

Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection

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Author contributions: Kim SJ wrote the manuscript; Choi CW organized the manuscript; Kang DH, Kim HW and Park SB contributed to the design, organization, and draft of the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests.

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Received: April 20, 2015
Peer-review started: April 21, 2015
First decision: September 8, 2015
Revised: October 1, 2015
Accepted: December 4, 2015
Article in press: December 8, 2015
Published online: February 10, 2016

Abstract

Endoscopic submucosal dissection (ESD) is a widely

used procedure as curative treatment for superficial gastric neoplasms, including early gastric cancer without lymph node metastasis. However, ESD requires advanced endoscopic skill and there is a major concern regarding complications from bleeding. So far, extensive efforts have been made to develop strategies to reduce post-ESD bleeding. Use of proton pump inhibitors and coagulating exposed vessels on the ulcer floor after ESD are strategies known to reduce the risk of delayed bleeding. Second-look endoscopy (SLE) is also carried out to reduce delayed bleeding following ESD in many institutions. However, the incidence of bleeding still remains around 5%, and further measures are needed to reduce delayed bleeding after gastric ESD. Recently, three randomized studies indicated that routine SLE was unnecessary. Although routine SLE may not be recommended for all patients after gastric ESD, SLE might be an important tool for the prevention of the delayed bleeding in selected high-risk patients. Thus, the identification of the risk factors, such as large size of resected specimen and treatment with multiple antiplatelet medications, may help to further guide clinicians in deciding whether to perform SLE. Studies carried out on larger cohorts are necessary to clarify the efficacy of SLE after ESD in the prevention of post-ESD bleeding in potentially high-risk patients.

Key words: Endoscopic submucosal dissection; Second-look endoscopy; Early gastric cancer

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Core tip: Second-look endoscopy (SLE) for selected patients might be an important tool for the prevention of delayed bleeding following endoscopic submucosal dissection (ESD). Risk factors for bleeding after ESD include large size of resected specimen and use of multiple antiplatelet agents. In addition, submucosal fibrosis and nausea might be risk factors associated with high-risk ulcer stigmata. Such risk factors require further evaluation as to whether SLE is indicated.

Kim SJ, Choi CW, Kang DH, Kim HW, Park SB. Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016; 8(3): 173-179 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/173.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.173>

INTRODUCTION

In recent years, endoscopic submucosal dissection (ESD) for superficial gastric epithelial neoplasms including early gastric cancer has been commonly used in clinical practice in Asian countries. While a snare is used in conventional endoscopic mucosal resection (EMR), various types of endoscopic surgical knives are used in ESD for the purpose of mucosal incision and submucosal dissection. Therefore, this technique enables higher en bloc resection and histologic complete resection rates in patients with larger or ulcerated tumors^[1,2]. However, with ESD, concerns still exist regarding technical difficulties and a higher risk of complications, especially bleeding and perforation^[1,2]. Immediate intraoperative bleeding is easily recognized at the time of the procedure and can be treated endoscopically in most cases. However, delayed bleeding, manifesting as hematemesis or melena, may occur days after the procedure, occasionally even after discharge from hospital. The reported incidence of delayed bleeding after gastric ESD varies from 5.4% to 22%^[3-9]. As any delay in the recognition of such an event may result in serious cardiovascular complications, such as hypovolemic shock, prevention of delayed bleeding is an important clinical problem following ESD to address.

ESD causes large artificial ulcers, but there is no consensus regarding second-look endoscopy (SLE), and when or whether the procedure should be used. Although recent randomized studies demonstrated no benefit for the use of SLE in the prevention of post-ESD bleeding, a multicenter survey of patient management following gastric ESD demonstrated that SLE was utilized by most institutions^[9]. In the present review article, the optimal perioperative management to reduce bleeding following ESD, including SLE, and the high-risk patients SLE will benefit most will be discussed.

SLE after endoscopic submucosal dissection

Delayed bleeding still occurs in approximately 5% of patients who have undergone gastric ESD, despite proton pump inhibitor (PPI) neutralization of intragastric acidity and endoscopic hemostasis through prophylactic coagulation of visible vessels at the ulcer base^[3,5,10-12]. SLE is generally defined as repeat endoscopy within 24 h after the initial endoscopy and hemostatic therapy. For the management of peptic ulcer bleeding, routine SLE is not recommended following successful endoscopic hemostasis. Repeat endoscopy should be performed

on patients with clinical evidence of recurrent bleeding. Hemostatic therapy should furthermore be applied to patients with higher risk stigmata of hemorrhage^[13]. For the perioperative management of post-ESD bleeding, the benefit of SLE remains controversial. However, routine SLE continues to be performed in many medical centers which have inpatients-based ESD treatment setting, probably because the delayed bleeding rate overall remains at approximately 5%^[9]. If high-risk ulcer stigmata after ESD are treated only using PPI without endoscopic therapy, the bleeding risk might be higher, and more serious complication may develop following discharge. Recently, the efficacy of SLE for ESD induced ulcers was evaluated in several retrospective studies and three prospective randomized trials^[8,14-17] (Table 1). The results indicated that the incidence of post-ESD bleeding was not significantly affected by SLE. However, three prospective studies had several limitations that should be taken into account. Ryu *et al.*^[17] reported that 12 patients (16.2%) in the SLE group and 9 (11.1%) in the no SLE group experienced bleeding after ESD ($P = 0.66$). The delayed bleeding was defined as the presence of any symptoms or signs of bleeding such as melena or hematemesis from 2 to 28 d. This definition can include the past bleeding episode and other site bleeding, therefore, it may be the reason of higher incidence of bleeding than other studies. The number of enrolled patients was smaller than the calculated sample size, it might be under powered to assess their statistics between two groups. Kim *et al.*^[15] demonstrated that delayed bleeding occurred in 8 lesions (3.6%) receiving a SLE and 6 (2.8%) not receiving a SLE ($P = 0.79$). Delayed bleeding was defined as bleeding at 3 to 56 d requiring emergency hemostasis for bleeding on artificial ulcer sites because of hematemesis, melena, hematochezia. The sample sized was not calculated statistically in this study. Mochizuki *et al.*^[8] reported that post-ESD bleeding occurred in 7 patients (5.4%) with SLE and five patients with (3.8%) non-SLE (95%CI: -6.7-3.5); meeting the non-inferiority criterion (7%). Delayed bleeding was defined as hemorrhage confirmed by emergency endoscopy from the time of the completion of ESD to 28 d and showed clinical symptoms including hematemesis, melena or a decrease in hemoglobin of > 2 g/dL. The sample sized was adequately calculated for the assessment of non-inferiority of the non-SLE compared with the SLE. The limitation of three randomized controlled trial (RCT) was different definitions of delayed bleeding used. In addition, the patients taking antiplatelet or anticoagulant drug during the perioperative period were excluded in all three RCT. Is it possible to conclude that the SLE is no longer necessary following gastric ESD? Unfortunately the results remain inconclusive, as the studies so far have been performed only on relatively small cohorts.

Most delayed bleeding events have been shown to occur within the first 24 to 48 h, but remained a possibility for up to 2 wk following ESD. In many institutions, SLE was routinely carried out within 1-2 d

Table 1 Influence of second-look endoscopy on the incidence of bleeding following endoscopic submucosal dissection

Ref.	Year	n	Study design	Bleeding: SLE vs no SLE (%)	Risk factors for delayed bleeding	SLE benefit
Ryu <i>et al</i> ^[17]	2013	182	Prospective, single center	16.2% vs 11.1%	No risk factors	No
Mochizuki <i>et al</i> ^[8]	2014	262	Prospective, Multicenter center	5.4% vs 3.8%	Resected specimen size > 40 mm	No
Kim <i>et al</i> ^[16]	2014	437	Prospective, single center	3.6% vs 2.8%	Large tumor size (> 20 mm)	No
Park <i>et al</i> ^[14]	2015	445	Retrospective	3.0% vs 2.0%	Tumor in the upper-third of the stomach, resected specimen size > 40 mm	No
Kim <i>et al</i> ^[15]	2015	502	Retrospective	1.0% vs 2.5%	Large tumor size (> 15 mm)	No

SLE: Second-look endoscopy.

following ESD as a precaution against the more serious clinical outcomes for delayed bleeding^[9]. The potential advantage of routine SLE is that the procedure can be used to evaluate the status of healing ulcers and to perform additional hemostasis if necessary. However, there are arguments concerning the cost/benefit of SLE for ESD ulcers as well as peptic ulcers. If a subgroup of patients at high risk for recurrent bleeding following ESD could be identified, this group potentially could derive benefit from SLE. Risk factors leading to postoperative bleeding remain controversial however because the perioperative management of gastric ESD has not been standardized. Although several factors are reported to be associated with an increased risk of delayed bleeding after ESD, none have been identified that reliably detect a high-risk population. It is therefore possible that risk factors for bleeding following ESD originate from technical parameters which are more difficult to assess objectively.

Role of proton-pump inhibitors in the prevention of bleeding events

Intraoperative bleeding is an unavoidable consequence during mucosal incision or submucosal dissections. Thus, most endoscopist never consider intraoperative bleeding as a complication except in cases requiring emergency surgery or blood transfusion, or in cases where ESD is discontinued because of bleeding^[18].

One strategy to control bleeding is to regulate intra-gastric acidity, as intragastric pH above 5.4 facilitates blood coagulation and platelet aggregation^[19]. In order to achieve this pH level, PPI is more effective than of H2RA. Previous meta-analysis result compared with PPI vs H2RA for the management of iatrogenic gastric ulcer after EMR or ESD showed that PPIs are more effective than H2RA^[20]. Therefore, PPI infusion therapy is routinely used to prevent bleeding and promote ulcer healing following ESD in most institutions. But, recent randomized controlled studies showed conflicting results that H2RA was comparable healing rate and delayed bleeding rate^[21-25].

Pre-endoscopic intravenous PPI therapy in peptic ulcer bleeding, which inhibits production of gastric

acid, significantly reduces the incidence of bleeding at higher risk stigmata of hemorrhage, such as active bleeding, non-bleeding visible vessels, and adherent clots^[26]. However, the effectiveness of preoperative administration of PPI in the management of artificial ulcers following ESD remains unclear. As raising intra-gastric pH preoperatively may lead to easy and complete endoscopic hemostasis during ESD and increases blood coagulation of iatrogenic ulcers, a randomized study has been conducted to determine the effectiveness of preoperative administration of a PPI for the prevention of bleeding. A trial of 24-h pre-administration of omeprazole increased intra-gastric pH at the time of ESD^[27]. However, results demonstrated no additional benefit of a higher intra-gastric pH in the prevention of bleeding, including intraoperative and post-operative delayed bleeding following the procedure.

Because intraoperative bleeding is generally characterized as spurting or oozing, a high intra-gastric pH might not be an effective preventive measure against intraoperative bleeding. In our opinion, the occurrence of intraoperative bleeding may be related not only to measurable risk factors, such as size of resected specimen and location, but also to unquantifiable technical factors, such as electrosurgical unit settings, the type of electrosurgical knife, injection solutions, and experience of the operator^[18,28]. Furthermore, this study was complicated by the fact that all patients in the study groups had been administered a regular dose of PPI for 4 wk. Thus, short course pre-operative administration of PPI might not be sufficient to produce a difference in the incidence of delayed bleeding events.

Prophylactic coagulation of visible vessel at the ulcer base following ESD

Recent guidelines for the management of peptic ulcer bleeding suggest that endoscopic therapy should be provided to patients with a non-bleeding visible vessel^[13,29]. In addition, endoscopic therapy may be considered for patients with an adherent clot resistant to vigorous irrigation. Furthermore, the benefit of endoscopy may be greater for patients with clinical features associated with a higher risk of rebleeding,

Table 2 Incidence of delayed bleeding and associated risk factors after gastric endoscopic submucosal dissection

Ref.	Year	n	Study design	Bleeding (%)	Risk factors	Remarks
Takizawa <i>et al</i> ^[5]	2008	968	Retrospective	5.8% (7.1% vs 3.1% with PEC)	Tumor location in middle and lower regions of the stomach, PEC	PEC of visible vessels in the resected area following ESD may lead to a decreased bleeding rate
Chung <i>et al</i> ^[30]	2009	952	Retrospective	15.60%	Upper region, size of the tumor (> 40 mm), recurrent lesion, flat morphology	A significant bleeding incidence was at 0.6%
Okada <i>et al</i> ^[10]	2011	582	Retrospective	4.81%	Resected specimen width (\geq 40 mm)	Mechanism of delayed bleeding may differ depending on the time elapsed between ESD and bleeding episodes
Toyokawa <i>et al</i> ^[11]	2012	1123	Retrospective	5.00%	Age \geq 80 yr, extended duration of procedure	-
Goto <i>et al</i> ^[9]	2012	1814	Retrospective	5.50%	No statistical parameters	Multicenter survey clarified that post-ESD management (duration of PPI use, resumption of food intake, and performance of SLE) varied among the medical centers
Koh <i>et al</i> ^[12]	2013	1032	Retrospective	5.30%	Size of resected specimen	The incidence of delayed bleeding in patients with two risk factors was 11.6%
Choi <i>et al</i> ^[3]	2014	614	Prospective observation	Early (3.7%) Late (1.9%)	(> 40 mm), use of antithrombotic drugs (only for delay bleeding) Surface erosion, high risk of stigmata during SLE, location in the middle of the stomach	Nausea and submucosal fibrosis increase the incidence of high risk of stigmata in SLE

PEC: Post-endoscopic submucosal dissection coagulation; ESD: Endoscopic submucosal dissection; PPI: Proton pump inhibitor; SLE: Second-look endoscopy.

such as older age, concurrent illness, and inpatient status at occurrence^[13]. For the management of artificial ulcers generated during ESD, prophylactic coagulation of exposed visible vessels at the base of a mucosal defect following ESD was shown to lead to a reduction in the incidence of bleeding (7.1% vs 3.1%; $P < 0.01$)^[5]. Routine coagulation of all non-bleeding visible vessels at the ulcer base is thus performed as standard practice. However, both prophylactic coagulation of all visible vessels at the ulcer bed and administration of PPIs do not completely eliminate the possibility of delayed bleeding (Table 2).

Patient-related risk factors associated with delayed bleeding

Most studies reported large resected specimen size to be an independent risk factor for delayed bleeding^[10,12,30] (Table 2). Theoretically, a large lesion has a more expansive vascular network than a small lesion, which enhances the possibility of bleeding during and following ESD.

Still, risks of lesion location were variable. Intraoperative bleeding risk was reported to be higher in the upper region than in the middle and lower regions of the stomach. Arteries in the submucosal layer of the upper stomach are significantly thicker or more stubby than in other gastric sites, and the diameter of

submucosal arteries is larger in the upper area than in the middle or lower stomach^[5]. Therefore, the risk of intraoperative bleeding is greater in the upper stomach, and intraoperative hemostasis is more frequently necessary during removal of a lesion in this region. In contrast, a delayed bleeding risk was reported to be greater in the lower region of the stomach^[5]. In other words, while intraoperative hemostasis is less frequently necessary in the middle and lower gastric regions, bleeding may still occur here later if vessels in these areas are not coagulated at the time of procedure. The occurrence of delayed bleeding might not have been due to insufficient hemostasis, but rather to insufficient coagulation during resection, because the sites where delayed bleeding occurred were different than those where immediate bleeding has been controlled endoscopically^[31]. Antral peristaltic activity and bile juice reflux might also contribute to some degree.

The Forrest classification provides prognostic information regarding the risk of rebleeding, and the need for therapeutic intervention in ulcer disease. Endoscopic therapy is indicated for patients with high-risk ulcer stigmata (Forrest type I and IIa). For this reason, additional hemostasis for high-risk ulcer stigmata may decrease the chance of further bleeding and/or emergency intervention. In a prospective observation study, submucosal fibrosis [odds ratios (OR) = 3.91;

Table 3 Antiplatelet medication and the risk of delayed bleeding

Ref.	Year	<i>n</i>	Design	Method	Comparison of bleeding incidence	Comments
Lim <i>et al</i> ^[32]	2012	1591	Retrospective	ESD	No antiplatelet medication: 5.2% Antiplatelet withdrawal: 5.9% Antiplatelet continuation: 11.6%	Continuous administration of antiplatelet medication was not found to have an independent significant association with bleeding
Cho <i>et al</i> ^[33]	2012	514	Retrospective	ESD	No aspirin medication: 3.4% Aspirin withdrawal: 3.6% Aspirin continuation: 21.1%	Continuous aspirin use increases the risk of bleeding after gastric ESD
Sanomura <i>et al</i> ^[35]	2014	94	Retrospective	ESD	Aspirin interruption: 7.1% Aspirin continuation: 4.8%	Continued use of aspirin does not increase the risk of bleeding during or after ESD
Tounou <i>et al</i> ^[34]	2015	377	Retrospective	ESD	No aspirin medication: 6.1% Aspirin continuation: 14.4% Single antiplatelet: 15.5% Dual antiplatelet: 35.5%	Aspirin was not a significant risk factor for post-ESD bleeding
Ono <i>et al</i> ^[36]	2015	28	Prospective, observational	ESD/EMR	The study was terminated in accordance with predetermined safety criteria because 7 of 28 consecutive patients experienced major bleeding complications (25.0%)	Subanalysis of gastric ESD (23 lesions in 19 patients) confirmed that the administration of thienopyridine derivatives (<i>P</i> = 0.01) and multiple agents (<i>P</i> = 0.02) were the significant factors Continuation of aspirin alone during these endoscopic procedures may be acceptable

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

95%CI: 1.92-7.94] and nausea after ESD (OR = 4.76; 95%CI: 2.39-9.43) were risk factors significantly associated with high-risk ulcers^[31]. To resect submucosal fibrosis, deeper submucosal dissection is generally necessary, but superficial proper muscle damage might occur. Such manipulation of the tissue might lead to the development of ulcers with a high-risk of bleeding. Furthermore, the lesions with more submucosal vessels may require more frequent coagulation during ESD. This treatment may result in coagulation-induced gastric edema and a more intense inflammatory response, which will cause nausea. A significant amount of blood from an artificial ulcer can also induce nausea. In fact, despite additive coagulation in patients with high-risk ulcer stigmata, the rebleeding incidence on SLE was 8.6% relative to patients with low-risk stigmata. A potential explanation is that ulcers at high risk for bleeding tend to also be rich in vascularity.

Drug-related risk factors for delayed bleeding

An increasing number of patients are taking multiple antiplatelet medications or antithrombotic drugs as the incidence of cardiovascular disease rises. Antiplatelet or antithrombotic medications to prevent cardiovascular events in patients present an additional concern, as ESD is a procedure with high risk of bleeding. Most endoscopists prefer to interrupt the use of antiplatelet or antithrombotic drugs for as long as possible. In one retrospective observational study, continuous administration of antiplatelet medication was not found to be a significantly associated with bleeding^[32] (OR = 1.596; 95%CI: 0.877-2.903; *P* = 0.126), whereas in another retrospective study, the use of aspirin by itself was associated with post-ESD bleeding^[33] (OR = 4.49; 95%CI: 1.09-18.38). In the latter, the resumption

specifically of clopidogrel combined with aspirin use (OR = 26.71; 95%CI: 7.09-100.53) was significantly associated with post-ESD bleeding. In recent two retrospective studies to evaluate the hemorrhagic risk of ESD in patients on antiplatelet drug, Tounou *et al*^[34] demonstrated that dual antiplatelet therapy markedly increased the risk for bleeding (HR = 16.3; 95%CI: 3.4-78.2), but continuous low dose aspirin does not. Sanomura *et al*^[35] also reported that continued use of low dose aspirin does not increase the risk of bleeding during or after ESD. In a recent prospective study, subanalysis of gastric ESD showed that administration of thienopyridine derivatives (*P* = 0.01) and multiple antiplatelet agents (*P* = 0.02) were significant contributing factors to bleeding^[36] (Table 3), but the continuation of aspirin alone appeared to be acceptable.

In general, post-ESD bleeding in patients taking aspirin can be managed effectively without increasing long-term morbidity or mortality. However, cerebral infarction upon discontinuation of aspirin intake is a critical complication. Therefore, ASGE and ESGE and JGES guideline recommend low dose aspirin should be continued for endoscopic treatment with high bleeding risk when the risk of thromboembolism is high^[37-39]. Taken together, the results indicate that if a patient has a low risk for a thromboembolic event, aspirin use should be ceased. However, if a patient has a high risk for thromboembolism, aspirin may be continued as a thromboembolic event could otherwise result in more serious consequences affecting quality of life.

CONCLUSION

Bleeding is a major potential complication both during and post-ESD. Decreased incidence of delayed bleeding

is associated with the use of anti-secretory agents, especially PPI, and prophylactic coagulation of visible vessels at the ulcer base following ESD. However, despite these therapeutic interventions, delayed bleeding still occurs in approximately 5% of patients who undergo gastric ESD. To date, SLE after ESD has been a common therapeutic strategy in order to avoid a bleeding event. The results of recent randomized studies however were unfavorable for routine SLE after gastric ESD. Although routine SLE for all patients after gastric ESD might be unnecessary, SLE may be an important tool in the treatment of a subgroup of patients at risk for bleeding or high-risk ulcer stigmata. Well-known potential risk factors of delayed bleeding are large size of resected specimen and treatment with multiple antiplatelet agents. Submucosal fibrosis and nausea after ESD might be associated with high-risk ulcer stigmata. Thus, these factors can be considered as indications for the use of SLE following ESD. To establish the optimal perioperative strategies for safe ESD, well-designed prospective studies should be conducted in the future to more clearly identify at risk patients.

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P- Reviewer: Abe S, Kiriya S **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Wu HL





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