Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms

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Background and study aim: The risk of bleeding after endoscopic submucosal dissection (ESD) in patients with early gastric neoplasms who do not discontinue aspirin for the procedure has not been established. We aimed to investigate whether post-ESD gastric bleeding is increased in patients who take aspirin.

Patients and methods: Patients who underwent ESD for early gastric neoplasms at the National Cancer Center Hospital, Korea, between November 2008 and January 2011 were enrolled. The risk of post-ESD bleeding was evaluated using Poisson regression analysis.

Results: We categorized 514 patients into three groups according to aspirin intake at the time of the procedure: patients who never used aspirin (n=439), patients who interrupted aspirin use for 7 days or more (n=56), and patients who continuously used aspirin (n=19). Post-ESD bleeding occurred in 4.1% (21/514) overall, and was more frequent in continuous aspirin users (4/19 [21.1%]) than in those who never used aspirin (15/439 [3.4%]) (P=0.006) and those with interrupted aspirin use (2/56 [3.6%]) (P=0.033). Multivariate analysis showed that use of aspirin by itself was associated with post-ESD bleeding (relative risk [RR] 4.49; 95% confidence interval [95%CI] 1.09–18.38). The resumption of clopidogrel combined with aspirin use (RR 26.71, 95%CI 7.09–100.53), and increased iatrogenic ulcer size (RR 1.52, 95%CI 1.14–2.02), were significantly associated with post-ESD bleeding.

Conclusions: Continuous aspirin use increases the risk of bleeding after gastric ESD. Aspirin use should be stopped in patients with a low risk for thromboembolic disease to minimize bleeding complications.

Introduction

The use of antiplatelet medications, including aspirin, for various cardiovascular diseases has increased over the past decade [1]. While aspirin is a very effective antiplatelet therapy for thromboembolic diseases [2,3], it increases the incidence of gastrointestinal bleeding [4]. Therefore, patients who are taking aspirin appear to have an increased risk of both hemorrhage after endoscopic procedures and thromboembolic events after medication cessation [5].

The American Society for Gastrointestinal Endoscopy (ASGE) and the British Society for Gastroenterology issued guidelines in 2009 and 2008, respectively, for the management of anticoagulant and antiplatelet therapy for endoscopic procedures [6,7]. These guidelines state that "aspirin may be continued for all endoscopic procedures, such as polypectomy or biliary sphincterotomy [6,7]." The risk of bleeding after polypectomy in the stomach (7.2%) [8] is higher than that after polypectomy in the colon (0.7%–3.3%) [9–11]. In general, the risk of bleeding after conventional endoscopic mucosal resection (EMR) at 22%) [12] is much higher than the risk of bleeding after a simple polypectomy (0.7%–10.3%) [8,11,13]. Although endoscopic submucosal dissection (ESD) has advantages compared with conventional EMR, particularly with respect to en bloc resection, curative resection, and local recurrence, ESD is associated with a higher incidence of bleeding complications (odds ratio 2.20, 95%CI 1.58–3.07) [14]. Thus, patients taking aspirin at the time of gastric ESD are more likely to bleed than those who undergo colonic polypectomy or EMR. The published guidelines do not include statements about the risk of bleeding after gastric EMR or ESD [6,7].

Given these observations, we investigated whether post-ESD gastric bleeding is more likely to occur in patients taking aspirin at the time of the procedure and attempted to determine the risk factors for post-ESD bleeding.

Patients and methods

Study population and data

This retrospective study was conducted at the National Cancer Center Hospital (Korea) and used a prospectively collected dataset of consecutive patients. Patients who were diagnosed, by means of a forceps biopsy, with early gastric cancer (EGC) or gastric adenoma (low or high grade) were eligible for inclusion. In cases of EGC, lesions were histologically confirmed to be a well- or moderately differentiated adenocarcinoma that had an endoscopic diagnosis of mucosal cancer, a maximum diameter of less than 3 cm, and no ulcerative findings. Exclusion criteria included a recurrent tumor at a previous endoscopic resection site, a metachronous lesion after previous endoscopic resection, and a patient's preference for argon plasma coagulation (APC) instead of ESD. Patients who had a coagulopathy or took corticosteroids or anticoagulants, such as warfarin or heparin, were also excluded.

Demographic and clinical data, such as age, sex, histology, esophagogastroduodenoscopy (EGD) results, and final pathological results after ESD were recorded prospectively. Information about co-morbidities, the use of antiplatelet agents, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was also recorded. The intragastric location of lesions was described using the Japanese Classification of Gastric Cancer [15].

The study protocol was approved by the Institutional Review Board of the National Cancer Center, Korea, and written informed consent for the ESD was obtained from all patients before the procedure.

Use of antiplatelet agents including aspirin during ESD

The decision to continue or discontinue aspirin for the ESD procedure was made according to each patient's risk stratification based on published criteria [6,7]. If a patient took aspirin for the primary prevention of thromboembolic disease but did not have any significant predisposing conditions, the patient was instructed to stop taking aspirin 7 days before the procedure. In those cases, aspirin intake usually resumed 4 weeks after ESD and each patient received a consultation with a cardiologist at that time. However, if a patient had a condition placing him or her at a high risk for a thromboembolic event, aspirin was continued without cessation even on the day of ESD. The followings were deemed to be high risk conditions [6,7]:

- atrial fibrillation with high risk factors (previous stroke, transient ischemic accident, mitral stenosis, prosthetic heart valves) and unable to take warfarin [16];
- use of a mechanical heart valve with inability to take warfarin [17];
- acute coronary syndrome [18];
- having undergone percutaneous coronary intervention with stent placement [19];
- recent cerebrovascular disease [20].

Patients taking concomitant antiplatelet medications, such as clopidogrel, dipyridamole, or ticlopidine, were recommended to cease taking those medications at least 7 days before the ESD but to continue aspirin intake. They were recommended to resume clopidogrel 7 days after the ESD procedure. An appropriate medication schedule was made for each patient after discussion with a cardiologist (M.H.K. or H.J.K.).

ESD procedure and hemostasis methods

The ESD method was used to remove all lesions, an all the procedures included in the study were performed by one of four endoscopists (S.-J.C., I.J.C, C.G.K., J.Y.L.). Each endoscopist had performed more than 7000 EGD examinations and at least 100 ESDs prior to this study. A circumferential incision was made using an electrosurgical insulation-tipped (IT)-knife (ESD-Knife; MTW Endoskopie Co, Ltd, Wesel, Germany), and/or a Fixed Flexible Snare (Kachu Technology, Seoul, Korea), and the submucosal layer was then dissected with an IT-knife and/or a Fixed Flexible Snare. Whenever active bleeding was observed during ESD, hemostasis was performed, using either an ESD knife adapted with an electrosurgical generator (swift coagulation, effect 4, 40 W; VIO300D; Erbe, Tübingen, Germany) or a hemostatic forceps (Radial Jaw 3; Boston Scientific, Heredia, Costa Rica) adapted with a generator (soft coagulation, effect 7, 80 W; VIO300D; Erbe). If bleeding continued, hemostasis was performed using metallic hemoclips (HX-160 – 090L; Olympus, Tokyo, Japan). Before removal of the scope, preventive hemostasis was routinely performed on any exposed vessels on the iatrogenic ulcer base and to quench any oozing. Ulcer dimensions were estimated by measuring both the maximal diameter of the resected specimens and the diameter perpendicular to it.

Management after ESD

All patients received 20 mg omeprazole orally twice daily on the day they underwent ESD and throughout the length of their hospital stay, which was usually 2 – 3 days. Routine "second look" endoscopies were not performed on patients who did not demonstrate signs of bleeding. Hemoglobin levels were checked in the morning after ESD. If no ESD-related complications occurred, patients were allowed to have a liquid diet on the first or second day after ESD. Patients were discharged the day after a diet was started. After discharge, patients were instructed to take 20 mg omeprazole once a day for 28 days.

Post-ESD bleeding

Post-ESD bleeding was defined as a decrease in blood hemoglobin level of more than 2 g/dL that was accompanied by the occurrence of hematemesis, melena, or the combination of unstable vital signs with fresh blood or clots upon Levin tube irrigation within 4 weeks after ESD. All patients with post-ESD bleeding underwent emergency EGD. Information was recorded about the time of bleeding, amount of blood transfused, duration of the hospital stay, whether any interventions were performed, and if temporary cessation of antiplatelet medications had been needed.

Statistical analysis

We categorized the enrolled patients into three groups according to their aspirin intake: patients who never used aspirin (aspirin non-use), patients who ceased to take aspirin for more than 7 days prior to ESD (interrupted aspirin use), and those who continued to use aspirin, including on the day of ESD (continuous aspirin use). Demographic and clinical characteristics were compared among the three groups and between those who bled post-ESD and those who did not. Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using Student's t test, one-way analysis of variance (ANOVA), or the Kruskal – Wallis test. Poisson regression analysis was used to identify independent variables associated with post-ESD bleeding. Through the use of robust standard errors to allow for overdispersion, relative risks (RRs) and 95 % con-

Table 1 Aspirin use in 514 patients undergoing endoscopic submucosal dissection (ESD) for early gastric neoplasms: baseline demographic and laboratory data.

	Aspirin non-use n=439	Interrupted aspirin use n=56	Continuous aspirin use n=19	*P* value
Age, mean (SD), years	61.7 (9.3)	64.5 (8.8)	66.8 (9.6)	0.008[3]
Sex (male), n (%)	325 (74.0)	44 (78.6)	16 (84.2)	0.499[1]
Co-morbid condition, n (%)				
Hypertension	134 (30.5)	45 (80.4)	12 (63.2)	<0.001
Diabetes mellitus	43 (9.8)	18 (32.1)	9 (47.4)	<0.001[1]
Coronary artery disease	4 (0.9)	8 (14.3)	7 (36.8)	<0.001[1]
Atrial fibrillation	2 (0.5)	1 (1.8)	3 (15.8)	<0.001[1]
Valvular heart disease	1 (0.2)	0 (0.0)	0 (0.0)	1.000[1]
Cerebrovascular disease	7 (1.6)	2 (3.6)	7 (36.8)	<0.001[1]
Peripheral vascular disease	0 (0.0)	0 (0.0)	2 (10.5)	0.001[1]
Combined medication, n (%)				
Clopidogrel intake	0 (0.0)	2 (3.6)	4 (21.1)	<0.001[1]
Other antiplatelets[2]	2 (0.5)	1 (1.8)	3 (15.8)	<0.001[1]
Other NSAIDs	18 (4.1)	2 (3.6)	0 (0.0)	0.724[1]
Pre-ESD Hb, mean (SD), g/dL	13.6 (1.5)	13.2 (1.5)	13.5 (2.2)	0.237[3]
Post-ESD Hb, mean (SD), g/dL	13.2 (1.5)	12.9 (1.6)	13.4 (1.6)	0.171[3]
Platelets, mean (SD), ×1000/μL	220.3 (51.9)	212.2 (48.9)	197.1 (40.4)	0.094[3]
Prothrombin time (INR), mean (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.226[3]
Bleeding time, mean (SD), seconds	90.1 (37.4)	96.4 (43.4)	98.3 (52.3)	0.394[3]

SD, standard deviation; NSAIDs; non-steroidal anti-inflammatory drugs; Hb, hemoglobin; INR, international normalization ratio
[1] Fisher's exact test.
[2] Ticlopidine or dipyridamole.
[3] One-way analysis of variance (ANOVA)

fidence intervals (CIs) were reported. Variables that had a *P* value <.05 in the univariate analysis were entered into the Poisson regression analysis model. A *P* value <.05 was considered significant.

If a patient had two or more lesions, the smaller lesion(s) for synchronous tumors and the later arising tumor(s) in the case of metachronous tumors were excluded from the analyses to avoid any correlation effect between two or more lesions from the same patient. Statistical analyses were performed using Stata 9.2 (STATA Corp, College Station, Texas, USA).

Results

A total of 551 patients were diagnosed with gastric neoplasms that could be treated with ESD between November 2008 and January 2011 at the National Cancer Center Hospital, Korea. Patients were excluded if they were currently taking warfarin (n=1), had a recurrent tumor at a previous endoscopic resection site (n=3), had a metachronous tumor after previous endoscopic resection (n=18), or preferred APC instead of endoscopic resection (n=15). A total of 514 patients underwent ESD for gastric dysplasia or EGC. Patients were distributed into three groups based on aspirin intake: patients who never used aspirin (n=439), patients with interrupted aspirin use (n=56), and those with continuous aspirin use (n=19).

Indications for continuous aspirin therapy were coronary artery disease, such as acute coronary syndrome or a coronary stent insertion (36.8%), cerebrovascular disease, including transient and evolved ischemic stroke (36.8%), atrial fibrillation (15.8%), and peripheral vascular disease (10.5%). All of the patients in the continuous use group were taking 100 mg aspirin once a day. Four of these patients (21.1%) were taking clopidogrel (75 mg once a day) concomitantly with aspirin; three patients (15.8%) were taking another antiplatelet agent concomitantly with aspirin, and among these three, one patient (5.3%) was simultaneously taking three antiplatelet agents (aspirin, clopidogrel, and dipyridamole).

Demographics and clinical characteristics

Examination of the baseline characteristics of the three groups (**Table 1**) revealed that coronary artery disease, atrial fibrillation, cerebrovascular disease, peripheral vascular disease, clopidogrel use, and other antiplatelet agent use were significantly higher in those with continuous aspirin use than in both aspirin non-users and those with interrupted use. Age, hypertension, and diabetes mellitus were lower in aspirin non-users than in those with interrupted or continuous use. The rate of complete resection (*P*=0.393; **Table 2**), as well as all other examined demographic data, baseline laboratory findings, and tumor characteristics, did not differ between the three groups.

Post-ESD bleeding

Post-ESD bleeding occurred in 4.1% (n=21) of the 514 patients. The rate of post-ESD bleeding differed among the groups (*P*=0.006). Post-ESD bleeding was more frequent in continuous aspirin users than in those who never used aspirin or those with interrupted aspirin use. Although the time at which post-ESD bleeding occurred tended to differ among the three groups, these differences did not reach statistical significance (*P*=0.067) (**Table 3**). In patients who had never used aspirin, bleeding usually occurred within the first week after undergoing ESD, while in continuous aspirin users, bleeding occurred during the second week after ESD. Among the five current aspirin users who had their clopidogrel interrupted for ESD, three episodes of bleeding occurred between the 4th and 7th days of clopidogrel resumption (which began 7 days after ESD).

Significant differences between the bleeding and nonbleeding groups were found for the following factors: coronary artery dis-

	Aspirin non-use n = 439	Interrupted aspirin use n = 56	Continuous aspirin use n = 19	*P* value
Number of lesions, mean (SD)	1.1 (0.3)	1.2 (0.5)	1.1 (0.3)	0.082[1]
Tumor size, mean (SD), cm	1.5 (0.8)	1.5 (0.6)	1.5 (0.7)	0.943[1]
Maximum diameter of ulcer, mean (SD), cm	4.2 (1.2)	4.3 (1.1)	4.2 (1.2)	0.963[1]
Vertical location, n (%)				0.316[2]
Lower	330 (75.2)	43 (76.8)	12 (63.2)	
Middle	73 (16.6)	11 (19.6)	3 (15.8)	
Upper	36 (8.2)	2 (3.6)	4 (21.1)	
Horizontal location, n (%)				0.490[2]
Anterior wall	72 (16.4)	12 (21.4)	5 (26.3)	
Posterior wall	95 (21.6)	13 (23.2)	4 (21.1)	
Lesser curvature	196 (44.6)	27 (48.2)	8 (42.1)	
Greater curvature	76 (17.3)	4 (7.1)	2 (10.5)	
Diagnosis, n (%)				0.367[2]
Early gastric cancer	337 (76.8)	47 (83.9)	16 (84.2)	
Adenoma	102 (23.2)	9 (16.1)	3 (15.8)	
Completeness of ESD, n (%)				0.393[2]
Complete	417 (95.0)	54 (96.4)	17 (89.5)	
Incomplete	13 (3.0)	0 (0.0)	1 (5.3)	
Not-checkable	9 (2.1)	2 (3.6)	1 (5.3)	

SD, standard deviation.
[1] One-way analysis of variance (ANOVA)
[2] Fisher's exact test.

Table 2 Aspirin use in 514 patients undergoing endoscopic submucosal dissection (ESD) for early gastric neoplasms: tumor and ESD-related factors.

	Aspirin non-use n = 439	Interrupted aspirin use n = 56	Continuous aspirin use n = 19	*P* value
Bleeding rate, n/n (%)	15/439 (3.4)	2/56 (3.6)	4/19 (21.1)	0.006[1]
Time of bleeding event[2], median (range), days	1.0 (0 – 20)	6.5 (0 – 13)	10.5 (6 – 15)	0.067[3]

SD, standard deviation.
[1] Fisher's exact test
[2] Among patients who had post-ESD bleeding
[3] Kruskal – Wallis test

Table 3 Aspirin use in 514 patients undergoing endoscopic submucosal dissection (ESD) for early gastric neoplasms: bleeding complications.

ease, current use of aspirin and/or clopidogrel, and the maximal diameter of ESD-induced ulcer (**Table 4**).

Multivariate analysis showed that continuous aspirin-only use was significantly associated with an increased risk of post-ESD bleeding. Diameter of ESD-induced ulcer and concomitant aspirin and clopidogrel use were also positively associated with post-ESD bleeding (**Table 5**). **Table 6** shows the clinical characteristics of the 21 patients who had a bleeding complication.

Management of post-ESD bleeding

All of the patients with post-ESD bleeding underwent emergency EGD and endoscopic treatment. All of the patients completely recovered after endoscopic and medical treatment (**Table 6**). Among the 21 patients who had bleeding complications, episodes of rebleeding occurred in two patients (9.5 %). Both of these patients never used aspirin, and both of the rebleeding episodes were successfully controlled with endoscopic hemostasis. There were no cases of surgery or angiographic intervention. There was also no long-term morbidity or mortality.

Aspirin and clopidogrel were withheld in all patients with post-ESD bleeding for 3 to 7 days. Aspirin and/or clopidogrel were resumed as soon as possible, based on the patient's risk stratification for thromboembolism. None of the patients who stopped taking antiplatelet medication had a thromboembolic event during the interruption period.

Discussion

Post-ESD gastric bleeding was significantly higher in those with continuous aspirin use than in those who had never used aspirin or who interrupted their use of aspirin. In multivariate analysis, aspirin-only use was an independent risk factor for post-ESD bleeding in this study (RR 4.49). Large iatrogenic ulcer size (RR 1.52) and the resumption of clopidogrel combined with the continuous use of aspirin (RR 26.71) were also significant risk factors associated with post-ESD gastric bleeding.

Although published guidelines recommend performance of colonoscopic polypectomy or sphincterotomy procedures without discontinuing the intake of aspirin medication [6,7], surveys of endoscopists show that actual practice varies [21,22], especially between Eastern and Western endoscopists [23]. This discrepancy may be because the published guidelines are primarily based on observational studies, expert opinion, and best clinical practice, and are rarely supported by prospective or randomized trial data [24]. Several reports suggest that aspirin at a standard dose does not increase the risk of significant bleeding after EGD with biopsy or colonic polypectomy [25 – 27]. However, to date, no data are available on how taking aspirin modifies a patient's risk for bleeding when they undergo other high risk procedures, such as gastric ESD. In a recent Japanese multicenter survey, most endoscopists stopped patient aspirin intake 7 days before gastric EMR procedures including ESD [22].

Table 4 Endoscopic submucosal dissection (ESD) for early gastric neoplasms in 514 patients: comparison of those with and without post-ESD bleeding.

	Patients with bleeding n = 21	Patients without bleeding n = 493	*P* value
Age, mean (SD), years	60.9 (11.8)	62.2 (9.3)	0.511
Sex (male), n (%)	17 (81.0)	368 (74.6)	0.514
Co-morbid condition, n (%)			
Hypertension	5 (23.8)	186 (37.7)	0.196
Diabetes mellitus	3 (14.3)	67 (13.6)	1.000[2]
Coronary artery disease	4 (19.0)	15 (3.0)	0.005[2]
Atrial fibrillation	6 (28.6)	0 (0.0)	1.000[2]
Valvular heart disease	1 (4.8)	0 (0.0)	1.000[2]
Cerebrovascular disease	1 (4.8)	15 (3.0)	0.661[2]
Peripheral vascular disease	2 (9.5)	0 (0.0)	1.000[2]
Current aspirin use[1], n (%)			< 0.001[2]
No aspirin use	16 (76.2)	477 (96.8)	
Aspirin-only use	2 (9.5)	14 (2.8)	
Concomitant aspirin plus clopidogrel use	3 (14.3)	2 (0.4)	
Lesions per patient, mean (SD), n	1.1 (0.3)	1.1 (0.3)	0.913
Tumor size, mean (SD), cm	1.5 (0.8)	1.7 (1.2)	0.112
Maximum diameter of ulcer, mean (SD), cm	4.8 (1.3)	4.2 (1.2)	0.037
Vertical location, n (%)			0.639[2]
Lower	15 (71.4)	370 (75.1)	
Middle	5 (23.8)	82 (16.6)	
Upper	1 (4.8)	41 (8.3)	
Horizontal location, n (%)			0.943[2]
Anterior wall	3 (14.3)	86 (17.4)	
Posterior wall	4 (19.0)	108 (21.9)	
Lesser curvature	10 (47.6)	221 (44.8)	
Greater curvature	4 (19.0)	78 (11.3)	
Diagnosis, n (%)			1.000[2]
Early gastric cancer	16 (76.2)	384 (77.9)	
Adenoma	5 (23.8)	109 (22.1)	
Completeness of ESD, n (%)			0.688[2]
Complete	20 (95.2)	468 (94.9)	
Incomplete	0 (0.0)	14 (2.8)	
Not-checkable	1 (4.8)	11 (2.2)	

SD, standard deviation.
[1] Patients were taking aspirin and/or clopidogrel at the time of the bleeding complication.
[2] Fisher's exact test.

Several studies on post-ESD gastric bleeding showed no difference in bleeding risk between users and non-users of anticoagulant or antiplatelet agents [28–30]. However, those studies did not include detailed data about the specific antiplatelet agents used and whether the medications were continued or discontinued [28–30]. A recent study of ESD for EGC in patients taking antiplatelet or anticoagulant agents indicated that bleeding occurred in 10.7% of patients taking antiplatelet or anticoagulant agents and in 5.2% of controls, a difference that was not statistically significant [31]. The study, however, included patients who stopped taking antiplatelet agents for 1 week before and after ESD in the group of "current users of antithrombotic agents" [31]. Another recent study showed that the use of antithrombotic medication was an independent risk factor for post-ESD bleeding. However, the "daily user of antithrombotic medication" group included patients who used steroids, NSAIDs, or anticoagulants as well as patients who ceased to take aspirin 3 days before ESD [32]. Only recently was a case report published that demonstrated a lack of bleeding complications in a patient who underwent an ESD while not discontinuing aspirin therapy [33]. In the present study, bleeding rates were similar in patients who never used aspirin and in those who interrupted aspirin use, but were more frequent in those with continuous aspirin use. Multivariate analysis showed that the RR of continuous aspirin-only use for post-ESD bleeding was 4.49 and that this risk was statistically significant. To the best of our knowledge, this is the first study to compare

Table 5 Risk factors of post-endoscopic submucosal dissection (ESD) bleeding: univariate and multivariate analysis, with crude and adjusted relative risks (RRs)[1].

	Crude RR (95%CI)	Adjusted RR (95%CI)[2]
Coronary artery disease	6.13 (2.28–16.48)	1.20 (0.41–3.52)
Current aspirin use		
No aspirin use	1.00	1.00
Aspirin-only use	4.12 (1.04–16.34)	4.49 (1.09–18.38)
Concomitant aspirin plus clopidogrel	18.53 (7.81–43.94)	26.71 (7.09–100.53)
Maximum diameter (cm) of ulcer	1.39 (1.04–1.85)	1.52 (1.14–2.02)

CI, confidence interval.
[1] RRs were calculated using Poisson regression analysis.
[2] Adjusted by age, sex, current use of aspirin and/or clopidogrel, and the maximum diameter (in cm) of iatrogenic ulcer.

Table 6 Clinical and endoscopic features of each patient with post-endoscopic submucosal dissection (ESD) bleeding.

Patient no.	Age, sex	Diagnosis	Stomach location	Co-morbidities	Antiplatelet agents	Time of bleeding after ESD	Time of bleeding after antiplatelet(s) resumption	Maximum iatrogenic ulcer size, cm	pRBC transfusion, units	Additional hospital stay, days	Intervention
1	71, M	EGC	Middle	CAD	Aspirin[1] Clopidogrel[2] Dipyridamole[3]	15 days	7 days (clopidogrel)	5.0	4	8	Hemoclips, coagulation, aspirin and clopidogrel withheld
2	54, M	EGC	Lower	CAD	Aspirin[1]	9 days		6.0	2	2	Hemoclips, coagulation, aspirin withheld
3	72, M	EGC	Upper	CAD Diabetes mellitus Hypertension	Aspirin[1] Clopidogrel[2]	12 days	4 days (clopidogrel)	3.4	2	6	Coagulation, aspirin and clopidogrel withheld
4	74, M	LGD	Lower	CAD Diabetes mellitus	Aspirin[2] Clopidogrel[2]	13 days	6 days (aspirin, clopidogrel)	4.2	5	3	Coagulation, aspirin and clopidogrel withheld
5	55, M	EGC	Lower	Diabetes mellitus	Aspirin[1]	6 days		2.5	2	3	Coagulation, aspirin withheld
6	62, F	EGC	Lower	CVA Diabetes mellitus		Within 12 hours		4.0	2	0	Coagulation
7	45, M	EGC	Lower	Hypertension		2 days		4.0	4	0	Coagulation
8	42, M	EGC	Lower			3 days		3.6	2	2	Coagulation
9	60, M	EGC	Lower			6 days		6.5		3	Coagulation
10	62, M	HGD	Middle			8 days		5.0		2	Coagulation
11	40, M	EGC	Lower			7 days		3.8		4	Coagulation
12	62, M	HGD	Middle	Hypertension Liver cirrhosis[4]	Aspirin[5]	Within 12 hours		4.0		0	Coagulation
13	69, M	EGC	Lower			Within 12 hours		4.5		0	Coagulation
14	76, F	EGC	Lower			Within 12 hours		7.9		0	Coagulation
15	79, F	EGC	Lower			Within 12 hours		5.0	2	0	Coagulation
16	52, F	EGC	Lower			Within 12 hours		4.5		0	Coagulation
17	81, M	HGD	Lower			Within 12 hours		7.6	4	2	Coagulation
18	55, M	EGC	Lower			8 days		4.8		0	Coagulation
19	60, M	LGD	Middle			20 days		4.4		9	Coagulation
20	54, M	EGC	Middle			2 and 5 days[6]		5.0	2	9	Coagulation for each episode
21	53, M	LGD	Lower			Within 12 hours and 4 days[6]		4.4	4	3	Coagulation for each episode

pRBC, packed red blood cells; M, male; F, female, EGC, early gastric cancer; CAD, coronary artery disease; LGD, low grade dysplasia; CVA, cerebrovascular accident; HGD, high grade dysplasia.

[1] The patient continued taking aspirin without interruption even on the day of ESD.

[2] The patient ceased taking the medication 7 days prior to ESD and resumed 7 days after ESD.

[3] The patient ceased taking the medication 7 days prior to ESD and did not resume the medication after ESD.

[4] The patients with liver cirrhosis had Child – Pugh A liver function and thus did not have coagulopathy.

[5] The patient ceased taking the medication 7 days prior to ESD and resumed 28 days after ESD.

[6] Two bleeding events occurred.

the risk of bleeding after gastric ESD in continuous aspirin users and patients who did not use aspirin.

Clopidogrel is a potent inhibitor of platelet adhesion and aggregation, and it is used worldwide to reduce thrombotic events. Recently, aspirin and clopidogrel were administered concomitantly to patients with a drug-eluting coronary stent to prevent fatal cardiac complications such as stent thrombosis [34], for at least 1 year after stent placement [19]. The use of dual antiplatelet therapy (DAT), combining aspirin and clopidogrel, may confer an approximately fourfold increase in the risk of upper gastrointestinal bleeding compared with aspirin single therapy (adjusted odds ratio, 7.4 versus 1.8, respectively) [35]. For patients who take both clopidogrel and aspirin, the ASGE guidelines also suggest reversion to a single agent, preferably aspirin, before elective endoscopy [6, 36]. In our study, despite the discontinuation of clopidogrel in continuous aspirin users for 7 days prior to ESD, post-ESD bleeding occurred in 3/5 (60%) of these patients after a maintenance dose (75 mg daily) of clopidogrel was reinitiated. Of note, most bleeding episodes occurred within 1 week after the resumption of clopidogrel, a drug known to achieve its maximal antiplatelet effect 5 to 10 days after its administration [37]. There is no consensus about the optimal timing for the resumption of clopidogrel after endoscopic intervention [6]. The present study suggests that resumption at 1 week after ESD may be too early to avoid post-ESD bleeding and indicates that further studies that investigate the appropriate post-ESD interval before the resumption of clopidogrel are necessary.

The present study suggests that post-ESD bleeding in patients taking aspirin can be managed conservatively without increasing long-term morbidity or mortality. Although there were no cases of thromboembolism in this study when patients had stopped taking aspirin, the cessation of aspirin in individuals with cardiovascular and atherothrombotic diseases may expose them to a serious risk of acute ischemic events. In a recent Japanese multicenter survey on anticoagulation and antiplatelet medication management [22], 15% of endoscopists reported that their patients experienced cerebral infarctions upon discontinuation of aspirin intake, but there were no reports of patients experiencing severe post-EMR bleeding. These results suggest that the cessation of aspirin intake may be more problematic than the continuation of its use. Therefore, an individualized approach should be applied that includes consultation with a cardiologist and considers both risk and benefit [7]. If a patient has a low risk for thromboembolic disease, aspirin use should be ceased. In contrast, if a patient has a high risk for thromboembolism, aspirin may be continued because post-ESD bleeding can be treated conservatively and a thromboembolic event could result in serious consequences and significantly decrease quality of life.

Other factors that may affect the post-ESD bleeding rate are the experience of the endoscopist and the adequate use of antisecretory agents. A recent Japanese study suggested that less experience in endoscopists was associated with post-ESD bleeding due to inadequate coagulation of the vessels at the ulcer margin during ESD [32]. However, in the present study, ESD experience is not likely to have an effect on ESD-related bleeding, as every ESD in the study was performed by an experienced endoscopist who coagulated exposed vessels meticulously during the procedure. With regard to the development of an iatrogenic ulcer after EMR or ESD, both the appropriate medication and the dosage of such medication have not yet been firmly established. In this study, we used omeprazole as an antisecretory agent because proton pump inhibitor (PPI) therapy seems to be superior to H_2-receptor antagonists (H_2RAs) in facilitating ulcer healing after ESD [38] and preventing delayed bleeding after ESD [39]. Moreover, if a patient with peptic ulcer disease should continue to take aspirin, a PPI is the preferred agent for the treatment of aspirin-associated gastrointestinal injury, including gastric ulcer [40]. In this study, we used the standard dose of a PPI, and the overall rate of post-ESD bleeding was 4.1%, comparable to that found in other studies [29], [39], [41]. However, whether high dose oral PPIs or the administration of intravenous PPIs immediately after ESD can prevent post-procedural bleeding, particularly in the case of aspirin users, remains to be elucidated in future studies.

There are several limitations to this study. First, this study is not a randomized controlled trial and may have selection bias because continuous aspirin users are older and have more co-morbid conditions. However, laboratory data and tumor characteristics, both of which might affect bleeding risk, were similar among the groups. Further study must consider the use of a randomized controlled design that stratifies patients based on the risk of thromboembolism. Second, this study has a retrospective design and is from a single center. On the other hand, we prospectively included consecutive patients into our database and decided to continue or discontinue antiplatelet agents based on risk stratification for thromboembolism. Third, the lack of a sample size calculation before the initiation of the study and the small number of bleeding complications that led to wide confidence intervals suggest that our study needs further validation.

In summary, aspirin-only use increased the risk of bleeding after gastric ESD. Our data suggest that aspirin use should be stopped in patients with low risk of thromboembolism because the bleeding risk in those with interrupted aspirin use was similar to that of patients who never used aspirin. On the other hand, aspirin may be continued with caution in patients who have a high risk for thromboembolic disease because post-ESD bleeding can be managed conservatively without increasing long-term morbidity or mortality. Further study is needed to confirm our results and to support the formulation of updated guidelines for antiplatelet therapy in patients undergoing ESD for gastric lesions.

Competing interests: None

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