preprocedural consultations with their attending physicians.

The patients in the antithrombotic agent continuation and withdrawal groups were hospitalized the day before the ESD. Patients switched to HBT from anticoagulant therapy were hospitalized three days before the ESD, and continuous intravenous drip infusions of unfractionated heparin were initiated. In the HBT group, we adjusted the dose to increase the activated partial thromboplastin time to 1.5-2-times that of the pretreatment value. We confirmed that the prothrombin time (PT)-international normalized ratio (INR) was not excessively prolonged on the day of the ESD. We interrupted the HBT 6 h before the ESD, and after the ESD, we confirmed adequate hemostasis at the ulcer's base and restarted the HBT 3 h later. Anticoagulant therapy was reinstated from POD 2 following second-look endoscopy (SLE) on POD 1 to confirm hemostasis. To reach the peak plasma concentrations rapidly, the patients received twice their usual doses of anticoagulant therapy on POD 2, 1.5-times their doses on POD 3, and their usual doses from POD 4 onwards. In the HBT group, we stopped treatment after confirming that the PT-INR had reached its optimum range following the reinstatement of oral treatment. We also reinstated oral treatment in the withdrawal group from POD 2 onwards following SLE. All of the patients received omeprazole drip infusions (40 mg/d) on POD 1. From POD 2 onwards, they received an oral proton pump inhibitor (PPI) that,

until 2014, comprised omeprazole (20 mg/d) and after 2015, comprised esomeprazole (20 mg/d); this treatment continued for at least eight weeks after ESD.

The gastric ESDs were performed using a conventional procedure<sup>[11,22]</sup>. After making the incision, a coagulation procedure was performed on the exposed blood vessels that remained in the ulcer's base using hemostatic forceps (Coagrasper; Olympus Medical Systems Corporation, Tokyo, Japan). A mixture containing aluminum hydroxide gel, liquid magnesium hydroxide, and 10000 U thrombin (approximately 100 mL) was dispersed.

SLE was performed on all patients on POD 1 to check the bleeding from the ulcers' bases, and if exposed blood vessels were detected, prophylactic hemostasis using a clip or coagulation hemostasis was performed. After confirming hemostasis, fluid intakes were resumed, and liquid meals were reinstated from POD 2. Solid meals, oral antithrombotic agents, and PPIs were reinstated simultaneously.

### **Postoperative bleeding definitions**

Postoperative bleeding was defined as clinical evidence of bleeding in ESD-induced ulcers, which included the occurrence of overt hematemesis, the presence of melena, the presence of blood or clots in the stomach, spots of bleeding observed endoscopically, or a reduction in the hemoglobin level of > 2 g/dL. Preventive hemostasis of visible vessels without evidence of bleeding during SLE was not included in the analysis. Most patients were hospitalized for six days after the ESD; hence, bleeding that occurred during hospitalization was defined as early-phase postoperative bleeding, and that which occurred after discharge was defined as late-phase postoperative bleeding.

### **Statistical analysis**

Some of the patients had more than one gastric neoplasm and underwent one or more ESDs. For the statistical analyses, the data from different ESD-induced ulcers were considered to represent statistically independent observations. The patients' characteristics are expressed as the means and the standard deviations. The groups' mean quantitative values were compared using analyses of variance followed by *t* tests. To investigate the potential risk factors associated with post-ESD bleeding, we analyzed the following variables: age; sex; the use of antithrombotic agents, including aspirin, thienopyridine, warfarin, DOACs, HBT, other antithrombotic agents, and DAPT/multidrug combinations; the resected specimen's maximum diameter; the tumor's location; pathological factors, including the macroscopic type, histological depth, and lymphovascular invasion; the ulcer's characteristics; the procedure time; complications, including perforations, postoperative perforations, postoperative bleeding, and thromboembolism; drug withdrawal or

**Table 1 Clinicopathological features and treatment outcomes of all 2094 patients (2434 lesions and 2378 ulcers) *n* (%)**

Age (mean $\pm$ SD, yr)	72 $\pm$ 6.9
Gender	
Male	1786 (75.1)
Female	592 (24.9)
Location	
U	412 (17.5)
M	742 (31.2)
L	122 (51.5)
Morphology	
Protruded	1042 (43.8)
Flat/depressed	1336 (56.2)
Specimen size, (mean $\pm$ SD, mm)	39 $\pm$ 9.8
Depth of invasion	
M	2227 (93.7)
SM	151 (6.3)
Ulcerative findings	
(+)	203 (8.5)
(-)	2175 (91.5)
Anticoagulant agents	
(+)	447 (18.8)
(-)	1931 (81.2)
En-bloc resection	99.2%
R0+curative resection	91.9%
Mean procedure time $\pm$ SD (min)	49 $\pm$ 30.1
Complications	
Perforation	74 (3.1)
Delayed perforation	2 (0.8)
Delayed bleeding	122 (5.1)
Thromboembolism	0

continuation; and the bleeding time frame. For the univariate analyses, the categorical variables were compared using the  $\chi^2$  test and Fisher's exact test, as appropriate, followed by Fisher's least significant difference post hoc test, and those variables with *P* values < 0.05 were included in the multivariate analyses. The ORs and 95% CIs were calculated using logistic regression analyses to identify the factors associated with postoperative bleeding. *P* values < 0.05 were considered statistically significant. All of the statistical analyses were conducted using SPSS, version 13.0 (SPSS Inc., Chicago, IL, United States).

## RESULTS

The ESD procedures were well tolerated by the patients, and their cardiac and respiratory parameters remained stable throughout the procedures. Table 1 presents the clinicopathological characteristics of and the treatment outcomes from the 2094 patients (2434 lesions and 2378 ulcers).

The en-bloc resection and complete curative resection rates were 99.2% and 91.9%, respectively. There were 74 (3.1%) cases with perforations, two (0.08%) postoperative perforations, and 122 (5.1%) cases of postoperative bleeding. No thromboembolic events occurred.

### Risk factors associated with postoperative bleeding

To investigate the risk factors associated with postoperative

bleeding, the ulcers (*n* = 2378) were divided into a bleeding group (*n* = 122) and a non-bleeding group (*n* = 2256). Overall, 447 ulcers (18.8%) occurred in the patients administered antithrombotic agents, and the rate of bleeding was 10.3% (46/447). The univariate analysis showed that being male (*P* = 0.002), a large specimen (*P* < 0.001), submucosal invasive cancer (*P* = 0.045), and antithrombotic agent use (*P* < 0.001) were significantly associated with post-ESD bleeding (Table 2). The multivariate analysis revealed that being male (OR = 2.103, 95%CI: 1.224-3.611, *P* = 0.007), the specimen size (OR = 1.025, 95%CI: 1.013-1.037, *P* < 0.001), and antithrombotic agent use (OR = 2.643, 95%CI: 1.796-3.889, *P* < 0.001) were independent risk factors for postoperative bleeding (Table 3).

### Risk factors for post-ESD bleeding according to the drug(s) administered

The antithrombotic agent group comprised 447 ulcers, and postoperative bleeding occurred in 211 (47.2%) cases on low-dose aspirin, 19 (4.3%) cases on thienopyridine, 17 (3.8%) cases on warfarin, 18 (4.0%) cases on DOACs, 70 (15.7%) cases on other antithrombotic monotherapies, 39 (8.7%) cases on HBT, and 75 (16.8%) cases on DAPT/multidrug combinations (Table 4). In addition, 94.9% (37 cases) of the HBT cases were warfarin users who were switched to HBT.

The bleeding rates were 5.7% (12/211 cases, *P* = 0.224) in the low-dose aspirin group, 0% (0/19 cases, *P* = 0.379) in the thienopyridine group, 5.9% (1/17 cases, *P* = 0.498) in the warfarin group, 5.6% (1/18 cases, *P* = 0.725) in the DOAC group, 4.3% (3/70 cases, *P* = 0.883) in the other antithrombotic monotherapy group, 15.4% (6/39 cases, *P* < 0.01) in the HBT group, and 30.7% (23/75 cases, *P* < 0.01) in the DAPT/multidrug combination group. The multivariate analysis determined that HBT and DAPT/multidrug combinations were independent risk factors for post-ESD bleeding [HBT: OR = 4.244, 95%CI: (1.736-10.380), *P* = 0.002; DAPT/multidrug combinations: OR = 10.325, 95%CI: (6.060-17.593), *P* < 0.001] (Table 5).

### Rates of bleeding associated with antithrombotic agent withdrawal or continuation

The postoperative bleeding rates in the control (1931 ulcers) and withdrawal (401 ulcers) groups were 3.9% (76/1931 ulcers) and 8.0% (32/401 ulcers), respectively, a difference that was significant (*P* < 0.01) (Table 6). The postoperative bleeding rates in the withdrawal (401 ulcers) and continuation (46 ulcers) groups were 8.0% (32/401 ulcers) and 30.4% (14/46 ulcers), respectively, a difference that was significant (*P* < 0.01) (Table 6).

### Bleeding times according to the drug(s) administered

Bleeding during the early period (up to POD 6) was common among the patients administered warfarin (*P*

**Table 2** Univariate analysis of risk factors of delayed bleeding *n* (%)

	<i>n</i> = 2378	Delayed bleeding		<i>P</i> value	OR	95%CI
		(+) <i>n</i> = 122	(-) <i>n</i> = 2256			
Age (mean ± SD, yr)		71.5 ± 8.7	71.1 ± 8.8	0.622 <sup>2</sup>	1.005	0.984-1.027
Gender						
Male	1786 (75.1)	106 (5.9)	1680 (94.1)	0.002 <sup>1</sup>	2.271	1.331-3.875
Female	24.9 (592)	16 (2.7)	576 (97.3)			
Location					Reference	1.0
U	412 (17.3)	17 (4.1)	395 (95.9)			
M	742 (31.2)	40 (5.4)	702 (94.6)	0.342	1.303	0.755-2.250
L	1224 (51.5)	65 (5.3)	1159 (94.7)	0.344	1.324	0.741-2.366
Morphology						
Protruded	1042 (43.8)	49 (4.7)	993 (95.3)	0.404 <sup>1</sup>	0.854	0.589-1.238
Flat/depressed	1336 (56.2)	73 (5.5)	1263 (94.5)			
Specimen size (mean ± SD, mm)	38.9 ± 2.2	44.4 ± 15.1	38.9 ± 13.1	< 0.001 <sup>2</sup>	1.025	1.014-1.037-
Depth of invasion						
M	2227 (93.7)	109 (4.9)	2118 (95.1)	0.045 <sup>1</sup>	1.830	1.004-3.336
SM	151 (6.3)	13 (8.6)	138 (91.4)			
Ulcerative findings						
(+)	203 (8.5)	12 (5.9)	191 (94.1)	0.598 <sup>1</sup>	1.179	0.638-2.179
(-)	2175 (91.5)	110 (5.1)	2065 (94.9)			
Anticoagulant agents						
(+)	447 (18.8)	46 (10.3)	401 (89.7)	< 0.001 <sup>1</sup>	2.800	1.911-4.101
(-)	1931 (81.2)	76 (3.9)	1855 (96.1)			
En-bloc resection rate	99.2%	99.1%	99.2%	0.979	0.973	0.129-7.329
R0+curative resection rate	91.9%	95.1%	97.1%	0.198	1.744	0.740-4.017
Median procedure time (min)	49 ± 30.1	50 ± 30.8	50 ± 32.2	0.885 <sup>2</sup>	1.033	0.840-2.354

<sup>1</sup>χ<sup>2</sup> test; <sup>2</sup>*t*-test.

**Table 3** Multivariate analysis of risk factors of delayed bleeding

	<i>P</i> value	OR	95%CI
Male	0.007	2.103	1.224-3.611
Median specimen size	< 0.001	1.025	1.013-1.037
SM	0.187	1.516	0.817-2.812
Anticoagulant agents (+)	< 0.001	2.643	1.796-3.889

= 0.015), and bleeding during the late period (from POD 7 onwards) was common among the patients administered DAPT/multidrug combinations (*P* = 0.007) (Table 7). Bleeding was commonly observed during the early period in patients administered HBT, a difference that was not significant compared with the other treatments.

## DISCUSSION

In this study, we investigated the risk of bleeding associated with gastric ESD, the bleeding time, and the risk of bleeding associated with treatment withdrawal or continuation according to the antithrombotic agent(s) administered. We determined that being male, a large specimen, and antithrombotic agent use were independent risk factors for postoperative bleeding. Previous reports revealed that the prevalence of ischemic heart disease and stroke is higher for male than for female<sup>[23-25]</sup>. Furthermore, since ischemic heart disease and stroke are closely related to antithrombotic therapy, we considered that male sex is an

independent risk factor.

Furthermore, HBT and DAPT/multidrug combinations were independent risk factors for postoperative bleeding. This study's findings showed that postoperative bleeding was significantly higher in the group that continued antithrombotic agents compared with the group that withdrew antithrombotic agents. Our findings also showed that early-phase bleeding was more frequent in association with HBT and that late-phase bleeding was more frequent in association with DAPT/multidrug combinations.

The bleeding rate for patients on antithrombotic agents is high at 23.3%-35.5%<sup>[26,27]</sup>, that associated with HBT is higher at 23.8%-61.5%, and it is even higher in association with multidrug combinations<sup>[12-14,28,29]</sup>. We found that HBT and DAPT/multidrug combinations were independent risk factors associated with postoperative bleeding, which concurs with previous reports. However, until now, the risk of post-ESD bleeding and the bleeding time frames in the context of individual antithrombotic agents had not been investigated in a large number of subjects. Furthermore, this is the first study to compare the risk of bleeding in a control group and a treatment withdrawal group, and in a withdrawal group and treatment continuation group.

In this investigation, 94.9% (37/39) of the patients treated with HBT were switched from warfarin therapy. When HBT patients are administered warfarin, they will be affected by the HBT; hence, the effect of warfarin alone on postoperative bleeding cannot be analyzed. Consequently, this study's analysis involved assigning the patients to an HBT group or a non-HBT warfarin

**Table 4 Univariate analysis of risk factors for delayed bleeding by each antithrombotic agent *n* (%)**

	Delayed bleeding		<i>P</i> value <sup>1</sup>	OR	95%CI
	(+)	(-)			
Aspirin					
(+) ( <i>n</i> = 211)	12 (5.7)	199 (94.3)	0.224	1.472	0.787-2.753
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			
Thienopyridine					
(+) ( <i>n</i> = 19)	0 (0)	19 (100)	0.379	0.990	0.985-0.994
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			
Warfarin					
(+) ( <i>n</i> = 17)	1 (5.9)	16 (94.1)	0.498	1.525	0.200-11.653
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			
DOAC					
(+) ( <i>n</i> = 18)	1 (5.6)	17 (94.4)	0.725	1.436	0.189-10.930
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			
Others					
(+) ( <i>n</i> = 70)	3 (4.3)	67 (95.7)	0.883	1.093	0.336-3.554
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			
HBT					
(+) ( <i>n</i> = 39)	6 (15.4)	33 (84.6)	< 0.01	4.438	1.805-10.911
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			
DAPT/multidrug combination					
(+) ( <i>n</i> = 75)	23 (30.7)	52 (69.3)	< 0.01	10.796	6.280-18.558
(-) ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)			

<sup>1</sup>χ<sup>2</sup> test. DOAC: Direct oral anticoagulants; HBT: Heparin bridging therapy; DAPT: Dual antiplatelet therapy.

**Table 5 Multivariate analysis of risk factors for delayed bleeding by each antithrombotic agent**

	<i>P</i> value	OR	95%CI
HBT	0.002	4.244	1.736-10.380
DAPT/multidrug combination	< 0.001	10.325	6.060-17.593

HBT: Heparin bridging therapy; DAPT: Dual antiplatelet therapy.

monotherapy group. In the warfarin group, 94% (16/17) of the patients continued their treatment, but there was no significant difference in relation to bleeding, a finding that has never been reported before.

The postoperative bleeding rate was high in the antithrombotic agent continuation group compared with the control and withdrawal groups. Therefore, to reduce the bleeding risk, antithrombotic agent withdrawal is preferable. However, between 1% and 4.2% of patients at a high risk of thromboembolism develop thromboembolisms following drug withdrawal<sup>[15-18]</sup>. Thus, drug withdrawal may trigger serious life-threatening complications. In contrast, another report states that the prognosis is significantly worse following the onset of gastrointestinal bleeding after percutaneous coronary intervention<sup>[30]</sup>. Regarding therapy withdrawal or continuation, physicians should examine a patient’s thromboembolism risk and the drug type, and consider implementing tailor-made treatment for each case.

The JGES guidelines recommend that for patients at a high risk of thromboembolism during endoscopic procedures that are associated with a high risk of

bleeding, including ESD, it is preferable to administer aspirin alone with no treatment withdrawal. The guidelines from the United States and Europe also recommend continuing aspirin therapy<sup>[7,31,32]</sup>. Therefore, the continuation of aspirin therapy was permitted in this study. However, the times at which drug treatments other than aspirin are resumed in DAPT and combination therapy regimens to reduce the risk of bleeding must be investigated. On the other hand, withdrawing anticoagulants, for example, warfarin, will likely induce serious thromboembolism. Therefore, HBT after withdrawal is recommended for endoscopic procedures<sup>[7]</sup>. Patients administered warfarin and periprocedural HBT are at a higher risk of bleeding compared with those who are not administered HBT<sup>[33,34]</sup>. Currently, insufficient evidence exists that supports the prevention of thromboembolism by HBT, and reports have been published that state that it either has no effect on or it has an equivalent efficacy at preventing arterial thromboembolism and reducing the risk of bleeding<sup>[15,33]</sup>. In this study, perioperative thromboembolism did not occur in any of the patients; hence, the prophylactic effect of HBT on blood clots could not be verified. This study’s results demonstrated that HBT is an independent risk factor associated with bleeding, and considering previous reports, we recommend that patients on warfarin should either be switched to DOAC rather than HBT, or that they should continue warfarin treatment when ESD is indicated.

The times at which HBT and antithrombotic agent treatments are reinstated are determined once hemostasis has been confirmed; however, definitive timings have not been established. We reinstated heparin treatment from 3 h after ESD, after performing

**Table 6 Investigation of rate of bleeding based on withdrawal or continuation of antithrombotic agent *n* (%)**

	Delayed bleeding		<i>P</i> value <sup>1</sup>	OR	95%CI
	(+)	(-)			
Control group/withdrawal group					
Control ( <i>n</i> = 1931)	76 (3.9)	1855 (96.1)	< 0.01	0.472	0.308-0.725
Withdrawal ( <i>n</i> = 401)	32 (8.0)	369 (92.0)			
Withdrawal group/continuation group					
Withdrawal ( <i>n</i> = 401)	32 (8.0)	369 (92.0)	< 0.01	5.045	2.445-10.411
Continuation ( <i>n</i> = 46)	14 (30.4)	32 (69.6)			

<sup>1</sup> $\chi^2$  test.**Table 7 Investigation of bleeding time by each drug**

	Bleeding (+) <i>n</i> = 46		<i>P</i> value <sup>1</sup>	OR	95%CI
	Early phase	Late phase			
Aspirin ( <i>n</i> = 12)	6	6	0.477	0.619	0.164-2.332
Thienopyridine ( <i>n</i> = 0)	0	0	-	-	-
Warfarin ( <i>n</i> = 7)	6	1	0.015	0.083	0.009-0.767
DOAC ( <i>n</i> = 1)	0	1	1.000	1.038	0.964-1.118
Others ( <i>n</i> = 3)	2	1	0.561	0.327	0.027-3.892
HBT ( <i>n</i> = 6)	5	1	0.068	0.108	0.011-1.015
DAPT/multidrug combination ( <i>n</i> = 23)	5	18	0.007	5.600	1.530-20.492

<sup>1</sup>Fisher's exact test. DOAC: Direct oral anticoagulants; HBT: Heparin bridging therapy; DAPT: Dual antiplatelet therapy.

adequate hemostasis of the ulcer base and accounting for the thromboembolism risk. Furthermore, we performed SLE on the day after ESD, and we performed preventive hemostasis on the exposed blood vessels in the ulcers' bases, even if there was no bleeding. Early bleeding was common before POD 6 in the HBT group. This may have been caused by the synergistic pharmacological effects of the heparin and the anticoagulants, which were reinstated from POD 2 onwards, reaching their peak plasma concentrations. In contrast, in the DAPT/multidrug combination group, the plasma concentrations of the respective antithrombotic agents were stable and required time to reach their peak ranges, and late bleeding became common from POD 7 onwards.

Many reports describe post-ESD bleeding prevention, and coagulation immediately after ESD is commonly used and is effective<sup>[5]</sup>. Applying a polyglycolic acid sheet to and spreading fibrin glue on ESD-induced ulcer bases are novel, easy, and effective approaches to the management of post-ESD bleeding in patients on antithrombotic agents<sup>[35-37]</sup>, and they will be useful for patients who are at a high risk of bleeding.

The findings from a multicenter prospective randomized study of SLE undertaken by Mochizuki *et al.*<sup>[38]</sup> showed that the postoperative bleeding rates did not differ significantly between the SLE and the non-SLE groups. These investigators reported that scheduled SLE could not be expected to reduce bleeding. However, another report states that SLE and third-look esophago-gastroduodenoscopy are useful for preventing post-ESD bleeding in patients on antithrombotic agents<sup>[39]</sup>. Further investigations into these approaches are warranted.

The limitations of this study are as follows. First, this is a single-center retrospective cohort study. Second, the relationship between *Helicobacter pylori* (*H. pylori*) and postoperative bleeding after gastric ESD was not investigated. We could not confirm the information about *H. pylori* infection and eradication, particularly in the initial cases, because of the long research period. As a result, only about 60% of the total information of *H. pylori* could be obtained; thus, the state of *H. pylori* infection was excluded as a factor for postoperative bleeding in this study.

This study's findings demonstrated that HBT and DAPT/multidrug combinations are independent risk factors for postoperative bleeding in patients on antithrombotic agents who undergo gastric ESD. Adequate management that considers the prevention of bleeding and thromboembolism is important.

#### **What is already known on this topic**

Antithrombotic agent therapy increases the risk of bleeding after ESD. Serious thromboembolism may occur following antithrombotic agent withdrawal.

#### **What this study adds to our knowledge**

HBT and DAPT/multidrug combinations are independent risk factors for bleeding post-ESD. Early-phase bleeding was more frequently associated with HBT, and late-phase bleeding was more frequently associated with DAPT/multidrug combinations. When patients on warfarin monotherapy and those who are switched from warfarin to HBT are investigated separately, HBT alone becomes a risk factor.

## COMMENTS

### Background

The most common complication associated with gastric endoscopic submucosal dissection (ESD) is postoperative bleeding. An increasing number of reports have revealed that antithrombotic agent therapy is a risk factor after ESD. Withdrawal or continuation of antithrombotic agents is decided depending on the patient's risk of thromboembolism. However, many reports showed that antithrombotic agents promote the risk of postoperative bleeding and withdrawal promotes thrombosis. Although it is clinically questionable whether all types of antithrombotic agents can be equally treated, detailed investigation has not yet been performed and the risk and benefit of continuation or withdrawal remain controversial. Thus, this study aimed to evaluate postoperative bleeding, the washout periods, and the thromboembolism incidence in relation to different antithrombotic agents following gastric ESD performed on patients administered antithrombotic agents.

### Research frontiers

A previous retrospective study showed that the bleeding rate for gastric ESD patients on antithrombotic agents is high at 23.3%-35.5%, that associated with heparin bridge therapy (HBT) is higher, and it is even higher in association with multidrug combinations. The Japan Gastrointestinal Endoscopy Society (JGES) guidelines indicate that withdrawal or continuation of antithrombotic agents depends on whether the patient is at a high or low risk of thromboembolism during ESD. The JGES guidelines recommend that for patients at a high risk of thromboembolism during ESD, administration of aspirin alone with no treatment withdrawal is preferred, and the guidelines from the United States and Europe also recommend continuing aspirin therapy. Although HBT after withdrawal is also recommended for endoscopic procedures in the JGES guidelines, patients administered warfarin and periprocedural HBT are reported at a higher risk of bleeding compared with those who are not administered HBT. Furthermore, only few reports are available on the relationship with direct oral anticoagulants or dual antiplatelet therapy (DAPT). Studies on drug continuation or withdrawal, by each drug, and the period to bleeding also remain unreported.

### Innovations and breakthroughs

The authors determined that being male, a large specimen, and antithrombotic agent use were independent risk factors for postoperative bleeding; this finding is almost the same as previously reported. Furthermore, HBT and DAPT/multidrug combinations were independent risk factors for postoperative bleeding. These study's findings showed that postoperative bleeding was significantly higher in the group that continued antithrombotic agents compared with the group that withdrew antithrombotic agents. These findings also showed that early-phase bleeding was more frequent in association with HBT and that late-phase bleeding was more frequent in association with DAPT/multidrug combinations. The authors recommend paying strict attention to observe multidrug combination users, especially after discharge. However, until now, the risk of post-ESD bleeding and the bleeding time frames in the context of individual antithrombotic agents have not been investigated in a large number of subjects. The present study is the first to compare the risk of bleeding in a control group and a treatment withdrawal group, and in a withdrawal group and a treatment continuation group.

### Applications

The results of this study serve as additional evidence to support the calculation of the risk of postoperative bleeding after gastric ESD posed by each antithrombotic agent based on continuation or withdrawal of the antithrombotic agent. Based on the present research, more robust evidence can be obtained in a prospective study.

### Terminology

ESD is one of the endoscopic treatment procedures for superficial gastrointestinal cancer, which can be resected in en-bloc manner.

### Peer-review

This original research paper investigates retrospectively postoperative bleeding in patients on antithrombotic therapy after gastric ESD from the clinical records

of patients in a large cohort. The authors showed that antithrombotic agent in particular heparin bridging therapy and DAPT/multidrug combination were independent risk factors for delayed bleeding, and furthermore, bleeding in the early period was significantly higher for warfarin, and bleeding in the late period was significantly higher for multidrug combination. They recommend to pay attention strictly to observe multidrug combination users especially after discharge. The structure of the manuscript is complete. The scientific question and the aim of the study was stressed clearly in the introduction. The study is well-designed, and all methods and techniques were explained in details. The results add new findings and information to current knowledge. The results were discussed comprehensively.

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