

The Need for Second-Look Endoscopy to Prevent Delayed Bleeding after Endoscopic Submucosal Dissection for Gastric Neoplasms: A Prospective Randomized Trial

Jong Sun Kim, Min Woo Chung, Cho Yun Chung, Hyung Chul Park, Dae Yeul Ryang, Dae Seong Myung, Sung Bum Cho, Wan Sik Lee, and Young Eun Joo

Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

See editorial on page 459.

Background/Aims: Many authors recommend performing a second-look endoscopy (SLE) to reduce the frequency of delayed bleeding after endoscopic submucosal dissection (ESD) for gastric neoplasms, but these recommendations have been made despite a lack of reliable evidence supporting the effectiveness of SLE. **Methods:** From January 2012 to May 2013, we investigated 441 gastric neoplasms treated by ESD to assess the risk factors for delayed bleeding. Delayed bleeding occurred in four of these lesions within 1 postoperative day. Therefore, we enrolled the patients with the remaining 437 lesions to determine the utility of SLE performed on the morning of postoperative day 2. All lesions were randomly assigned to SLE (220 lesions) groups or non-SLE (217 lesions) groups. **Results:** Delayed bleeding occurred in 18 lesions (4.1%). A large tumor size (>20 mm) was the only independent risk factor for delayed bleeding ($p=0.007$). The chance of delayed bleeding was not significantly different between the patients receiving a SLE (eight cases) and those patients not receiving a SLE (six cases, $p=0.787$). Furthermore, SLE for lesions with a large tumor size did not significantly decrease delayed bleeding ($p=0.670$). **Conclusions:** SLE had little or no influence on the prevention of delayed bleeding, irrespective of the risk factors. (*Gut Liver* 2014;8:480-486)

Key Words: Hemostasis, endoscopic; Hemorrhage; Gastric neoplasms; Endoscopic resection

INTRODUCTION

Gastric neoplasms, including gastric adenoma (GA) and early gastric cancer (EGC), are among the most common neoplasms worldwide. Endoscopic submucosal dissection (ESD) is the preferred treatment for GA and EGC due to its low recurrence rate and high complete resection rate for gastric neoplasms.¹⁻³ However, several complications of ESD, such as perforation, bleeding, prepyloric or pyloric stenosis, transient bacteremia, and aspiration pneumonia, have been reported in several previous studies and were attributed to its technical difficulties and invasiveness.⁴⁻⁷

The most common concern for patients after gastric ESD is delayed bleeding. Delayed bleeding has been reported to occur in approximately 5% to 15% of artificial ulcers, which are disruptions in the mucosal integrity of the stomach after ESD.⁴⁻⁶ Fortunately, most delayed bleeding cases are controlled by appropriate emergency endoscopic treatment, although a surgery is required as part of the treatment in some cases.

Several previous studies have reported that second-look endoscopy (SLE) prevents further bleeding after endoscopic treatment for peptic ulcer bleeding in the stomach.⁸⁻¹⁰ A significant number of authors recommend performing SLE for artificial ulcers, especially for lesions with significant risk factors for delayed bleeding, including tumor location,¹¹ tumor size,^{5,12,13} specimen size,^{5,14} and ulcerative findings.¹² However, artificial ulcers after ESD are exposed to relatively high pH conditions in comparison with peptic ulcers. Lately, a retrospective study reported that SLE might not be necessary for avoiding delayed bleeding.⁴ By contrast, another retrospective study suggested the use of SLE could prevent delayed bleeding, especially in high-risk gastric lesions.¹⁴ Therefore, we conducted a prospective,

Correspondence to: Sung Bum Cho

Department of Internal Medicine, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 501-757, Korea
Tel: +82-62-220-6296, Fax: +82-62-225-8578, E-mail: portalvein@naver.com

Received on June 23, 2013. Revised on July 23, 2013. Accepted on August 6, 2013. Published online on February 24, 2014

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl13226>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

randomized, single-blind, controlled trial to investigate whether SLE prevents delayed bleeding and is necessary after ESD and to validate the predictive factors of delayed bleeding.

MATERIALS AND METHODS

1. Patients and materials

A total of 446 lesions histologically diagnosed as gastric neoplasms and consecutively treated with ESD at Chonnam National University Hwasun Hospital, Hwasun, Korea from January 2012 to May 2013 were enrolled. The Ethical Committee of the Chonnam National University Medical School approved the study (clinical trial number: CNUHH-2012-20), which was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients included in the study signed a written informed consent prior to inclusion.

2. Inclusion criteria and exclusion criteria

In the study, all patients who visited our hospital to receive ESD treatment for gastric neoplasms were included. ESD was principally indicated for GAs and EGCs corresponding to the expanded criteria suggested by Gotoda *et al.*¹⁵ as based on endoscopic findings, including chromoendoscopy, narrow band imaging, biopsy, and abdominal computed tomography. Exclusion criteria were as follows: pregnancy; breast feeding; bleeding on resected lesions within 24 hours after ESD; taking gastric mucosal protectors, acid suppressants, anticoagulants, and/or antiplatelets within 1 week of the ESD; known allergies to proton pump inhibitors (PPIs); mental and/or physical disabilities; and refusal to consent to participate in the study.

3. Study design

The study design was a prospective, randomized, single-blind, controlled trial, as shown in Fig. 1. All patients included in the study were assigned randomly using sealed, numbered enve-

Admission day	Operation day	POD 1	POD 2	POD 3-POD 56
	Intravenous administration pantoprazole 40 mg per day or lansoprazole 40 mg per day		Oral pantoprazole 40 mg or oral lansoprazole 30 mg per day	
	ESD in the morning		Endoscopy in the morning	Discharge at POD 4
Liquid diet	Nothing per oral	WF after noon Liquid diet at dinner	Soft diet (POD 3-POD 14)	Regular diet (POD 15-)

Fig. 1. The study design. POD, postoperative day; ESD, endoscopic submucosal dissection; WF, water feeding.

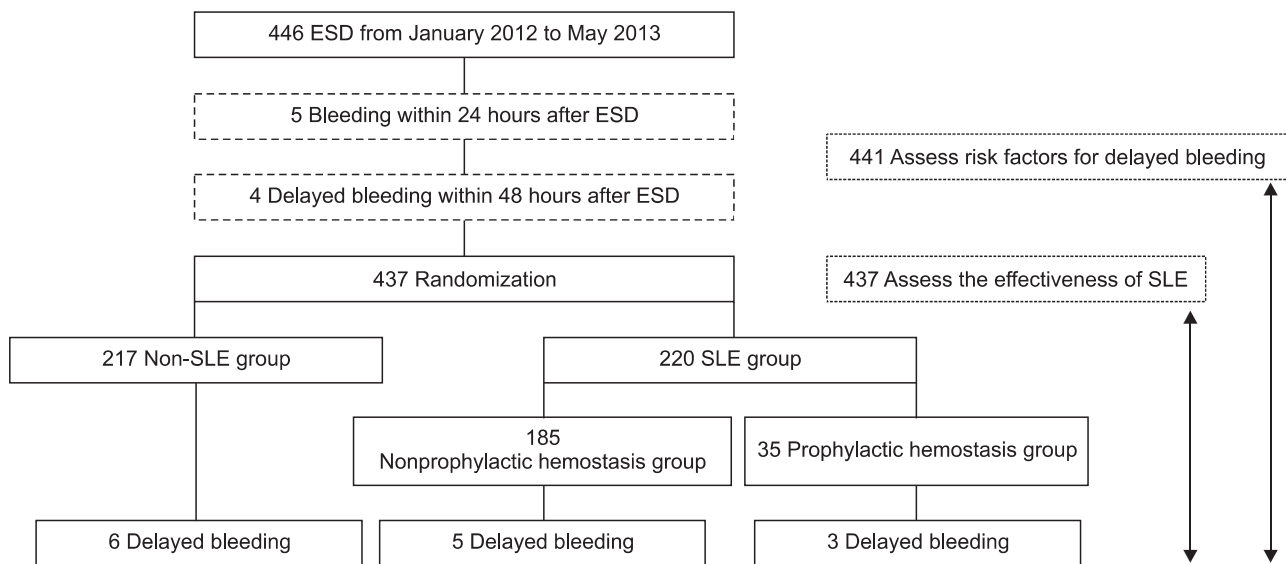


Fig. 2. A flowchart of the allocation of the enrolled gastric neoplasms. ESD, endoscopic submucosal dissection; SLE, second-look endoscopy.

lopes to either a non-SLE group or a SLE group that received SLE on the morning of the second postoperative day (POD), as shown in Fig. 2. The randomization number was not exposed to the endoscopist until the study completion date. The endoscopist was instructed not to ask other doctors or patients whether the patients had received SLE. The patients ate only a liquid diet at admission day. Patients fasted from midnight at admission day until noon of POD 2. Based on a standard protocol,^{16,17} the ESDs were performed for the patients under conscious sedation on Tuesday and Wednesday. The operator was a single experienced endoscopist (S.B. Cho) who had performed ESD over 500 times for more than 5 years. The normal mucosa located more than 5 mm away from the tumor margin was marked using an argon plasma coagulator (VIO 300D; Erbe Elektromedizin, Tübingen, Germany). Epinephrine mixed with hypertonic saline (1:100,000) containing 1% indigo carmine was injected into the submucosal layer to raise the lesion. Hyaluronic acid was used if the tumor was insufficiently elevated. A circumferential mucosa was cut around the marks. Subsequently, the submucosal layer, including the tumor, was dissected using an insulation-tipped diathermic knife (KD-611L; Olympus, Tokyo, Korea) or dual knife (KD-650; Olympus). We used hemostatic forceps (FD-410LR; Olympus) and hemostatic clips (HX-610-135 or HX-610-090L; Olympus) for bleeding and for all exposed vessels on the resected lesion during ESD. Additionally, all the lesions underwent prophylactic coagulation for nonbleeding exposed vessels on resected lesions after the removal of lesions on the stomach.¹¹

SLE was performed to inspect the artificial ulcer on the morning of POD 2 to evaluate whether there was recent bleeding or the possibility of bleeding lesions (nonbleeding visible vessels and adherent clots). Three days after ESD, pantoprazole (Pantoloc injection; Takeda Pharm Co., Osaka, Japan) at 40 mg per day or lansoprazole (Lanston injection; Takeda Pharm Co.) at 40 mg per day was administered intravenously and continuously. After POD 3, patients took orally 40 mg of pantoprazole (Pantoloc®; Takeda Pharm Co.) or 30 mg of lansoprazole (Lanston®; Takeda Pharm Co.) once daily for the following 54 days. All patients resumed food intake when the afternoon had passed on POD 2 and were discharged at POD 4 unless there were any of signs of complications, such as hematemesis, hematochezia, melena, fever, or abdominal pain. All participants were instructed to contact our hospitals when experiencing these signs of complications after discharge, and were asked to visit the outpatient clinic at 2 and 8 weeks after ESD. Based on the healing process of the artificial ulcer, the follow-up period was 56 days.¹⁸ If the patient had 2 or more gastric neoplasms, we treated each gastric neoplasm at intervals of about 3 months.

If the patient showed any bleeding signs or symptoms after ESD, we performed emergency endoscopy to check whether any of the lesions required endoscopic hemostasis, such as for bleeding or possibly bleeding lesions, and treated these lesions with a

hemostatic clip and/or thermocoagulator. We prescribed blood transfusion only for patients with bleeding artificial ulcers and decreases in hemoglobin levels >2 g/dL.

4. Data analysis

Delayed bleeding was defined as massive bleeding at 1 to 56 days after ESD and as requiring emergency endoscopic hemostasis for endoscopically evident bleeding sites on resected lesions because of hematemesis, melena, hematochezia. *En bloc* resection was defined as resection in a single piece with negative lateral and vertical margins. A long procedure time was defined as a procedure time (from passing the endoscopy through the mouth to complete withdrawal) of more than 60 minutes. The longitudinal parts of the stomach were equally divided into the upper, middle, and lower portions. The circumferential parts of the stomach were equally separated into four portions: the anterior wall, posterior wall, greater curvature, and lesser curvature. A large tumor size was defined as one greater than 20 mm. All tumors were divided into three histologic types based on the Vienna classification:¹⁹ low-grade dysplasia, high-grade dysplasia, and EGC. The macroscopic types, differentiation, depth of invasion, and lymphovascular invasion of the gastric neoplasms were classified according to the Japanese Gastric Cancer Association classification.²⁰

The following variables were analyzed to demonstrate predictive factors for delayed bleeding: age, sex, body mass index, laboratory findings on admission (white blood count, hemoglobin, platelet, prothrombin time, and activated partial thromboplastin time), history of stomach operation, history of gastric ESD, the use of anticoagulants and/or antiplatelet drugs 1 week before the procedure, tumor location (longitudinal and circumferential), gross tumor type (elevated, flat, or depressed), endoscopic ulcerative findings, the presence of fibrosis in the submucosal layer during ESD, the resection type (*en bloc* or piecemeal), resected specimen size (largest diameter), tumor size (largest diameter), depth of cancer (epithelium, lamina propria, muscularis mucosae, or submucosa), histologic type, infection by *Helicobacter pylori*, PPI type, and ESD procedure time. In addition, we evaluated the incidence of delayed bleeding and the frequencies of various risk factors for delayed bleeding between the SLE and non-SLE groups to investigate whether SLE prevented delayed bleeding.

5. Statistical analysis

The SPSS software version 18.0 (IBM Co., Armonk, NY, USA) was used to perform the statistical analysis. All values are expressed as the means±SD and were analyzed by the Student t-test. The categorical variables were analyzed by the chi-square test or Fisher exact test. A value of $p < 0.05$ was accepted as statistical significance. If more than one of these factors was significant in the univariate analysis, a multiple logistic regression analysis was performed to identify an independent factor.

Table 1. A Univariate Analysis of the Risk Factors for Delayed Bleeding

Characteristic	Delayed bleeding		p-value
	Present (n=18)	Absent (n=423)	
Age, yr	67.1±7.5	65.8±9.6	0.570*
Sex, male/female	14/4	277/146	0.323 [†]
Body mass index, kg/m ²	23.1±2.2	24.0±3.0	0.233*
Platelet, ×1,000	213.1±68.0	229.4±55.1	0.223*
Hgb	13.5±1.9	13.9±2.2	0.499*
PT, sec	12.6±0.9	12.5±0.8	0.434*
aPTT	35.4±2.2	35.2±3.0	0.790*
Anticoagulants/Antiplatelets	3	37	0.218 [†]
Previous history of ESD	2	24	0.287 [†]
History of stomach operation	1	10	0.371 [†]
Underlying disease			
Hypertension	4	174	0.142 [‡]
Diabetes mellitus	2	76	0.752 [‡]
Cerebrovascular accident	1	5	0.222 [‡]
Ischemic heart disease	1	6	0.255 [‡]
Liver cirrhosis	1	10	0.371 [†]
Chronic renal failure	2	24	0.287 [†]
Type of PPI, pantoprazole/lansoprazole	10/8	203/220	0.633 [‡]
Size of specimen, mm	44.8±12.2	39.9±11.0	0.068*
Long procedure time, >60 min	8	74	0.004 [‡]
Location of lesion			
Longitudinal, U/M/L	2/3/13	23/88/312	0.603 [‡]
Circumferential, AW/PW/LC/GC	3/3/9/3	95/78/127/123	0.327 [‡]
Type of lesion, elevated/flat/depressed	10/4/4	219/54/150	0.972 [‡]
Ulcerative finding	4	42	0.106 [‡]
Resection style, piecemeal/ <i>en bloc</i>	1/17	10/413	0.371 [†]
Fibrosis in submucosa	6	79	0.131 [‡]
Large tumor size, >20 mm	7	39	<0.001 [‡]
Histologic type, LGD/HGD/cancer	7/3/8	202/52/169	0.552 [‡]
Depth of cancer, E/LP/MM/S	0/5/3/0	7/108/48/6	0.779 [‡]
<i>H. pylori</i> infection	15	366	0.723 [‡]

Data are presented as mean±SD or number.

Hgb, hemoglobin; PT, prothrombin time; aPTT, activated partial thromboplastin time; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; U, upper; M, middle; L, lower; AW, anterior wall; PW, posterior wall; LC, lesser curvature; GC, greater curvature; LGD, low grade dysplasia; HGD, high grade dysplasia; E, epithelium; LP, lamina propria; MM, muscularis mucosae; S, submucosa; *H. pylori*, *Helicobacter pylori*.

*Unpaired t-test; [†]Fisher exact test; [‡]Chi-square test.

RESULTS

Of the 446 lesions with gastric neoplasms in this study, *en bloc* resections were performed in 435 lesions (97.5%). All the tumor lesions had tumor-free margins histologically. Only one case was managed with surgery due to lymphovascular invasion. No perforations after ESD and no deaths related to ESD and/or the subsequent surgery were observed. Bleeding occurred within 24 hours after ESD for five of the resected lesions; these

cases were consequently excluded from the study. Delayed bleeding occurred in 18 (4.1%) of 441 lesions and was successfully controlled by emergency endoscopic treatment. According to the Forrest classification,²¹ these cases were classified into four categories: spurting bleeding (four cases), oozing bleeding (six cases), nonbleeding visible vessels (six cases), and adherent clots (two cases). Blood transfusions were performed in five of the 18 delayed bleeding cases. No additional cases of delayed bleeding were observed after the endoscopic treatment.

Table 2. A Multivariate Analysis of the Factors Associated with Delayed Bleeding

Factor	Multivariate analysis		
	OR	95% CI	p-value
Long procedure time, >60 min	2.38	0.83–6.87	0.108
Large tumor size, >20 mm	4.47	1.50–13.34	0.007

OR, odds ratio; CI, confidence interval.

We investigated the 441 lesions to validate various risk factors for delayed bleeding. Univariate analysis indicated a long procedure time (odds ratio [OR], 3.77; 95% confidence interval [CI], 1.44 to 9.88; $p=0.004$) and large tumor size (OR, 6.27; 95% CI, 2.30 to 17.09; $p<0.001$) were significantly associated with delayed bleeding, as shown in Table 1. Multivariate logistic regression analysis showed that large tumor size was the only independent risk factor related to late delayed bleeding ($p=0.007$), as shown in Table 2.

Delayed bleeding occurred in four lesions within 48 hours after ESD. Hence, we enrolled the remaining 437 lesions to determine the utility of SLE for delayed bleeding. Table 3 shows the incidence of risk factors for delayed bleeding and the frequencies of delayed bleeding between the SLE and non-SLE groups. SLE was performed on 220 lesions on the morning of POD 2. The chance of delayed bleeding was not significantly different between the SLE (eight cases) and non-SLE (six cases) groups ($p=0.787$). Moreover, no significant differences were observed in the risk factors for delayed bleeding between the SLE and non-SLE groups. Thirty five lesions were treated with prophylactic hemostasis using hemostatic clips for nonbleeding visible vessels after the removal of adherent clots. Three cases (8.6%) in the SLE group showed delayed bleeding after prophylactic endoscopic treatment.

DISCUSSION

According to Takizawa *et al.*,¹¹ the subsequent coagulation of nonbleeding visible vessels in lesions resected by ESD significantly prevented delayed bleeding in most but not all cases. This prevention of delayed bleeding is the reason why most hospitals routinely perform SLE after ESD. Contrary to expectations, the incidence of delayed bleedings between the SLE and non-SLE groups was not significantly different in our study. Additionally, the incidence of delayed bleeding with prophylactic endoscopic hemostasis was higher than that without prophylactic endoscopic hemostasis, although this trend was not statistically significant ($p=0.093$). Given these findings, we suggest that SLE has limited value, if any, for reducing the incidence of delayed bleeding, and that the treatment of prophylactic hemostasis for adherent clots may be an unnecessary or immoderate procedure. These findings from our study are consistent with those of

a previous report, which found that endoscopic treatment may result in rebleeding because new blood vessels can arise from a lesion treated through endoscopic hemostasis.⁴ As well, another previous study noted the natural healing reactions of artificial ulcers might be one of the major contributors in preventing delayed bleeding.¹⁴

As shown by a univariate analysis, a long procedure time and a large tumor size were risk factors for delayed bleeding in the present study. In the multivariate analysis, a large tumor size was the only independent predictive factor for delayed bleeding. These results suggested the procedure time was positively related with tumor size, and are in keeping with the findings of previous reports.^{5,22} Further, several retrospective studies have reported that a large tumor size was a significant factor for delayed bleeding.^{5,12,13} The current prospective study showed that SLE for lesions with risk factors for delayed bleeding did not significantly reduce the incidence of delayed bleeding, suggesting SLE has little or no influence on the prevention of delayed bleeding, irrespective of the risk factor for it.

Previous reports have shown that specimen size is a significant predictive factor for delayed bleeding.^{5,14} The present study revealed that tumor size rather than lesion size was a significant risk factor for delayed bleeding. In general, specimen size is directly proportional to tumor size. We believe the reason as to why tumor size is the only predictive factor for delayed bleeding might be the relatively inaccurate ESD procedure.

Because *H. pylori* infection is one of factors influencing the healing of gastric ulcers,²³ we performed Campylobacter-like organism (Asan Pharm Co., Ltd., Hwasung, Korea) tests for the diagnosis of *H. pylori* for all patients and evaluated whether this bacterium affected the rate of delayed bleeding. In accordance with previous reports,^{6,24} the present study did not find any significant correlations between *H. pylori* status and the delayed bleeding rate.

In our cases, the incidence of complications after ESD, such as perforations, delayed bleeding, and positive lymphovascular invasion, was lower than that of previous studies.⁴⁻⁶ Several possible reasons could explain these results. First, recent improvements in the therapeutic modalities and techniques have led to a decrease in the incidence of complications for gastric neoplasms. Second, none of the ESD lesions had positive/intermediate lateral margins. Recently, Nakamura *et al.*⁶ suggested that a positive/intermediate lateral margin was a significant risk factor for delayed bleeding. Third, the tumor size (mean \pm SD, 10.4 \pm 7.3 mm) in the present study was relatively smaller than those in other studies.⁴⁻⁶

The current study had at least two limitations. First, the study was a relatively small single-center one. Second, the study did not evaluate the different cytochrome P450 2C19 (CYP2C19) genotypes of each individual. These genotypes can influence the metabolism of PPIs and thereby might be related to the healing rate of artificial ulcers after ESD.²⁵ For these reasons, a large

Table 3. Comparisons between the Second-Look Endoscopy (SLE) and Non-SLE Groups

Characteristic	SLE (n=220)	Non-SLE (n=217)	p-value
Age, yr	65.9±9.3	67.1±7.5	0.934*
Sex, male/female	145/75	142/75	0.920 [†]
Body mass index, kg/m ²	24.0±2.8	23.9±3.2	0.793*
Platelet, ×1,000	228.9±47.5	228.7±63.4	0.974*
Hgb	13.9±2.7	13.8±1.4	0.862*
PT, sec	12.5±0.7	12.5±0.8	0.894*
aPTT	35.0±2.8	35.5±3.2	0.125*
Anticoagulants/Antiplatelets	15	24	0.133 [†]
Previous history of ESD	13	13	1.000 [†]
History of stomach operation	5	6	0.770 [†]
Underlying disease			
Hypertension	91	87	0.846 [†]
Diabetes mellitus	43	34	0.316 [†]
Cerebrovascular accident	2	4	0.447 [†]
Ischemic heart disease	2	5	0.282 [†]
Liver cirrhosis	5	6	0.770 [†]
Chronic renal failure	13	13	1.000 [†]
Type of PPI, pantoprazole/lansoprazole	107/113	104/113	0.924 [†]
Size of specimen, mm	40.4±11.4	39.6±10.7	0.449*
Long procedure time, >60 min	45	35	0.267 [†]
Location of lesion			
Longitudinal, U/M/L	11/41/168	13/50/154	0.243 [‡]
Circumferential, AW/PW/LC/GC	50/43/67/60	48/38/66/65	0.579 [‡]
Type of lesion, elevated/flat/depressed	114/29/77	112/28/77	0.938 [‡]
Ulcerative finding	26	20	0.437 [†]
Resection style, piecemeal/en bloc	6/214	4/213	0.751 [‡]
Fibrosis in submucosa	41	43	0.809 [†]
Large tumor size, >20 mm	24	21	0.754 [†]
Histologic type, LGD/HGD/cancer	110/27/83	97/26/94	0.224 [‡]
Depth of cancer, E/LP/MM/S	4/49/27/3	3/64/24/3	0.495 [‡]
<i>H. pylori</i> infection	193	184	0.406 [†]
Delayed bleeding	8	6	0.787 [†]
With long procedure time	3/45	3/35	1.000 [†]
With large tumor size	4/24	2/21	0.670 [†]

Data are presented as mean±SD or number.

SLE, second-look endoscopy; Hgb, hemoglobin; PT, prothrombin time; aPTT, activated partial thromboplastin time; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; U, upper; M, middle; L, lower; AW, anterior wall; PW, posterior wall; LC, lesser curvature; GC, greater curvature; LGD, low grade dysplasia; HGD, high grade dysplasia; E, epithelium; LP, lamina propria; MM, muscularis mucosae; S, submucosa; *H. pylori*, *Helicobacter pylori*.

*Unpaired t-test; [†]Fisher exact test; [‡]Chi-square test.

prospective, multicenter, randomized control trial evaluating the differences between CYP2C19 genotypes is required to provide more definitive evidence.

In conclusion, based on our prospective study, a large tumor size is an independent risk factor for delayed bleeding. However, SLE has little or no influence on the prevention of delayed

bleeding, irrespective of the risk factor for it.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Fujishiro M. Endoscopic submucosal dissection for gastric cancer. *Curr Treat Options Gastroenterol* 2008;11:119-124.
2. Ohkuwa M, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001;33:221-226.
3. Katsube T, Murayama M, Isohata N, et al. The efficacy of endoscopic submucosal dissection compared with modified endoscopic aspiration mucosectomy by assessing the short-term therapeutic results for differentiated mucosal gastric cancer. *Anticancer Res* 2009;29:4271-4274.
4. Goto O, Fujishiro M, Kodashima S, et al. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest Endosc* 2010;71:241-248.
5. Chung IK, Lee JH, Lee SH, et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009;69:1228-1235.
6. Nakamura M, Nishikawa J, Hamabe K, et al. Risk factors for delayed bleeding from endoscopic submucosal dissection of gastric neoplasms. *Scand J Gastroenterol* 2012;47:1108-1114.
7. Muraki Y, Enomoto S, Iguchi M, Fujishiro M, Yahagi N, Ichinose M. Management of bleeding and artificial gastric ulcers associated with endoscopic submucosal dissection. *World J Gastrointest Endosc* 2012;4:1-8.
8. Saeed ZA, Cole RA, Ramirez FC, Schneider FE, Hepps KS, Graham DY. Endoscopic retreatment after successful initial hemostasis prevents ulcer rebleeding: a prospective randomized trial. *Endoscopy* 1996;28:288-294.
9. Chiu PW, Lam CY, Lee SW, et al. Effect of scheduled second therapeutic endoscopy on peptic ulcer rebleeding: a prospective randomised trial. *Gut* 2003;52:1403-1407.
10. Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000;343:310-316.
11. Takizawa K, Oda I, Gotoda T, et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection: an analysis of risk factors. *Endoscopy* 2008;40:179-183.
12. Uedo N, Takeuchi Y, Yamada T, et al. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol* 2007;102:1610-1616.
13. Kim JW, Kim HS, Park DH, et al. Risk factors for delayed postendoscopic mucosal resection hemorrhage in patients with gastric tumor. *Eur J Gastroenterol Hepatol* 2007;19:409-415.
14. Kim HH, Park SJ, Park MI, Moon W. Clinical impact of second-look endoscopy after endoscopic submucosal dissection of gastric neoplasms. *Gut Liver* 2012;6:316-320.
15. Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219-225.
16. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006;41:929-942.
17. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001;48:225-229.
18. Kakushima N, Yahagi N, Fujishiro M, et al. The healing process of gastric artificial ulcers after endoscopic submucosal dissection. *Dig Endosc* 2004;16:327-331.
19. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000;47:251-255.
20. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011;14:101-112.
21. Heldwein W, Schreiner J, Pedrazzoli J, Lehnert P. Is the Forrest classification a useful tool for planning endoscopic therapy of bleeding peptic ulcers? *Endoscopy* 1989;21:258-262.
22. Goto O, Fujishiro M, Kodashima S, Ono S, Omata M. Is it possible to predict the procedural time of endoscopic submucosal dissection for early gastric cancer? *J Gastroenterol Hepatol* 2009;24:379-383.
23. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. *Ann Intern Med* 1992;116:705-708.
24. Kakushima N, Fujishiro M, Yahagi N, Kodashima S, Nakamura M, Omata M. *Helicobacter pylori* status and the extent of gastric atrophy do not affect ulcer healing after endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2006;21:1586-1589.
25. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokin* 2005;20:153-167.