Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4998-20
Intern Med 59: 2643-2651, 2020
http://internmed.jp

【 ORIGINAL ARTICLE 】

Continued Aspirin Treatment May Be a Risk Factor of Delayed Bleeding after Gastric Endoscopic Submucosal Dissection under Heparin Replacement: A Retrospective Multicenter Study

Kenta Hamada[1], Hiromitsu Kanzaki[1], Masafumi Inoue[2], Shuhei Ishiyama[3], Kenji Yamauchi[4], Koji Miyahara[5], Tatsuya Toyokawa[6], Takao Tsuzuki[7], Jiro Miyaike[8], Minoru Matsubara[9], Sakuma Takahashi[10], Mamoru Nishimura[11], Ryuta Takenaka[12], Naoko Yunoki[13], Shinichiro Hori[14], Sayo Kobayashi[15], Yasushi Yamasaki[1], Yoshiro Kawahara[16], Hideki Ishikawa[17] and Hiroyuki Okada[1]

Abstract:

Objective Gastric endoscopic submucosal dissection (ESD) under heparin replacement (HR) of warfarin reportedly has a high risk of delayed bleeding (24-57%). It is possible that the delayed bleeding risk may have changed over the years. We evaluated the current risk of delayed bleeding after gastric ESD under HR of anticoagulant agents.

Methods We retrospectively reviewed the delayed bleeding rate and analyzed the risk factors for delayed bleeding.

Patients Consecutive patients who underwent gastric ESD under HR of anticoagulant agents from July 2015 to June 2017.

Results A total of 32 patients with a solitary early gastric cancer and taking anticoagulant agents were analyzed, including 24 patients on warfarin (the warfarin group) and 8 patients on direct oral anticoagulants (the DOAC group). Three (9.4%) patients experienced delayed bleeding: three (12.5%) patients in the warfarin group and no patients in the DOAC group. Continued aspirin treatment was identified to be a risk factor of delayed bleeding (p=0.01).

Conclusion Careful management may be required for patients undergoing gastric ESD under continued aspirin treatment in addition to HR of anticoagulant agents; although the delayed bleeding risk after gastric ESD under HR of anticoagulant agents might have decreased over the years.

Key words: anticoagulant agent, bleeding, endoscopic submucosal dissection, gastric cancer, heparin replacement, warfarin

(Intern Med 59: 2643-2651, 2020)
(DOI: 10.2169/internalmedicine.4998-20)

[1]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan, [2]Department of Gastroenterology, Japanese Red Cross Okayama Hospital, Japan, [3]Department of Internal Medicine, Okayama Saiseikai General Hospital, Japan, [4]Department of Gastroenterology, Mitoyo General Hospital, Japan, [5]Department of Internal Medicine, Hiroshima City Hospital, Japan, [6]Department of Gastroenterology, National Hospital Organization Fukuyama Medical Center, Japan, [7]Department of Internal Medicine, Japanese Red Cross Society Himeji Hospital, Japan, [8]Department of Internal Medicine, Saiseikai Imabari Hospital, Japan, [9]Department of Internal Medicine, Sumitomo Besshi Hospital, Japan, [10]Department of Gastroenterology, Kagawa Prefectural Central Hospital, Japan, [11]Department of Internal Medicine, Okayama City Hospital, Japan, [12]Department of Internal Medicine, Tsuyama Chuo Hospital, Japan, [13]Department of Internal Medicine, Akaiwa Medical Association Hospital, Japan, [14]Department of Endoscopy, National Hospital Organization Shikoku Cancer Center, Japan, [15]Department of Internal Medicine, Fukuyama City Hospital, Japan, [16]Department of Endoscopy, Okayama University Hospital, Japan and [17]Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Japan
Received: April 1, 2020; Accepted: May 18, 2020; Advance Publication by J-STAGE: July 7, 2020
Correspondence to Dr. Kenta Hamada, paosishou@yahoo.co.jp

Introduction

Patients with valvular heart disease or atrial fibrillation (AF) with a high $CHADS_2$ or CHA_2DS_2-VASc score have a high risk of developing thromboembolic diseases (1). Anticoagulant agents are generally recommended for the primary and secondary prevention of such diseases. For the thromboembolic complications associated with warfarin withdrawal in gastroenterological endoscopic procedures, the incidence of stroke was reported in 1.06% of patients (2). The Japan Gastroenterological Endoscopy Society (JGES) guidelines (2012) (3), the British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines (2016) (4), and the American Society for Gastrointestinal Endoscopy (ASGE) guidelines (2016) (5) recommend that patients using warfarin should be treated under heparin replacement (HR) as a bridge therapy to reduce the risk of thromboembolic complications during the perioperative period of therapeutic endoscopy. However, several investigators have reported that gastric endoscopic submucosal dissection (ESD) under HR of warfarin has a high risk of delayed bleeding (24-57%) (6-8). Based on these reports, the JGES guidelines were revised in 2017 (9), which allow for continued warfarin treatment in patients where the prothrombin time international normalized ratio (PT-INR) fell within the therapeutic range, or a temporary switch to direct oral anticoagulant (DOAC) in those with non-valvular atrial fibrillation as an alternative to HR. However, since these studies were small and included old data (6-8), the delayed bleeding risk after gastric ESD under HR might have changed over the years. We therefore planned a retrospective multi-center study to evaluate the current risk of delayed bleeding after gastric ESD under HR of anticoagulant agents, by analyzing data collected during a few years prior to the revision of the JGES guidelines.

Materials and Methods

Participants

This was a retrospective, multi-center study conducted at 15 institutes (Okayama Gut Study Group) in Japan, comprising 1 university hospital, 1 cancer center and 13 general hospitals. To determine the study period, a preliminary questionnaire survey was conducted. Based on the survey, as a study group, >50 cases with anticoagulant agents underwent gastric ESD every year. Therefore, the study period was determined for 2 years as >100 cases were expected to be included. The records for all patients who underwent ESD for adenocarcinomas or suspected adenocarcinomas of the stomach from July 2015 to June 2017 were extracted from the database and reviewed. The inclusion and exclusion criteria were determined prior to the data collection. Patients were included if they met the following criteria: (i) under anticoagulant therapy using warfarin or DOAC, (ii) aged 20 years or older, (iii) Eastern Cooperative Oncology Group performance status of 0-2, (iv) hemoglobin ≥9 g/dL, (v) platelet ≥100,000/mm^3, (vi) aspartate aminotransferase and alanine aminotransferase ≤150 U/L. The exclusion criteria were as follows: (i) anticoagulant therapy withdrawal or continuance without HR during the perioperative period, (ii) simultaneous ESD for two or more lesions, (iii) dialysis treatment, (iv) the systemic administration of corticosteroids or non-steroidal anti-inflammatory drugs, (v) a history of gastrectomy or reconstruction of the gastric tube, (vi) pregnant or lactating. Patients taking DOAC were included in the present study since the JGES guidelines (2012) recommended HR of DOAC; although the BSG and ESGE guidelines (2016) and the ASGE guidelines (2016) do not have such a recommendation. As only anonymous retrospective data was used in the present study, the opt-out method was used for obtaining informed consent. The study protocol was approved first by the ethics committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, and subsequently by each institutional review board. The ethics committee approved that the present study waived the need for written informed consent as part of the study approval. The study was performed in accordance with the Declaration of Helsinki.

Treatments

Endoscopic submucosal dissection (ESD)

All ESD procedures were performed by either an experienced endoscopist or a resident under the supervision of an experienced endoscopist. The ESD procedure was carried out as previously described (10). The ESD procedure consisted of the following: Marking around a lesion, mucosal incision, submucosal dissection, and lesion removal. Just after the removal of the specimen, the created ulcer was carefully examined, and any visible vessels and adherent clots were coagulated. Clip closure or cover with a polyglycolic acid sheet was not performed in any of the cases. The time for the ESD procedure was measured from the start of marking until the completion of post-ESD coagulation. The ESD procedure was performed using an ITKnife2 (KD-611 L; Olympus Medical Systems, Tokyo, Japan), a DualKnife (KD-650L; Olympus), an ITKnife (KD-610L; Olympus), or an ITknife nano (KD-612; Olympus). A Coagrasper (FD-411UR; Olympus) was mainly used as hemostatic forceps and a VIO 300D (ERBE Elektromedizin, Tübingen, Germany) was used as a high-frequency generator. Either a proton pump inhibitor or a vonoprazan was administered for 5 to 8 weeks after the ESD.

Management of anticoagulant and HR

In the present study, anticoagulant agents included warfarin and DOAC such as dabigatran, rivaroxaban, and apixaban. Anticoagulant withdrawal and HR were generally conducted according to the JGES guidelines (2012) (3). In the case of warfarin, warfarin was withdrawn ≥3 days before ESD and the continuous intravenous administration of un-

fractionated heparin (10,000-20,000 units per day) was started after warfarin withdrawal. The activated partial thromboplastin time (APTT) during HR was controlled from 1.5- to 2-fold higher than the normal value and heparin was discontinued 3-6 hours before ESD. Heparin was re-administered the night of ESD or the day after ESD after the absence of bleeding was confirmed. Warfarin was re-administered after heparin was started. Heparin was discontinued after the PT-INR level had reached the effective range (≥1.50). In the case of DOAC, DOAC was withdrawn ≥24 hours before ESD and heparin was started after DOAC withdrawal. HR was controlled as mentioned before, and heparin was discontinued soon after the DOAC re-administration. Heparin, warfarin, and DOAC were all re-administered with the same dose at the time of discontinuation before the ESD.

Management of antiplatelet agents

The antiplatelet agents included aspirin, ticlopidine, clopidogrel, eicosapentaenoic acid, and limaprost alfadex. The drug holidays of antiplatelet agents before ESD consisted of 5-8 days for aspirin, 7 days for ticlopidine, 9 days for clopidogrel, 6 days for eicosapentaenoic acid, and 5 days for limaprost alfadex. The antiplatelet agent was re-administered 2-8 days after ESD. In cases where the antiplatelet agent could not be withdrawn due to a high risk of thromboembolic complications, aspirin was continued during the perioperative period.

Measured outcomes

The primary endpoint was the delayed bleeding rate after gastric ESD under HR of anticoagulant agents. The delayed bleeding was defined as hematemesis, melena, or a decrease in hemoglobin of ≥2 g/dL; this was endoscopically confirmed as active bleeding from an ESD-induced gastric ulcer or blood in the stomach, occurring from soon after ESD to 28 days after ESD.

The secondary endpoints were (i) the delayed bleeding rate according to the anticoagulant agent (warfarin or DOAC); (ii) the rate of intra-ESD bleeding requiring transfusion; (iii) the rate of thromboembolic complications from soon after anticoagulant agent withdrawal to 28 days after ESD; and (iv) the timing of the delayed bleeding. A subgroup analysis was conducted to identify the risk factors for delayed bleeding after gastric ESD.

Statistical analysis

All continuous variables are expressed as the median with the range. Statistical analyses were conducted using Fisher's exact test for categorical outcomes. The computer software JMP version 12 (SAS, Cary, USA) was used for the data analysis. The significance level was set at $p<0.05$.

Results

Participant flow

From July 2015 to June 2017, 2,480 patients with gastric neoplasms were treated by gastric ESD and were assessed for eligibility. A total of 116 patients took anticoagulant agents and 47 patients were treated under HR during the perioperative period of gastric ESD. Fifteen patients were excluded based on the exclusion criteria, and a total of 32 patients taking anticoagulant agents were thus analyzed; these included 24 patients on warfarin (the warfarin group) and 8 patients on DOAC (the DOAC group), including 4 patients on apixaban, 3 patients on rivaroxaban, and 1 patient on dabigatran (Fig. 1).

Characteristics of the patients, lesions, perioperative management, and ESD procedures

The median age of patients was 79 years (65-91 years), and 88% were male. The most frequent comorbidity associated with cardiovascular disease was hypertension (72%) followed by AF (69%), dyslipidemia (34%), congestive heart failure (31%), and diabetes mellitus (25%). Of these, 31% of the patients were taking an antiplatelet agent. The DOAC group had a higher frequency of AF than the warfarin group since DOAC is usually used for non-valvular AF. While, patients in the warfarin group had more severe comorbidities than those in the DOAC group, such as congestive heart failure, valvular heart disease, prior deep vein thrombosis, pulmonary hypertension, cardiomyopathy, and old myocardial infarction. The median tumor size was 15.5 mm; 41% were located in the antrum, and 13% had an ulcer or scar (Table 1a).

Continued aspirin therapy was only used in the warfarin group. Multiple antiplatelet therapy was not used in this study population. A proton pump inhibitor was used in 66% of the patients and vonoprazan was used in 34% of the patients to treat ESD-induced gastric ulcers. The median resected specimen size was 38 mm. The en bloc resection rate and complete resection rate were 100% and 97%, respectively. Second-look endoscopy was performed on all patients either before oral food intake or discharge (Table 1b).

Delayed bleeding and other complications

In total, three (9.4%) patients experienced delayed bleeding after gastric ESD under HR of anticoagulant agents. In the warfarin group, three (12.5%) patients experienced delayed bleeding and two (8.3%) received transfusion; in the DOAC group, no patients experienced these complications. Delayed bleeding was managed by endoscopic hemostasis using hemostatic forceps with a soft coagulation mode in all the three cases. No patients in either group experienced intra-ESD bleeding requiring transfusion, thromboembolic complications, or perforation (Table 2).

Characteristics and timing of delayed bleeding

Delayed bleeding occurred in three patients taking warfarin. Two (67%) patients were taking aspirin and both continued with aspirin therapy because of an old myocardial infarction. The median days until delayed bleeding was 10 days (4-13 days); two (67%) patients experienced delayed bleeding after discharge (5 and 8 days after heparin with-

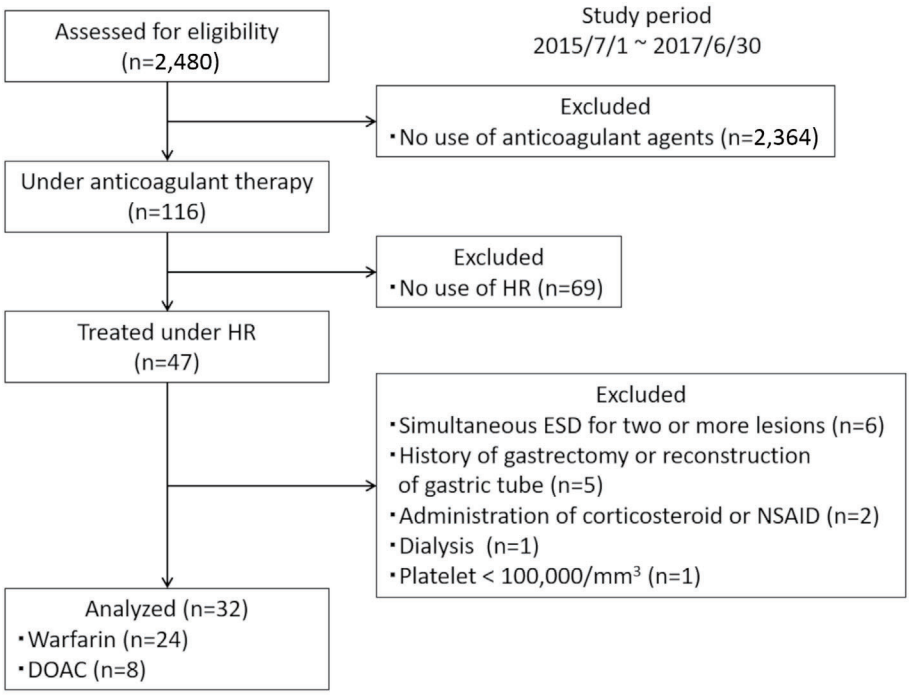


Figure 1. **Flow diagram of the study participants. HR: heparin replacement, ESD: endoscopic submucosal dissection, NSAID: nonsteroidal anti-inflammatory drug, DOAC: direct oral anticoagulant**

Table 1a. **Characteristics of the Patients, Antithrombotic Therapy and Lesions.**

	Total n=32	Warfarin n=24	DOAC n=8
Age (years)	79 (65-91)	80 (65-91)	72.5 (65-83)
Male	28 (88)	21 (88)	7 (88)
Comorbidities associated with cardiovascular disease			
Hypertension	23 (72)	18 (75)	5 (62)
Atrial fibrillation	22 (69)	14 (58)	8 (100)
$CHADS_2$ score[a]	2 (0-5)	2 (0-5)	2 (0-3)
CHA_2DS_2-VASc score[a]	5 (1-7)	5 (1-7)	4 (1-5)
Dyslipidemia	11 (34)	8 (33)	3 (38)
Congestive heart failure	10 (31)	9 (38)	1 (13)
Diabetes mellitus	8 (25)	7 (29)	1 (13)
Valvular heart disease	3 (9)	3 (13)	0 (0)
Pulmonary hypertension	2 (6)	2 (8)	0 (0)
Cardiomyopathy	2 (6)	2 (8)	0 (0)
Peripheral artery disease	2 (6)	1 (4)	1 (13)
Past history associated with cardiovascular disease			
Stroke or TIA	6 (19)	4 (17)	2 (25)
Deep vein thrombosis	3 (9)	3 (13)	0 (0)
Myocardial infarction	2 (6)	2 (8)	0 (0)
Antiplatelet agent	10 (31)	7 (29)	3 (38)
Aspirin	6 (19)	4 (17)	2 (25)
Ticlopidine	1 (3)	1 (4)	0 (0)
Clopidogrel	1 (3)	0 (0)	1 (13)
Eicosapentaenoic acid	1 (3)	1 (4)	0 (0)
Limaprost alfadex	1 (3)	1 (4)	0 (0)
Helicobacter pylori (positive/negative/unknown)	9/18/5	7/14/3	2/4/2
Tumor located in the antrum	13 (41)	10 (42)	3 (38)
Pathological tumor size (mm)	15.5 (6-65)	15.5 (6-65)	14.5 (6-30)
Tumor with ulcer/scar	4 (13)	2 (8)	2 (25)

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

[a]$CHADS_2$ and CHA_2DS_2-VASc scores were evaluated in 22 patients with atrial fibrillation.

DOAC: direct oral anticoagulant, TIA: transient ischemic attack

Table 1b. Characteristics of Perioperative Management, ESD Procedures and Outcomes.

	Total n=32	Warfarin n=24	DOAC n=8
Anticoagulant therapy			
Period of anticoagulant agent withdrawal before ESD (days)	4 (1-7)	5 (3-7)	2.5 (1-5)
Period of HR before ESD (days)	3 (1-6)	4 (2-6)	2 (1-4)
Period until HR re-start after ESD (days)	1 (0-2)	1 (0-2)	0 (0-1)
Period until anticoagulant agent re-administration after ESD (days)	1 (1-6)	1.5 (1-6)	1 (1-3)
Period of HR after ESD (days)	5 (1-15)	5 (1-15)	2 (1-2)
Antiplatelet therapy			
Continued aspirin treatment[a]	3 (9)	3 (13)	0 (0)
Period of aspirin withdrawal before ESD (days)[b]	6 (5-8)	5.5 (5-6)	7 (6-8)
Period until antiplatelet agent re-administration after ESD (days)[c]	7 (2-8)	6 (2-8)	7 (2-8)
Acid suppressant	32 (100)	24 (100)	8 (100)
Proton pump inhibitor	21 (66)	16 (67)	5 (62)
Vonoprazan	11 (34)	8 (33)	3 (38)
ESD			
ESD procedural items			
ITKnife2	16 (50)	15 (62)	1 (12.5)
DualKnife	11 (34)	7 (30)	4 (50)
ITKnife	4 (13)	2 (8)	2 (25)
ITknife nano	1 (3)	0 (0)	1 (12.5)
Procedure time for ESD (min)	65 (23-348)	59 (23-348)	80 (51-250)
Resected specimen size (mm)	38 (20-100)	37 (20-100)	40 (24-50)
En bloc resection	32 (100)	24 (100)	8 (100)
Complete resection	31 (97)	23 (96)	8 (100)
Second-look endoscopy	32 (100)	24 (100)	8 (100)
Timing of SLE			
1-2 days after ESD (before oral food intake)	24 (75)	19 (79)	5 (62)
6-8 days after ESD (before discharge)	8 (25)	5 (21)	3 (38)
Prophylactic hemostasis during SLE[d]			
Yes	9 (29)	5 (22)	4 (50)
No	22 (71)	18 (78)	4 (50)

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

[a]Ticlopidine was switched to aspirin in one patient.

[b]The aspirin withdrawal period was evaluated in 4 patients who stopped taking aspirin.

[c]The period until antiplatelet agent re-administration was evaluated in 7 patients who stopped taking antiplatelet agents.

[d]One patient was excluded from the Warfarin group because the patient experienced delayed bleeding before the scheduled second-look endoscopy.

ESD: endoscopic submucosal dissection, DOAC: direct oral anticoagulant, HR: heparin replacement, SLE: second-look endoscopy

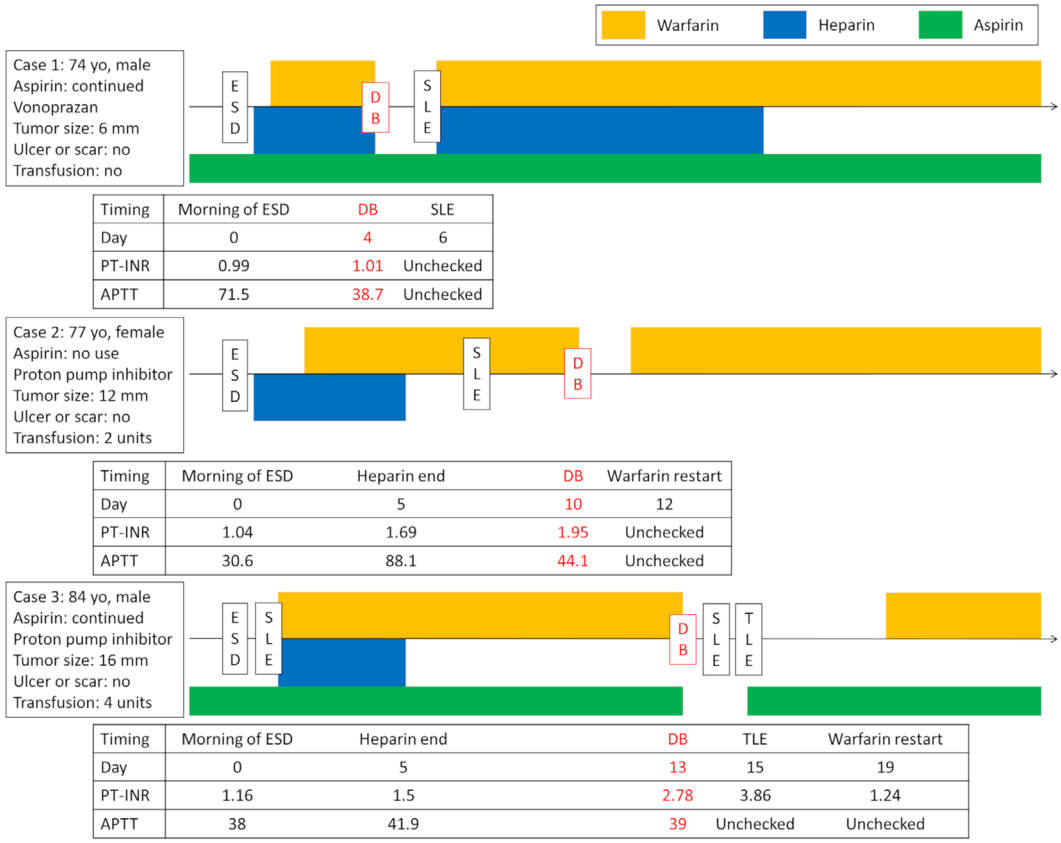
Table 2. Complications of Gastric ESD under Heparin Replacement.

	Total n=32	Warfarin n=24	DOAC n=8
Delayed bleeding	3 (9.4)	3 (12.5)	0 (0)
Transfusion due to delayed bleeding	2 (6.3)	2 (8.3)	0 (0)
Intra-ESD bleeding requiring transfusion	0 (0)	0 (0)	0 (0)
Thromboembolic complications	0 (0)	0 (0)	0 (0)
Perforation	0 (0)	0 (0)	0 (0)

Data are presented as n (%).

ESD: endoscopic submucosal dissection, DOAC: direct oral anticoagulant

drawal). In all three cases, the delayed bleeding was managed by endoscopic hemostasis using hemostatic forceps with a soft coagulation mode and the same kind and dose of acid suppressant were continued. The detailed information on the patient, lesion, and perioperative management of antithrombotic therapy is shown in Fig. 2.



Timing	Morning of ESD	DB	SLE
Day	0	4	6
PT-INR	0.99	1.01	Unchecked
APTT	71.5	38.7	Unchecked

Timing	Morning of ESD	Heparin end	DB	Warfarin restart
Day	0	5	10	12
PT-INR	1.04	1.69	1.95	Unchecked
APTT	30.6	88.1	44.1	Unchecked

Timing	Morning of ESD	Heparin end	DB	TLE	Warfarin restart
Day	0	5	13	15	19
PT-INR	1.16	1.5	2.78	3.86	1.24
APTT	38	41.9	39	Unchecked	Unchecked

Figure 2. Patient and lesion characteristics, antithrombotic therapy, and timing of bleeding in three patients with delayed bleeding. yo: years old, DB: delayed bleeding, ESD: endoscopic submucosal dissection, SLE: second-look endoscopy, TLE: third-look endoscopy

Subgroup analysis of the risk factors for delayed bleeding

In the subgroup analysis, continued aspirin treatment was identified as a risk factor for delayed bleeding. Two of the 3 (67%) patients under continued aspirin treatment experienced delayed bleeding; however, 1 of 29 (3.4%) patients without continued aspirin treatment experienced delayed bleeding (p=0.01) (Table 3).

Discussion

This study included only the latest 2 year's data and therefore represented the current risk of delayed bleeding after gastric ESD under HR of anticoagulant agents. The delayed bleeding rate was 9.4%: 12.5% in the warfarin group and 0% in the DOAC group, and no life-threatening complications were observed. Continued aspirin treatment was identified to be a risk factor for delayed bleeding after gastric ESD under HR of anticoagulant agents.

In the present study, antiplatelet agents as a whole, including both cases of cessation and aspirin continuation, were not identified to be a risk factor of delayed bleeding after gastric ESD under HR of anticoagulant agents, contrary to the findings of previous studies (6, 11). However, continued aspirin treatment was identified to be a risk factor of delayed bleeding after gastric ESD under HR. Although it remains controversial as to whether continued aspirin treatment alone increases the bleeding risk after gastrointestinal ESD (12, 13), and our results indicate an elevated risk of delayed bleeding with the co-use of HR and aspirin.

The delayed bleeding rates did not differ significantly between the warfarin and DOAC groups. However, since delayed bleeding only occurred in the warfarin group, DOAC is expected to be an alternative to warfarin. A recent nationwide database analysis from Japan demonstrated that DOAC may reduce delayed bleeding after therapeutic endoscopy, including gastric ESD, compared with warfarin regardless of whether HR was also performed (14). However, since the drug indications were different between warfarin and DOAC, the patient's backgrounds might be different between the patients using warfarin and those with DOAC. In the present study, the same limitation was noted, and the sample size was too small to accurately discuss the safety of DOAC. To date there are few reports describing the delayed bleeding risk after gastric ESD for patients using DOAC (11). Therefore, more data are required to accurately determine the safety of DOAC during the perioperative period of gastric ESD.

In the present study, the delayed bleeding rate in the warfarin group (12.5%) was lower than that suggested by previous studies (24-57%) (6-8). Although HR of warfarin was

Table 3. A Univariable Analysis of the Risk Factors for Delayed Bleeding.

	Delayed bleeding (+) n=3	Delayed bleeding (-) n=29	p value
Anticoagulant agent			0.55
Warfarin	3 (13)	21	
DOAC	0 (0)	8	
Antiplatelet agent including both cases of cessation and aspirin continuation			0.22
Yes	2 (20)	8	
No	1 (5)	21	
Continued aspirin treatment			0.01
Yes	2 (67)	1	
No	1 (3)	28	
Acid suppressant			1.0
Proton pump inhibitor	2 (10)	19	
Vonoprazan	1 (9)	10	
Tumor size			0.55
>2 cm	0 (0)	11	
≤ 2 cm	3 (14)	18	
Ulcer or scar in the tumor			1.0
Present	0 (0)	4	
Absent	3 (11)	25	
Tumor location			1.0
Antrum	1 (8)	12	
Body	2 (11)	17	
Timing of SLE			0.14
1-2 days after ESD	1 (4)	23	
6-8 days after ESD	2 (25)	6	

Data are presented as n (delayed bleeding rate, %).

DOAC: direct oral anticoagulant, SLE: second-look endoscopy, ESD: endoscopic submucosal dissection

identified to be a risk factor of delayed bleeding after gastric ESD (10, 11, 14-16), the risk may have decreased over the years. Vonoprazan, a novel potassium-competitive acid blocker, is expected to reduce the delayed bleeding rate after gastric ESD based on the results of a single arm observational study (17), because of its rapid, strong, and sustained acid inhibitory effect (18). However, a randomized phase II study showed that the difference in the delayed bleeding rate after gastric ESD between patients using vonoprazan and proton pump inhibitors was only 1.4% (19). In the present study, the difference was almost the same as that reported in the randomized study and did not show significance (Table 3). The effectiveness of vonoprazan may be small in terms of the prevention of the delayed bleeding after gastric ESD in patients under HR, contrary to expectations. Based on our experience in clinical practice, prophylactic coagulation might be carefully performed in patients immediately after gastric ESD under HR of warfarin owing to the high risk of delayed bleeding in such patients from previous studies. This may have contributed to the decrease in delayed bleeding observed in the present study.

Patients who undergo gastric ESD under HR of warfarin are reported to experience delayed bleeding later than those without HR; this tendency has been explained by the effects of warfarin reaching the therapeutic range under HR, that is, the enhanced anticoagulant effect due to dual anticoagulant therapy of warfarin and heparin (6, 8, 10). In the present study, two of three patients experienced delayed bleeding on postoperative day 10 and 13, and these late onsets were consistent with previous studies (Fig. 2). However, two patients experienced delayed bleeding after discharge, five and eight days after heparin withdrawal. While the other patient who experienced delayed bleeding on postoperative day 4 was under HR at delayed bleeding; however, neither APTT nor PT-INR was abnormally high (Fig. 2). Therefore, the enhanced anticoagulant effect due to dual anticoagulant therapy cannot be applied to the three patients in the present study. From the data, we suspected that the patients who experienced delayed bleeding had a potential bleeding risk regardless of HR. If so, delayed bleeding might have occurred even if HR had not been performed in such cases.

No thromboembolic complications were observed in the present study. Indeed, some patients who underwent gastric ESD under HR of warfarin experienced thromboembolism during the perioperative period (7, 11, 14). Thromboembolism can cause critical complications such as cerebral embolism, deep vein thrombosis, pulmonary embolism, or death. From this point of view, continued warfarin may be a more suitable management method if it does not increase the risk of perioperative bleeding. One observational study reported that there was no significant difference in the delayed bleeding rate among patients who underwent gastric

ESD under the cessation (10%), HR (12%), and continuation (8%) of anticoagulant agents including warfarin and DOAC (20). These results suggest that HR and the continuation of anticoagulant agents may not increase the perioperative bleeding risk. On the other hand, a large randomized, double-blind, placebo-controlled trial showed that HR of warfarin increased bleeding during the perioperative period of various elective invasive procedures compared to a placebo; however, this study only included 10 patients who underwent a high-bleeding-risk endoscopic procedure (21). It remains controversial as to which management method of anticoagulant agents is most suitable during the perioperative period of high-bleeding-risk endoscopic procedures, including gastric ESD. Therefore, we now need to evaluate these methods based on the data from a well-designed randomized controlled trial.

The present study is associated with some limitations. First, this was a retrospective study. Second, the treatments were not performed according to a unified protocol, mainly because of restrictions arising from the study's retrospective design. Third, the sample size was smaller than what we had expected, especially in the DOAC group, mainly owing to the number of non-HR cases being unexpectedly large. However, the sample size of the warfarin group was comparable to previous studies (6-8, 10, 16). Given that there are few reports describing the risk of delayed bleeding after gastric ESD for patients using DOAC, the present study is valuable despite its small sample size. Most previous studies included old data to increase the sample sizes because the number of patients undergoing gastric ESD under HR of anticoagulant agents is not so large (6-8, 10, 11). We therefore collected only the latest two year's data (2015 to 2017) to elucidate the current situation. This is the greatest strength of the present study, and we also chose to conduct a multicenter study in order to compensate for the short study period. Fourth, as a result of the small sample size and low bleeding rate, the number of delayed bleeding events was lower than what we had expected. Therefore, a multivariable analysis to reduce any confounding bias could not be conducted. Finally, the present study lacked a control group, precluding comparisons with other management methods of anticoagulant agents.

In conclusion, this latest, retrospective, multi-center study suggests that careful management may be required for patients undergoing gastric ESD under continued aspirin treatment in addition to HR of anticoagulant agents; although the delayed bleeding risk after gastric ESD under HR of anticoagulant agents might have decreased over the years.

The study protocol was approved first by the ethics committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, and subsequently by each institutional review board. As only anonymous retrospective data was used in the present study, the opt-out method was used for the informed consent. The ethics committee approved that the present study waived the need for written informed consent as part of the study approval.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Dr. Junichiro Nasu (Department of Internal Medicine, Okayama Saiseikai General Hospital), Dr. Masahiro Nakagawa (Department of Internal Medicine, Hiroshima City Hospital), Dr. Masahiro Takatani (Department of Internal Medicine, Japanese Red Cross Society Himeji Hospital), and Dr. Tomoki Inaba (Department of Gastroenterology, Kagawa Prefectural Central Hospital) for their assistance with the data collection.

References

1. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J **31**: 2369-2429, 2010.
2. Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. Neurology **61**: 964-968, 2003.
3. Fujimoto K, Fujishiro M, Kato M, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. Dig Endosc **26**: 1-14, 2014.
4. Veitch AM, Vanbiervliet G, Gershlick AH, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Gut **65**: 374-389, 2016.
5. Acosta RD, Abraham NS, et al.; ASGE Standards of Practice Committee. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc **83**: 3-16, 2016.
6. Takeuchi T, Ota K, Harada S, et al. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. BMC Gastroenterol **13**: 136, 2013.
7. Yoshio T, Nishida T, Kawai N, et al. Gastric ESD under heparin replacement at high-risk patients of thromboembolism is technically feasible but has a high risk of delayed bleeding: Osaka University ESD Study Group. Gastroenterol Res Pract **2013**: 365830, 2013.
8. Matsumura T, Arai M, Maruoka D, et al. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. BMC Gastroenterol **14**: 172, 2014.
9. Kato M, Uedo N, Hokimoto S, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment: 2017 appendix on anticoagulants including direct oral anticoagulants. Dig Endosc **30**: 433-440, 2018.
10. Gotoda T, Hori K, Iwamuro M, et al. Evaluation of the bleeding risk with various antithrombotic therapies after gastric endoscopic submucosal dissection. Endosc Int Open **5**: E653-E662, 2017.
11. Yoshio T, Tomida H, Iwasaki R, et al. Effect of direct oral anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection. Dig Endosc **29**: 686-694, 2017.
12. Wu W, Chen J, Ding Q, Yang D, Yu H, Lin J. Continued use of low-dose aspirin may increase risk of bleeding after gastrointestinal endoscopic submucosal dissection: a meta-analysis. Turk J Gastroenterol **28**: 329-336, 2017.
13. Dong J, Wei K, Deng J, et al. Effects of antithrombotic therapy on bleeding after endoscopic submucosal dissection. Gastrointest Endosc **86**: 807-816, 2017.

14. Nagata N, Yasunaga H, Matsui H, et al. Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: results from a large nationwide database analysis. Gut **67**: 1805-1812, 2018.
15. Sanomura Y, Oka S, Tanaka S, et al. Taking warfarin with heparin replacement and direct oral anticoagulant is a risk factor for bleeding after endoscopic submucosal dissection for early gastric cancer. Digestion **97**: 240-249, 2018.
16. Shindo Y, Matsumoto S, Miyatani H, Yoshida Y, Mashima H. Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics. World J Gastrointest Endosc **8**: 349-356, 2016.
17. Kagawa T, Iwamuro M, Ishikawa S, et al. Vonoprazan prevents bleeding from endoscopic submucosal dissection-induced gastric ulcers. Aliment Pharmacol Ther **44**: 583-591, 2016.
18. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects: a randomized open-label cross-over study. Aliment Pharmacol Ther **42**: 719-730, 2015.
19. Hamada K, Uedo N, Tonai Y, et al. Efficacy of vonoprazan in prevention of bleeding from endoscopic submucosal dissection-induced gastric ulcers: A prospective randomized phase II study. J Gastroenterol **54**: 122-130, 2019.
20. Igarashi K, Takizawa K, Kakushima N, et al. Should antithrombotic therapy be stopped in patients undergoing gastric endoscopic submucosal dissection? Surg Endosc **31**: 1746-1753, 2017.
21. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med **373**: 823-833, 2015.