의학석사 학위논문

Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms?

– Effect of antiplatelets on post-ESD bleeding –

항혈소판제가 위 종양에 대한 내시경적 점막하 절제술 후 출혈 위험을 증가시키는가?

– 항혈소판제가 ESD 후 출혈에 미치는 영향 –

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Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms?

– Effect of antiplatelets on post–ESD bleeding –

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ABSTRACT

Introduction: It is rarely known whether antiplatelets increase the risk of bleeding after endoscopic submucosal dissection (ESD). This study was designed to evaluate the effect of antiplatelets on post-ESD bleeding.

Methods: This study involved 1591 gastric neoplasms (815 adenoma and 776 early gastric cancers) in 1503 patients who had ESD between April 2005 and April 2010. Primary outcome event was defined as overt hematemesis/hematochezia, a drop of hemoglobin >2 g/dL from baseline, or requirement of endoscopic hemostasis, angiographic embolization and/or transfusion.

Results: Of 1591 subjects, 274 took antiplatelets, among whom 102 discontinued them for 7 days or more before ESD. Post-ESD bleeding occurred in 94 subjects including 20 from the continuation group, 6 from the withdrawal group, and 68 from the no-antiplatelet group. In univariate analysis, antiplatelets, early gastric cancer (EGC), comorbidity and specimen diameter

were related to post-ESD bleeding. In multivariate analysis, EGC (odds ration [OR] 1.839;95% confidence interval [CI], 1.168-2.896, P = .009), comorbidity (OR 2.246;95% CI, 1.280-3.939, P = .005), and specimen diameter (OR 2.315;95% CI, 1.282-4.180, P = .005) were independent risk factors of post-ESD bleeding, whereas antiplatelet usage was not (OR 1.596;95% CI, 0.877-2.903, P = .126). In subgroup analysis, continuous antiplatelet usage was not found to be an independent risk factor of post-ESD bleeding in multivariate analysis (OR, 2.027; P = .146). Among 102 subjects who discontinued antiplatelets, 1 developed an acute cerebral infarction (1.0%).

Conclusions: In ESD for antiplatelet users, continuous administration was not found to have an independent significant association with bleeding. (Gastrointest Endosc 2012;75:719-27.)

Keywords: endoscopic submucosal dissection, antiplatelet agent, bleeding

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LIST OF ABBREVIATIONS

ESD, endoscopic submucosal dissection

EMR, endoscopic mucosal resection

EGC, early gastric cancer

CI, confidence interval

OR, odds ratio

INTRODUCTION

Currently, endoscopic submucosal dissection (ESD) is a widely used procedure as a curative treatment of gastric tumors, which preserves the stomach and allows 1-piece resection with tumor-free margins, even in cases of large and ulcerative lesions [1, 2]. As previously reported, the resection rate of complete en bloc ESD was over 80%, which was significantly better than that of conventional EMR [3]. Despite its convenience and noninvasiveness, there is a major concern about its bleeding complication. ESD has a greater risk of bleeding compared with ordinary EMR because of the larger resection diameter and depth. Thus there have been efforts to find out ways to reduce post-ESD bleeding. Pantoprazole was found to be more effective than famotidine for the prevention of delayed bleeding after ESD [4], and in another study, coagulating exposed vessels on the ulcer floor after ESD, which is known as post-ESD coagulation preventive therapy, reduced the risk for delayed bleeding [5]. However, there are still bleeding concerns, and further measures are needed to prevent post-ESD bleeding.

The usage of antiplatelet agents increases as the incidence of cardiovascular disease increases. In the absence of pre-existing bleeding disorder, endoscopic procedures can be performed on patients who take aspirin in standard doses [6]. However, this is true only for ordinary procedures, and it is not yet known whether it applies to ESD.

The rate of post-ESD bleeding is reported to be 1.7% to 38%, based on the definition of bleeding [1, 5, 7, 8]. There have been controversies over the potential risk of post-ESD bleeding in antiplatelet users. In a retrospective study, tumor location, coagulator experience, and medicine potentially related to gastric injury/bleeding were revealed to be associated with a higher rate of post-ESD bleeding [9]. Another study showed that resected specimen width of > 40 mm was the only significant factor associated with delayed bleeding after ESD [10].

In a previous guideline, it is recommended to discontinue antiplatelet therapy other than aspirin 7 to 10 days before high-risk endoscopic procedures, such as polypectomy, biliary sphincterotomy, pneumatic/bougie dilatation, pergutaneous endoscopic gastrostomy placement, EUS-guided FNA, laser

ablation/coagulation, or treatment of varices [11]. However, this guideline had a recommendation about non-aspirin antiplatelet agents rather than aspirin for endoscopic procedures. A recently published guideline recommends discontinuation of all antiplatelet agents, including aspirin, before EMR or ESD, in case of low risk for a thrombotic event [12]. However, this is a low-grade recommendation without results of large-scaled trials, and there is no specific guideline for patients with high thrombotic risks. The aim of this study was to evaluate the effect of antiplatelet agents, including aspirin, on post-ESD bleeding and find evidence for whether or not to discontinue antiplatelet agents before ESD.

MATERIALS AND METHODS

1. Patients

A total of 1525 patients underwent ESD for 1613 gastric neoplasms, including 831 adenomas and 782 cases of early gastric cancer (EGC), at Seoul National University Hospital between April 2005 and April 2010. Endoscopic resection was performed entirely by ESD techniques, which were indicated if the following criteria were met: any lesions with low-grade to high-grade dysplasia, regardless of size, or well-to-moderately differentiated adenocarcinoma confined to mucosa <2 cm by endoscopic measurements without evidence of lymph nodal/distant metastases on abdominal CT/EUS. Ten subjects were excluded because of unclear medication history, and 12 patients were excluded because of anticoagulation before the procedure. Therefore, a total of 1591 lesions in 1503 patients, including 815 adenomas and 776 EGC, were reviewed retrospectively (Fig. 1).

Gastric adenoma was defined as intraepithelial neoplasia of category 3 or 4 in revised Vienna classification including epithelial dysplasia regardless of mucosal elevation, and EGC was defined as invasive carcinoma of category 5 [13].

Antiplatelet agents were defined as drugs that decrease platelet aggregation or inhibit thrombus formation as follows: cyclooxygenase inhibitors like aspirin, phosphodiesterase inhibitors like cilostazol, adenosine diphosphate receptor inhibitors like clopidogrel or ticlopidine, and 5 HT2 antagonists like sarpogrelate.

We used the terminology of *subject* for each lesion treated with one ESD procedure. When there were two specimens resected from one ESD procedure, it was counted as one subject, and the diameter of the larger specimen was taken for analysis.

This study was approved by the Institutional Review Board of the Seoul National University Hospital. Patient consent was waived, given the retrospective nature of this study.

2. Procedures

ESD was performed with patients under sedation with intravenous midazolam by using an insulation-tipped-knife (Kachu Tech., Seoul, Korea) through a standard single-channel endoscope (Olympus H260; Olympus Optical Co, Tokyo, Japan) by a single experienced endoscopist (S.G.K). After the

chromo-endoscopic observation with indigo carmine, we placed marking dots 5 mm outside the tumor margin by using a needle knife (KD-1L; Olympus) with a forced 20-W coagulation current (VIO 300D; Erbe, Tübingen, Germany). Then a mixture of normal saline solution and indigo carmine with diluted epinephrine (1:100,000) was injected into the submucosal layer along with the marking dots to make the submucosal cushion beneath the lesion. After a small initial incision was made with the needle-knife, a circumferential mucosal incision was made around the marking dots, and the submucosal layer was dissected by using the insulation-tipped-knife in 80-W endocut mode. Hemostasis was performed for bleeding spots or visible vessels with a coagrasper (MTN-BF-2; Standard Sci.tech, Seoul, Korea). All of the patients were administered proton pump inhibitors intravenously at the day of procedure and were discharged with oral proton pump inhibitors for 4 weeks on the next day when there were no signs of bleeding. In cases of overt bleeding after discharge, the patients were educated to call the hospital and visit the emergency room immediately. After 2 weeks from discharge, all of the patients visited the outpatient department to confirm the final pathologic

results, when the clinical assessment of complete resection and delayed bleeding was made.

3. Data analysis

All subjects were grouped into one of the following groups; no-antiplatelet group, continuation group and withdrawal group. Patients who had continued antiplatelet therapy or had it interrupted <7 days before ESD were counted as continuous users, and those who had never used antiplatelet therapy or had it discontinued 30 days or more before the procedure were counted as non-users. Others were counted in withdrawal group. Post-ESD bleeding was defined as an episode of any of the followings: overt hematemesis/hematochezia; a drop of hemoglobin >2 g/dL; or requirement of endoscopic hemostasis or angiographic embolization and/or transfusion. Early bleeding was defined as a bleeding episode within 72 hours after ESD, and delayed bleeding was defined as such beyond 72 hours after ESD.

To investigate the potential risk factors that influence post-ESD bleeding, the following variables were analyzed; age (<65 or ≥65 years), sex, comorbidity that may affect bleeding or

coagulation (cardiovascular disease, liver cirrhosis, chronic renal failure, or hematologic disease), coagulation abnormality, pathologic diagnosis of the lesion (adenoma or EGC), the diameter of the resected specimen (<4 cm or ≥4 cm), location (upper, middle, or lower third), and status of antiplatelet therapy (no antiplatelets, continuation, or withdrawal) .

We used the cut-off value of 4 cm for the specimen diameter, taking into account a previous study that showed that the size larger than 4 cm was a risk factor for post-ESD bleeding [10].

4. Statistical analysis

Although some of the patients had more than one procedure, and some procedures involved more than one specimen, the different subject data quantities observed were assumed to constitute statistically independent observations for the purposes of statistical analysis. Categorical variables were compared by using the chi-square test and Fisher exact test for univariate analysis. Those variables with $p < .200$ in the univariate analyses and some of their interactions were examined in multivariate binary logistic regression models. A P value <.05 was considered significant. The p values for the

univariate statistical tests were not corrected for multiple testing, because those tests were taken as exploratory. The subsequent multivariate logistic regression analyses were considered the main definitive results because they determined those variables independently associated with bleeding, after we adjusted for the contributions of the other variables. As there was a second multivariate modeling of usage subgroups, it is noted that correction by the Bonferroni method would not have removed statistical significance from any of the multivariate findings. All *P* values are presented uncorrected for multiple testing. All of the analyses were performed with the Statistical Package for the Social Sciences, version 18.0 for Windows (SPSS, Chicago, IL).

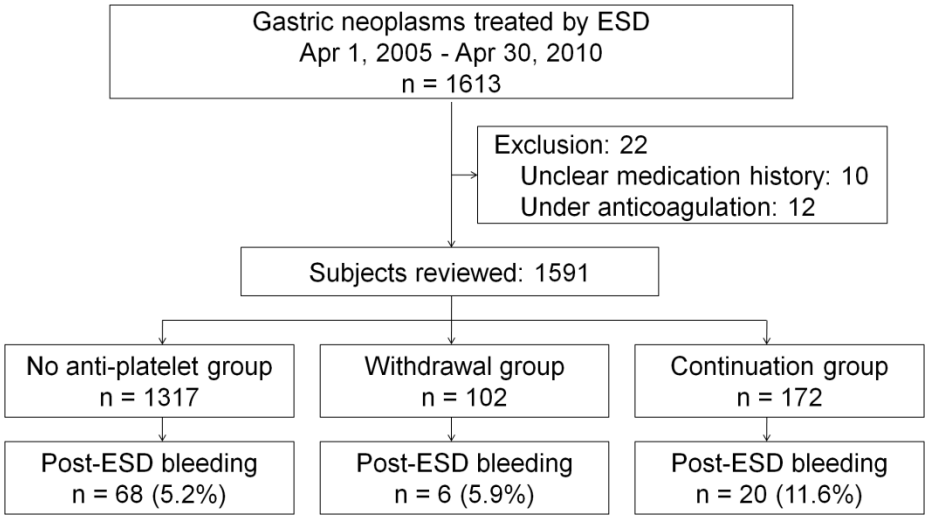

Figure 1.

A total of 1591 lesions in 1503 patients, including 815 adenomas and 776 EGCs, were reviewed retrospectively.

RESULTS

Among a total of 1591 subjects, 274 took antiplatelet agents, among whom 102 discontinued therapy for 7 days or more before ESD. Thus, there were 1371 subjects in no-antiplatelet group, 102 in the withdrawal group, and 172 in the continuation group.

The mean age of each group presented a linear tendency of older age among the antiplatelet users, with statistical significance (P <.001) (Table 1). The male proportion was 70.1% in the no-antiplatelet group, whereas that was larger in the withdrawal group and continuation group, with 83.3% and 78.5%, respectively (P = .003). Also, antiplatelet users had a greater rate of comorbidities (4.8% in the no-antiplatelet group, 34.3% in the withdrawal group, and 50.6% in the continuation group, P < .001). Coagulation abnormality was rare in all 3 groups, without significant differences among them. Also, there were no significant differences among the groups in terms of the carcinoma rate, the specimen diameter, and location of the tumor. Antiplatelet users were taking either 1 or a combination of 2 among 5 kinds of antiplatelets. Aspirin users made up the biggest proportion, 77.0%, followed by 7.3% for dual

antiplatelet users with aspirin and clopidogrel (Table 2).

Among 1591 subjects, 94 bleeding events occurred (5.9%). All of the episodes of bleeding were well-controlled with endoscopic hemostasis or angiographic embolization when endoscopic hemostasis failed. Angiographic embolization was performed in 3 subjects. There were no perforations or deaths related to ESD. Twenty of the bleeding episodes occurred in the continuation group (11.6%), 6 in the withdrawal group (5.9%), and 68 in the no-antiplatelet group (5.2%), which showed a relationship between major bleeding and antiplatelet use (P = .001) (Fig. 1). In terms of the time of bleeding, 13 episodes were delayed bleeding (13.8%), including 4 in the continuation group (2.3%), 9 in the no-antiplatelet group (0.7%), and 0 in the withdrawal group, with near significance at P = .061. However, early bleeding episodes occurred in 16 from the continuation group (9.3%), 6 in the withdrawal group (5.9%), and 59 in the no-antiplatelet group (4.5%), which showed a linear tendency of early bleeding among antiplatelet users (P = .007).

Univariate analysis showed that the diagnosis of carcinoma, comorbidity that may affect coagulation activity, the diameter of

the resected specimen, and uninterrupted antiplatelet usage were related to post-ESD bleeding, with statistical significance (Table 3). In multivariate analysis, however, the diagnosis of carcinoma, comorbidity, and specimen diameter were revealed to be independent risk factors for post-ESD bleeding, whereas uninterrupted antiplatelet usage was not (Table 4).

We performed subgroup analysis among the subjects under antiplatelet therapy, regardless of whether interrupted or not, to evaluate the effect of continuous administration on post-ESD bleeding. In univariate analysis, specimen diameter and uninterrupted antiplatelet therapy showed P value <.200 (Table 5), however, none of them were revealed to be independent risk factors of post-ESD bleeding in multivariate analysis (Table 6).

Among continuous antiplatelet users, there were no significant differences in bleeding rates among single aspirin users, non-aspirin antiplatelet users, and combination users of aspirin with non-aspirin antiplatelets (P = .404). At the same time, no significant differences in specimen diameters were found among these 3 groups (P = .089). When comparing single aspirin users and single non-aspirin antiplatelet users, there

were no significant differences in bleeding rates (P = .366). Clopidogrel, known to be more potent than low-dose aspirin, did not show more risk of bleeding, compared with aspirin alone (5.6% vs 13.8%; P = .468). In subgroup analysis among single aspirin users, regardless of whether therapy was interrupted or not, specimen diameter (OR 8.000; P = .019), location of the lesion (P = .130), and continuous aspirin usage (OR 2.880; P = .039) were related to post-ESD bleeding in univariate analysis (Table 7). However, in multivariate analysis, none of them were independent risk factors of post-ESD bleeding (OR 7.057; CI, 0.913-54.533, P = .061; P = .929; and OR 2.609; 95% CI, 0.900-7.567; P = .078, respectively) (Table 8). In this analysis, specimen diameter showed an OR well above 1.00 but had such wide 95% CIs that there was nonsignificance. This is assumed to be because of the small number of subjects included in this subgroup.

In respect to the time of bleeding, specific analyses for early and delayed bleeding were performed separately. In univariate analysis for early bleeding, comorbidity, the diagnosis of carcinoma, specimen diameter, and uninterrupted antiplatelet usage were revealed to be related to early bleeding, which was

the same as in analysis for overall post-ESD bleeding. However, multivariate analysis for early bleeding showed that comorbidity (OR 2.429; 95% CI, 1.339-4.406; P = .003), carcinoma (OR 1.756; 95% CI, 1.081-2.854; P = .023) and specimen diameter (OR 2.593; 95% CI, 1.344-5.003, P = .005) were independent risk factors of early bleeding, whereas uninterrupted antiplatelet usage was not (OR 1.363; 95% CI, 0.709-2.621, P = .353). For delayed bleeding, univariate analysis failed to clarify any risk factors.

Univariate analysis for early bleeding among the subgroup of antiplatelet users showed that specimen diameter was the only variable related to early bleeding (OR 4.777; P = .047), whereas uninterrupted administration of antiplatelets was not (OR 1.057; P = .314). Among single aspirin users, univariate analysis showed a relationship between specimen diameter and early bleeding (OR, 6.652; P = .047), but continuous aspirin usage showed no relationship with early bleeding (OR, 2.272; P = .124) . Of 102 patients who discontinued antiplatelets before ESD, 1 developed an acute cerebral infarction during the withdrawal period (1.0%).

	No-antiplatelet group (n = 1317)	Withdrawal group (n = 102)	Continuation group (n = 172)	*P* value
Age (years) (mean (SD))	61.61 (9.321)	66.45 (7.341)	67.60 (7.807)	<0.001
Age ≥ 65	541 (41.1)	64 (62.7)	120 (69.8)	<0.001
Male sex (%)	923 (70.1)	85 (83.3)	135 (78.5)	0.003
Co-morbidity (%) *	63 (4.8)	35 (34.3)	87 (50.6)	<0.001
Coagulation abnormality (%) †	14 (1.2)	0 (0.0)	2 (1.4)	0.907
Carcinoma (%)	628 (47.7)	59 (57.8)	89 (51.7)	0.131
Specimen diameter (cm) (mean (SD))	4.55 (1.391)	4.59 (1.125)	4.78 (1.502)	0.110
Specimen diameter ≥ 4 cm	880 (67.4)	71 (70.3)	128 (74.4)	0.160
Location				0.327
Upper	116 (8.8)	15 (14.7)	20 (11.6)	
Middle	428 (32.5)	21 (20.6)	56 (32.6)	
Lower	773 (58.7)	66 (64.7)	96 (55.8)	

Table 1. Baseline characteristics

SD, Standard deviation.

* Comorbidity denotes cardiovascular disease, liver cirrhosis, chronic renal failure or hematologic disease.

† Coagulation abnormality was defined as a partial-thromboplastin or prothrombin time above the normal value, a platelet count of <100,000/mm^3.

	No.	%
Aspirin	211	77.0
Clopidogrel	19	6.9
Cilostazol	8	2.9
Triflusal	6	2.2
Sarpogrelate	2	0.7
Aspirin + Clopidogrel	20	7.3
Aspirin + Cilostazol	2	0.7
Aspirin + Triflusal	2	0.7
Aspirin + Sarpogrelate	3	1.1
Clopidogrel + Sarpogrelate	1	0.4

Table 2. Types of antiplatelets

	Post-ESD bleeding	No post-ESD bleeding	OR	95% CI	*P* value
Age ≥ 65	47	678	1.208	0.796-1.833	0.374
Male sex	72	1071	1.302	0.797-2.126	0.291
Co-morbidity	24	161	2.843	1.739-4.648	<0.001
Coagulation abnormality	2	14	2.267	0.507-10.140	0.249
Carcinoma	63	713	2.235	1.437-3.476	<0.001
Specimen diameter ≥ 4 cm	79	1000	2.742	1.538-4.896	<0.001
Location					0.657
Upper	10	141			
Middle	33	472			
Lower	51	884			
Uninterrupted antiplatelet use	20	152	2.392	1.419-4.029	0.001

Table 3. Univariate analysis for post-ESD bleeding

ESD, Endoscopic submucosal dissection; *OR*, odds ration; *CI*, confidence interval.

	OR	95% CI	*P* value
Co-morbidity	2.246	1.280-3.939	0.005
Carcinoma	1.839	1.168-2.896	0.009
Specimen diameter ≥ 4 cm	2.315	1.282-4.180	0.005
Uninterrupted antiplatelet use	1.596	0.877-2.903	0.126

Table 4. Multivariate analysis for post-ESD bleeding

ESD, Endoscopic submucosal dissection; *OR*, odds ration; *CI*, confidence interval.

	Post-ESD bleeding	No post-ESD bleeding	OR	95% CI	*P* value
Age ≥ 65	16	168	0.672	0.331-1.754	0.522
Male sex	22	198	1.389	0.458-4.213	0.560
Co-morbidity	14	108	1.512	0.672-3.403	0.315
Coagulation abnormality	0	2			1.000
Carcinoma	17	131	1.687	0.724-3.930	0.221
Specimen diameter ≥ 4 cm	23	176	3.093	0.900-10.627	0.060
Location					0.235
Upper	1	34			
Middle	10	67			
Lower	15	147			
Uninterrupted antiplatelet use	20	152	2.105	0.816-5.430	0.117

Table 5. Subgroup univariate analysis among antiplatelet users

ESD, Endoscopic submucosal dissection; *OR*, odds ration; *CI*, confidence interval.

	OR	95% CI	*P* value
Specimen diameter ≥ 4 cm	3.019	0.876–10.405	0.080
Uninterrupted antiplatelet use	2.027	0.782–5.255	0.146

Table 6. Multivariate analysis among antiplatelet users

OR, odds ration; *CI*, confidence interval.

	Post-ESD bleeding	No post-ESD bleeding	OR	95% CI	*P* value
Age ≥ 65	15	124	1.331	0.493-3.591	0.572
Male sex	18	150	1.600	0.449-5.703	0.579
Co-morbidity	9	64	1.477	0.591-3.687	0.402
Coagulation abnormality	0	1			1.000
Carcinoma	13	103	1.373	0.544-3.464	0.501
Specimen diameter ≥ 4 cm	20	135	8.000	1.048-61.096	0.019
Location					0.130
Upper	0	28			
Middle	8	50			
Lower	13	112			
Uninterrupted aspirin use	16	100	2.880	1.014-8.179	0.039

Table 7. Subgroup univariate analysis among single aspirin users

ESD, Endoscopic submucosal dissection; *OR*, odds ration; *CI*, confidence interval.

	OR	95% CI	*P* value
Specimen diameter ≥ 4 cm	7.057	0.913–54.533	0.061
Location			0.929
Uninterrupted aspirin use	2.609	0.900–7.567	0.078

Table 8. Multivariate analysis among single aspirin users

OR, odds ration; *CI*, confidence interval.

DISCUSSION

Currently, ESD is one of the most commonly performed procedures for early gastric neoplasms. At the same time, the number of antiplatelet users has been growing with the increase of cardiovascular diseases. Especially, there are patients who cannot interrupt antiplatelet agents because of high thromboembolic risks, such as those who have recently undergone coronary stent insertion. There are no published trials primarily dealing with the effects of antiplatelets, including aspirin, on post-ESD bleeding except for few expert opinions. Therefore, this study was designed to find out whether antiplatelet agents increase post-ESD bleeding, so that we can establish a guideline for antiplatelet users in high risk endoscopic procedures.

Previous guidelines for antiplatelets in endoscopic procedures have classified procedural and patients' risks into low and high [6, 11]. In a high-risk procedure such as EMR, antiplatelets are generally recommended to be discontinued to prevent bleeding, but whether this can be applied to single aaspirin use is controversial. Most Western endoscopists did not recommend single aspirin users to stop taking aspirin but

suggested that patients taking non-aspirin antiplatelets discontinue therapy for more than a week before endoscopic polypectomy. Meanwhile, Eastern endoscopists recommended that their patients discontinue both of the medications for more than a week [14, 15]. Recently, the European Society of Gastrointestinal Endoscopy published a guideline for endoscopy and antiplatelet agents, which recommended discontinuation of any antiplatelet agents, including aspirin, for EMR and ESD, provided the patient was not at high risk for a thrombotic event [12]. However, this recommendation was based on a low level of evidence from a retrospective study that showed that use of "drugs potentially related to gastric injury/bleeding" (ie, aspirin, nonsteroidal anti-inflammatory drugs, anticoagulants, and corticosteroids) was associated with an increased risk of post-ESD bleeding [9]. It did not distinguish antiplatelets from anticoagulants and did not evaluate the effect of continuous administration of the drugs compared with that of interruption of therapy.

ESD has a potential of a higher risk of postprocedural bleeding compared with conventional EMR or polypectomy because of the larger and deeper resection. Antiplatelets can augment the

risk of bleeding after ESD, but unconditional discontinuation can also augment the risk of cardiovascular events by thromboembolism in high-risk patients. In this study, a massive cerebral infarction developed in a patient with atrial fibrillation after discontinuation of aspirin for 5 days.

This study revealed that comorbidity, the pathologic diagnosis of carcinoma, and the size of the resected specimen were independent risk factors for post-ESD bleeding. Previous studies have shown that post-ESD bleeding occurred more frequently in the lower third of the stomach than in the upper or middle thirds [5, 9, 10, 16], whereas the location of a tumor was not a risk factor for bleeding in this study. This might be because of the prophylactic coagulation we performed for all the visible vessels during the procedure, which is known to be effective in preventing delayed bleeding [5]. It is thought to be easier to perform prophylactic coagulation in the lower third with better vision, because endoscopic hemostasis can be easily performed for bleeding ulcers located in the lower part of the stomach compared with those in the upper part of the stomach [17, 18].

Like previous studies [10, 19], this study showed that the size

of the resected specimen was related to post-ESD bleeding. This suggests that it is essential to achieve meticulous prophylactic hemostasis for large lesions.

Our study showed that uninterrupted antiplatelet therapy was not related to higher bleeding risks independently, even in ESD, which is known as a higher risk procedure than EMR [8]. Continuous administration was not an independent risk factor for bleeding among antiplatelet users. This is an important finding for those who cannot discontinue the administration of antiplatelets, especially single aspirin, because of high cardiovascular risks.

In regard to the type of antiplatelets, there were no significant differences in bleeding risks between single aspirin users and non-aspirin users. Also, clopidogrel, a novel antiplatelet agent known to be more potent than conventional antiplatelets, did not show more risk of bleeding than single aspirin in this study. However, this should be further evaluated with more patients taking clopidogrel.

When known to be under anticoagulation, patients were recommended to discontinue it for more than 5 days before the procedure. On the other hand, no recommendations for

discontinuation were given by the physicians for antiplatelet therapy. Nevertheless, some patients discontinued antiplatelet therapy voluntarily for various durations of interruption. In this study, patients who interrupted antiplatelet therapy less than 7 days before ESD were counted as continuous users. This might explain why continuation did not appear to be a risk factor in this study. However, when we performed the univariate analysis with various cut-off values from 1 to 14 days, the cut-off value of 7 days showed the lowest *P* value in our population. Continuous administration of aspirin was not revealed to be an independent risk factor in multivariate analysis, although it showed considerable significance in univariate analysis. This is thought to be because there were significantly more subjects with comorbidities in the continuation group. Also, it showed a tendency toward larger specimens among these patients, even though statistical significance was not found (P = .069). Uninterrupted antiplatelet therapy did not show significant risk when these factors were excluded in multivariate analysis. Thus, its independent risk is thought to be inconsiderable.

In terms of the time of bleeding, the results for early bleeding

were similar to those of overall bleeding. However, no variables were revealed to be risk factors of delayed bleeding in this study. Unlike the previous study, which showed that early bleeding is an independent risk factor of delayed bleeding [20], each of the events occurred exclusively in this study.

So far, endoscopic procedures have been improved, and their uses have been broadened continuously. As the use of these procedures grew, studies suggested that endoscopic procedures such as sphincterotomy [21, 22], polypectomy, or biopsy [23] could be performed without interrupting therapy with aspirin or other nonsteroidal anti-inflammatory drugs. On the other hand, there are opinions recommending avoiding high-risk endoscopic procedures while dual antiplatelet therapy is needed after percutaneous coronary intervention with stent placement [24]. The result of our study suggests that continuous antiplatelet therapy would not increase the bleeding risk in ESD. However, considering that those who are taking antiplatelets carry more comorbidities, ESD should be done more carefully in this group.

There are several limitations to this study. One is that it is a retrospective review from a single center. However, it has an

advantage of a large number of subjects. Also, there are the problems of model instability and the small (<20%) proportion of subjects with antiplatelet usage. Another limitation is that the types and dosages of antiplatelets were not clarified. There is a possibility of various risks of bleeding depending on the different types and dosages of antiplatelets. Also, there is the possibility that patients who did not interrupt antiplatelet therapy had more thrombotic risks than patients in the withdrawal group. This might have affected the result of less bleeding in continuous users, which should be further evaluated in a prospective, randomized trial.

In conclusion, this study suggests that patients on antiplatelet therapy because of high cardiovascular risks may undergo ESD without increased risks of post-ESD bleeding. Prospective, randomized studies are mandatory for those who are at high cardiovascular risks to decide whether or not to interrupt antiplatelet therapy before ESD for gastric neoplasms.

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국문 초록

서론: 내시경적 점막하 박리술 시 항혈소판제 복용이 출혈을 증가시키는지는 알려져 있지 않다. 본 연구는 항혈소판제 복용이 점막하 박리술 시 출혈의 위험도를 높이는지를 알아보았다.

방법: 2005 년 4 월부터 2010 년 4 월까지 위 종양으로 내시경 점막하 박리술을 시행받은 1591 명의 환자(위 선종 815 명, 조기위암 776 명)를 대상으로 하였다. 일차 결과 변수는 현성 토혈/혈변 또는 기저치로부터 2 g/dL 이상의 헤모글로빈 저하, 내시경적 지혈술이나 색전술 또는 수혈이 필요한 경우로 정하였다.

결과: 총 1591 명 중, 항혈소판제를 복용한 환자는 274 명이었고 그 중 102 명은 시술 전 7 일 이상 투약을 중단하였다. 시술 후 출혈은 투약지속군 중 20 명, 중단군 중 6 명, 항혈소판제 미사용군 중 68 명을 포함하여 94 명에서 발생하였다. 단변량 분석 시 항혈소판제 복용, 조기위암, 동반질환, 표본 장경은 시술 후 출혈과 관련이 있었다. 다변량 분석에서는 조기위암(OR 1.839; 95% CI, 1.168−2.896; P = .009)과 동반질환(OR 2.246;95% CI, 1.280−3.939; P = .005), 표본 장경(OR 2.315; 95% CI, 1.282−4.180; P = .005)이 출혈의 독립적 위험인자로

나타났으며 항혈소판제 사용은 위험인자가 아닌 것으로 나타났다(OR 1.596; 95% CI, 0.877-2.903; P = .126). 소집단 다변량 분석에서 지속 투약은 시술 후 출혈의 독립적인 위험인자가 아닌 것으로 나타났다(OR 2.027; P = .146). 항혈소판제 투약을 중단한 102 명 가운데 1 명에서 급성 뇌경색이 발생하였다(1.0%).

결론: 항혈소판제를 복용하는 환자에서 내시경적 점막하 박리술 시 항혈소판제 투약지속은 출혈을 유의하게 증가시키지 않는 것으로 나타났다. (Gastrointest Endosc 2012;75:719-27.)

주요어 : 내시경적 점막하 박리술, 항혈소판제, 출혈

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