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Postoperative Bleeding after Gastric Endoscopic Submucosal Dissection in Patients on Anticoagulant Therapy, Especially Warfarin and DOAC

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Abstract

Background and Aims: It is controversial whether anticoagulant therapy increases the risk of bleeding after Endoscopic Submucosal Dissection (ESD). The aim of this study is to evaluate the effects of anticoagulant therapy on gastric ESD.

Methods: Patients who underwent gastric ESD in Toranomon Hospital between April 2005 and July 2017 were enrolled. The risk of post-ESD bleeding was evaluated using multivariate cox proportional hazards analysis.

Results: Of 1979 patients enrolled, 49 were taking anticoagulant agent; 25 discontinued warfarin and switched to heparin alternative therapy during ESD, whereas 24 discontinued DOAC (Direct oral anticoagulant). During 2 months of the entire observational period, post-ESD bleeding occurred in 88 patients (4.4%): 80 patients without any anticoagulant agent (4.1%), 8 patients with anticoagulant agent (9.1%); 4 patients with a warfarin (16.0%), 4patients with DOAC (16.7%). In multivariate analysis, anticoagulant therapy [hazards ratio (HR) 6.24, 95% confidence interval (CI): 2.93–13.27], warfarin (HR4.19, 95% CI: 2.10–16.62), DOAC (HR6.71, 95% CI: 2.39-18.82) were independent risk factors of post-ESD bleeding.

Conclusion: Because anticoagulant therapy significantly increases the risk of post-ESD bleeding, it should be necessary to strictly management at least two weeks after ESD.

Keywords: ESD, Anticoagulant, DOAC, Warfarin, 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 (EMR), ESD has curative advantages because of the high rate of R0 resection, even in patients with ulceration or difficult gastric location [1-4]. 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% [5-7], which is higher than the rate of post-ESD bleeding in the colon (1.5% to 6.6%) 5 {Terasaki, 2014 #26, [7-9]} and esophagus (0% to 5.2%) [5,10,11]. Previous studies have shown that tumor location, size, and non-coagulated vessels exposed on the ESD ulcer bed are significantly associated with a higher rate of post-ESD bleeding in the stomach [12,14-16]. Moreover, our recent study showed that heparin alternative therapy and multiple antithrombotics significantly increases the risk of post-ESD bleeding and heparin alternative therapy may not decrease thromboembolic events. In recent years, there is some report that supports our result [15-17]; on the other hand, there are a few informative data on the relationship between post-ESD bleeding and DOAC (Direct oral anticoagulant). Nagata et al. reported that the risk of post endoscopy GI bleeding was higher in warfarin than DOAC users, however this study did not include information on the lesion location and specific size, lesion morphology, lesion histopathology, and timing of post-ESD bleeding 15. Therefore, endoscopists face the practical difficulty of deciding how best to manage patients taking anticoagulants during the perioperative period of gastric ESD. The aim of the present study was to evaluate the effects of anticoagulant therapy especially warfarin and DOAC on bleeding after gastric ESD.

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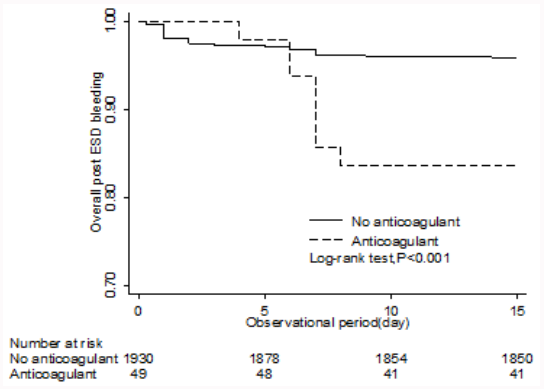

Figure 1: Kaplan-Meier curves for overall post ESD bleeding between patient with no anticoagulant agent and warfarin.

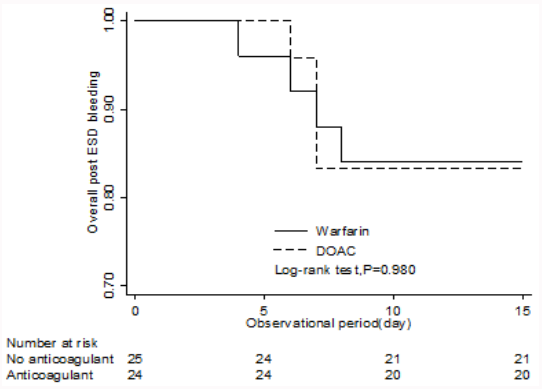

Figure 2: Kaplan-Meier curves for overall post ESD bleeding between patient with warfarin and DOAC.
*No patient occurred post ESD bleeding aftet 2 weeks of ESD

Methods

Subjects

Patients who underwent gastric ESD in Toranomon Hospital between April 2005 and July 2017 were enrolled in the present study, with the exception of patients with a past history of upper Gastrointestinal (GI) tract surgery, including esophagectomy or gastrectomy, were except in this study. 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 pathological findings. Patients were also excluded if the polyglycolic acid sheet sheets were placed over the surgical wound. 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 anticoagulant agents (discontinuation of warfarin and replaced heparin alternative therapy, discontinued DOAC), the tumor size, tumor location (upper, middle, or lower one-third of the stomach, anterior wall, posterior wall, lesser curvature, or greater cuvature of the stomach), pathological factors (cancer or adenoma, histologic depth, ulcer presence), and operation time. The indications for ESD were determined on the basis of endoscopic findings, including chromo endoscopy with indigo carmine dye, and biopsy. The criteria for gastric ESD used in Toranomon Hospital are those published by the Japanese Gastric Cancer Association [18,19]. 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 using a hook knife (KD-620LR; Olympus Medical Science, Tokyo, Japan), flex knife (KD-630L; Olympus Medical Science), and dual knife (KD-650Q; Olympus Medical Science) through a two-channel scope equipped with multi bending and water jet functions (GIF-2TQ260M; Olympus Medical Science) or a single-channel endoscope (Q260J 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 due to 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 (HDB2422W; 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 right 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 mg to 20 mg) and pethidine hydrochloride (35–70). However, if the procedure was expected to exceed 2 hr, patients were administered general anesthesia.

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 (PPI) or Vonoprazan was administered in all patients on the day of ESD, and was regularly continued for 60 days after ESD. In most cases, second-look endoscopy was performed on Day 7 after ESD, and hospital discharge was decided if there was no stigma of bleeding (Forest type I or IIa) on the artificial ESD ulcer. In cases in which massive intra-procedural bleeding occurred or was considered as at high risk for post-ESD bleeding, second-look endoscopy was performed within 3 days 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, using 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 anticoagulant treatment

If patients were being treated with oral anticoagulant agents, such as warfarin or DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban), the prescribing doctors were consulted as to how best to manage anticoagulant therapy during the peri-ESD period. The patients who were taking warfarin before ESD, warfarin was discontinued 3 days to 4 days, and treated with intravenous heparin

Table 1: Clinicopathologic characteristics of the patients and univariate analysis of the relationship between post-endoscopic submucosal dissection (ESD) bleeding and various clinicopathologic factors unless indicated otherwise, data are given as the mean ± SD or as the number of patients in each group.

	Non bleeding N=1891	Bleeding N=88	Bleeding rate (%)	Univariate Model	
				Hazard Ratio (95%CI)	P Value
Age (year)	68.7 ± 9.6	66.2 ± 10.4	-	0.980(0.96 to 1.00)	0.016
Male	1416	66	4.50	refarence	
Females	475	22	4.40	1.11(0.61 0 to 1.61	0.986
Comorbidities					
Central neurological disease	82	6	6.8	1.59(0.69 to 3.64)	0.275
Cardiovascular disease	129	9	6.5	1.52(0.76 to 3.03)	0.234
Pulmonary disease	132	8	5.7	1.33(0.64 to 2.75)	0.444
Hepatic disease	133	11	7.6	1.83(0.97 to 3.44)	0.061
Renal disease	81	3	3.6	0.79(0.25 to 2.48)	0.681
Hypertension	627	28	4.3	0.94(0.60 to 1.47)	0.786
Diabetes mellitus	307	12	3.8	0.82(0.45 to 1.51)	0.525
Anticoagulant	41	8	16.3	3.98(1.92 to 8.24)	<0.001
Warfarin	21	4	16	4.04(1.44 to 10.71)	0.008
DOAC	20	4	16.7	4.04(1.48 to 11.04)	0.006
Tumor Location					
Upper one-third of the stomach	109	1	0.9	0.19(0.03 to 1.38)	0.101
Middle one-third of the stomach	252	5	1.9	0.40(0.16 to 0.98)	0.046
Lower one-third of the stomach	298	24	7.5	1.98(1.24 TO 3.16)	0.004
Anteriror wall of the stomach	250	15	5.7	1.33(0.76 TO 2.32)	0.312
Posterior wall of the stomach	462	20	4.1	0.91(0.55 to 1.49)	0.702
Lesser curvature of the stomach	822	41	4.8	1.14(0.75 to 1.73)	0.552
Greater curvature of the stomach	357	12	3.3	0.69(0.37 to 1.26)	0.226
Tumor size (mm)	19.1 ± 14.5	24 ± 19.6		1.02(1.01 to 1.03)	0.002
Pathological finding					
Adenoma	249	6	2.4	refarence	
Cancer	1642	82	4.8	2.04(0.89 to 4.67)	0.093
Tumor Depth					
M	1650	81	4.7	refarence	
SM1	152	3	1.9	0.41(0.13 to 1.29)	0.127
SM 2	89	4	4.3	0.91(0.33 to 2.49)	0.858
Presence of ulcer in tumor	274	22	7.4	1.92(1.18 to 3.11)	0.008
Operation time	82.5 ± 51.6	105 ± 64.6		1.01(1.00 to 1.01)	<0.001

ESD: Endoscopic Submucosal Dissection

as an alternative therapy. The patients who were taking DOAC before ESD, DOAC was discontinued 1day to 2 days, whereas patients at high risk of cardiovascular events were treated with intravenous heparin as an alternative only before ESD. 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 (aPTT) extended 1.5- to 2.5-fold that of the control. Heparin was stopped 6 hr before ESD. In patients on warfarin, heparin was discontinued when the prothrombin time-international normalized ratio (PT-INR) level reached approximately 1.5–2.5. DOAC was restarted within 2 days after ESD when hemostasis was confirmed by the absence of symptoms of gastrointestinal bleeding or no significant decrease in hemoglobin level.

Definitions of post-ESD bleeding

In the present study, the patient observed for 2 months, post-ESD bleeding was defined as an episode of hematemesis/melena, or a decrease in hemoglobin levels (>2 g/dL). All patients meeting these criteria underwent emergency Esophagogastroduodenoscopy (EGD), and endoscopic hemostatic procedures were performed when active bleeding (Forest type I) or stigmata of potential bleeding (Forest type IIa) was observed. Preventive hemostasis for visible vessels without the clinical criteria of bleeding at second-look endoscopy was not included post-ESD bleeding.

Evaluation of resected specimens

Gastric neoplasms were categorized according to location (i.e. upper, middle, or lower one-third of the stomach, anterior wall, posterior wall, lesser curvature, or greater cuvature of the stomach).

Table 2: Clinical characteristics and outcomes of gastric endoscopic submucosal dissection (ESD) according to antithrombotic use unless indicated otherwise, data are given as the mean ± SD or as the number of patients in each group, with percentages in parentheses. OR, odds ratio; CI, confidence interval; CR, coefficient of regression.

	Noanticogulant	Warfarin	Anticoagulant	
			DOAC	Total
No.patients	1930	25	24	49
Age	68 ± 9.6	75.4 ± 8.18	74.8 ± 6.4	75.1 ± 7.3
CR(95% CI)	refarence	6.97(3.18 to 10.75)	6.36(2.50 to 10.22)	6.67 (3.95 to 9.39)
No. males/females)	1442:488	18:07	22:02	40:09:00
Curaticve resection	1678(86.9%)	20(80.0%)	22(91.7%)	42(85.7%)
Non-curative resection	252(13.1%)	5(20%)	2(8.3%)	7(14.3%)
Perforation	33(1.7%)	0(0%)	1(4.2%)	1(2.0%)
Post -ESD bleeding	80(4.1%)	4(16.0%)	4(16.7%)	8(16.3%)
HR(95% CI)	refarence	4.19(1.53 to 11.46)	4.14(1.51 to 11.32|)	4.25(2.05 to 8.82)
Timing of post - ESD bleeding(days)	3.5 ± 3.4	6.3 ± 1.7	6.8 ± 0.5	6.5 ± 12
CR(95% CI)	refarence	2.8(-0.59-6.11)	3.3(-0.092-6.62)	3.01(0.60 to 5.43)
Blood transfusion	9(0.5%)	1(4.0%)	1(4.2%)	2(4.1%)
OR(95% CI)	refarence	8.89(1.084 to 72.98)	9.28 (1.12 to 76.27	9.08 (1.91 to 43.19)
Operation time (min)	83.9 ± 52.5	78.2 ± 54.4	62.9 ± 39.7	70.7 ± 47.5
CR(95% CI)	refarence	5.63(-26.3 to 15.1)	21.0(-42.11to 0.13)	13.2(-28.03 to 1.72)
Hospital stay days)	10 ± 5.4	18.3 ± 5.2	12.8 ± 6.1	15.6 ± 6.3
CR(95% CI)	refarence	8.3(6.16 to 10.39	2.7(0.55 to 4.87)	5.55 (4.02 to 7.08)

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 ± SD. Mean quantitative values among groups were compared statistically using analysis of variance followed by the t-test.

These categorical variables were compared statistically using the Chi-squared test or Fisher's exact test in univariate analysis. The effectiveness of anticoagulant on the post ESD bleeding was compared using the log-rank test, Kaplan-Meier method, univariate and multivariate cox proportional hazards ratio (HR) and 95% confidence interval (CI). Two-tailed P<0.05 was considered significant. All data analyses were conducted using Stata version 14 (Stata Corp, College Station, TX, USA).

Results

In all, 1979 patients were enrolled in the study (Table 1 and 2). Mean patient age was 68.6 years; many patients had comorbidities, including cardiovascular disease (7.0%) and central neurological disease (4.4%), which required anticoagulant therapy. Of the 1979 patients, 49 (2.5%) were being treated with anticoagulant agents. Table 3 provides details of the anticoagulant agents. During the peri-ESD period, about half of these 49 patients discontinued warfarin and were switched to heparin during ESD, of the other half of the patients discontinued DOAC.

During 2 months of the entire observational period, post-ESD bleeding occurred in 88 patients (4.4%) within 2 weeks after ESD. The timing of post-ESD bleeding tended to be later in patients on anticoagulant therapy compared with patients who were not on any antithrombotic agent (6.5 ± 1.2 days *vs.* 3.5 ± 3.4 days after ESD, log-rank test: P<0.001). However, the timing of post-ESD bleeding was equivalent in patients on warfarin compared with patients who were on DOAC (6.3 ± 1.7 days *vs.* 6.8 ± 0.5 days after ESD, log-rank test: P=0.980) (Figure 1 and 2).

Table 3: Details of the anticoagulant agents used in all patients.

	Total	Bleeding	Bleeding rate
No anticoagulant	1930	80	4.10%
Warfarin	25	4	16%
DOAC	20	4	20%
Dabigatam	7	1	14.30%
Rivaroxaban	7	0	0%
Apixaban	9	3	33.30%
Edoaaban	1	0	0%

*NOAC: novel oral anticoagulant

Relationships between post-ESD bleeding and various clinicopathological factors were examined by univariatecox proportional hazardsanalysis (Table 1). Significant relationships were identified between post-ESD bleeding and seven factors: age, anticoagulant use, tumor location (middle and lower one-third of the stomach), tumor size, the presence of an ulcer in the tumor, and operation time, whereas age and tumor location in the middle one-third of the stomach was associated with a low rate of bleeding. With regard to anticoagulant therapy, warfarin and DOAC were significantly related to post-ESD bleeding. Multivariate cox proportional hazardsanalysis was then performed on these factors to determine which factors remained associated with post-ESD bleeding (Table 4). Anticoagulant agents, hepatic disease, tumor location in the lower one-third of the stomach, and operation time were significantly related to post-ESD bleeding. Of these factors, the HR was higher for anticoagulant therapy (HR=6.24, 95% CI 2.93–13.27), warfarin and

Table 4: Multivariate analysis of factors related to post-endoscopic submucosal dissection bleeding CI, confidence interval.

	Univariate Mode		Multivariate Model	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Anticoagulant	3.98 (1.92 to 8.24	<0.001	6.24 (2.93 to 13.27)	<0.001
Warfarin	4.19 (1.53 to 11.46)	0.005	5.84 (2.10 to 16.22)	0.001
DOAC	4.14 (1.51 to 11.32)	0.006	6.71 (2.39 to 18.82)	<0.001
Lower one-third of the stomach	1.98 (1.24 to 3.16)	0.004	1.81 (1.12 to 2.92)	0.015
Presence of ucler in tumor	1.92 (1.19 to 3.11)	0.008	1.56 (0.96 to 2.54)	0.075
Tumor size (mm)	1.02 (1.01 to 1.03)	0.002	1.01 (1.00 to 1.01)	0.421
Operation time	1.01 (1.00 to 1.01)	<0.001	(1.00 to 1.01)	0.01
Age(year)	0.98 (0.96 to 1.00)	0.016	0.97 (0.95 to 0.99)	0.006
Middle one-third of the stomach	0.4 (0.16 to 0.98)	0.046	0.38 (0.15 to 0.95)	0.038

DOAC were as same significantly related to post-ESD bleeding.

Next, we examined relationships between clinical outcomes of ESD and subgroups based on anticoagulant type (Table 2). If patients who were not using anticoagulant agents were set as the reference group, the HR of post-ESD bleeding were significantly higher for patients on anticoagulant therapy (HR=3.98, 95% CI 1.92–8.24), those who discontinued warfarin (HR=4.19, 95% CI 1.53–11.46), and DOAC (HR=4.14, 95% CI 1.51–11.32). Similarly, the odds ratios (ORs) of blood transfusion were significantly higher for patients on anticoagulant therapy (ORs=9.08, 95% CI 1.91–43.19). Furthermore, the timing of post-ESD bleeding tended to be later in patients on anticoagulant therapy compared with patients who were not on any antithrombotic agent (6.5 ± 1.2 days *vs.* 3.5 ± 3.4 days after ESD; coefficient of regression (CR) 3.01, 95% CI 0.60–5.43, if patients not on antithrombotic agents were set as the reference group). The length of hospital stay was almost 1.5 times longer in patients on anticoagulant therapy compared with patients not on any antithrombotic agent (15.6 ± 6.3 *vs.* 10.0 ± 5.4 days, respectively), especially longer in patient on heparin alternative therapy (18.3 ± 5.2 days). Perforation occurred in 34 patients (1.7%). All perforations were cured without surgery by conservative treatment with intravenous administration of antibiotics, PPI and by withholding oral intake for a few days. Thromboembolism and major bleeding other than GI bleeding did not occur during the peri-ESD period in any patients in this study.

Discussion

The present study provides detailed information regarding the relationship between bleeding after gastric ESD and anticoagulant therapy in a large cohort of 1979 patient, including 49(2.5%) who were being treated with anticoagulant agents. Multivariate analysis identified that anticoagulant increased the risk of post-ESD bleeding. A possible explanation for this is that anticoagulants, not only anticoagulant action, which may have anti-platelet activity through inhibiting the production or direct inhibition of thrombin. Patients with anticoagulant agent have an antithrombotic effect equivalent to that of multiple antithrombotic drugs, so the post-ESD bleeding risk is high.

Compared with patients who were not on anticoagulant therapy, hemorrhage occurred later (on around Day 7 after ESD) in patients on anticoagulant therapy. For patient with warfarin, during the switch from heparin to warfarin, a certain degree of overwrapped action of these two drugs might cause a stronger antithrombotic effect in a later period and consequently caused delayed bleeding. The time to peak onset of the DOAC is 0.5 hr to 4 hr and the half-life is 5 hr to 13 hr, however there are individual differences in coagulability and renal function, so, and the anticoagulation effect might be differed for individuals, even if the same amount of DOAC is administered. Since DOAC was restarted within 2 days after ESD in the present study, it takes time for blood concentration to equilibrium, so that the post-ESD bleeding occurred later. Although the number of patients was limited and could not monitor the blood concentration of the DOAC in the present study, it could not elucidate about this.

There are several limitations in this study. Firstly, this study is a retrospective design from a single high volume center of endoscopy, and thus the results obtained needs to be confirmed by further studied of prospective type. Another limitation is that we could not evaluate the relationship between post-ESD bleeding and there starting time of antithrombotic. The restarting times were too broad to make a clear threshold or criteria of the restarting time for assessing if it influenced the risk of post-ESD bleeding.

Conclusion

Perioperative management of anticoagulation is a challenging clinical issue that requires balancing the risk of acute thromboemobolism against perioperative bleeding. Because anticoagulant, especially warfarin and DOAC increases post-ESD bleeding, it should be necessary to strictly management at least two weeks after ESD.

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 being included in the study.

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