

## 2016 Gastrointestinal Endoscopy: Global view

**Bleeding after endoscopic submucosal dissection: Risk factors and preventive methods**

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**Abstract**

Endoscopic submucosal dissection (ESD) has become widely accepted as a standard method of treatment for superficial gastrointestinal neoplasms because it enables en block resection even for large lesions or fibrotic lesions with minimal invasiveness, and decreases the local recurrence rate. Moreover, specimens resected in an en block fashion enable accurate histological assessment. Taking these factors into consideration, ESD seems to be more advantageous than conventional endoscopic mucosal resection (EMR), but the associated risks of perioperative adverse events are higher than in EMR. Bleeding after ESD is the most frequent among these adverse events. Although post-ESD bleeding can be controlled by endoscopic hemostasis in most cases, it may lead to serious conditions including hemorrhagic shock. Even with preventive methods including administration of acid secretion inhibitors and preventive hemostasis, post-ESD bleeding cannot be completely prevented. In addition high-risk cases for post-ESD bleeding, which include cases with the use of antithrombotic agents or which require large resection, are increasing. Although there have been many reports about associated risk factors and methods of preventing post-ESD bleeding, many issues remain unsolved. Therefore, in this review, we have

overviewed risk factors and methods of preventing post-ESD bleeding from previous studies. Endoscopists should have sufficient knowledge of these risk factors and preventive methods when performing ESD.

**Key words:** Endoscopic submucosal dissection; Risk factor; Bleeding; Prevention; Antithrombotic agents

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**Core tip:** Antithrombotic agents and large resection are known to be significant risk factors for post-endoscopic submucosal dissection (post-ESD) bleeding, and as the indications for antithrombotic agents increase, and the indications for endoscopic resection are expanded, endoscopists have a chance to face an increasing number of patients with a high risk of post-ESD bleeding. Acid secretion inhibitors and preventive hemostasis are effective for the prevention of post-ESD bleeding, but do not seem to be completely effective in its prevention. Developing additional preventive methods which can reduce post-ESD bleeding more effectively will become an increasingly important issue in the future.

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## INTRODUCTION

Endoscopic submucosal dissection (ESD) has become a well-established method of treatment for superficial neoplasms in the gastrointestinal tract. ESD was first developed as an advanced technique which was intended to overcome the limitations of conventional endoscopic mucosal resection (EMR) in the 1990s<sup>[1-3]</sup>. ESD is curatively advantageous over EMR in that it enables en block fashion, regardless of tumor size, shape, ulceration or location, which contributes to the decrease in local recurrence rate. Moreover, specimens obtained by en block resection enable accurate histological diagnosis of target lesions<sup>[4-11]</sup>.

However, ESD is technically more difficult and requires a longer procedure time than EMR. In addition, ESD is accompanied by a relatively high risk of procedure-related adverse events<sup>[4,5,7,11]</sup>. Especially, bleeding after ESD is one of the most severe adverse events because post-ESD bleeding may lead to serious conditions including hemorrhagic shock. Moreover, post-ESD bleeding can occur later than other adverse events, and may require additional treatment even

after discharge<sup>[12-14]</sup>. Therefore, in this review article, we will focus on risk factors and preventive methods of post-ESD bleeding.

## POST-ESD BLEEDING

Post-ESD bleeding, or bleeding after ESD is the most frequent adverse event associated with ESD. The incidence of bleeding after gastric ESD has been reported to range from 1.8% to 15.6%<sup>[4,9,15-18]</sup>. On the other hand, there have been many reports that bleeding rates after esophageal or colorectal ESD are a much smaller percentages<sup>[19-25]</sup> (Tables 1 and 2). Therefore, the reports listed in the following section are focused on the risk factors and methods of preventing bleeding after gastric ESD.

Post-ESD bleeding is generally defined as the condition that presents any clinical signs of bleeding such as hematemesis, melena, hemodynamic deterioration or downtick of > 2 g/dL in hemoglobin level and requires endoscopic hemostasis<sup>[12,13,26]</sup>.

Oda *et al* reported that 76% of post-ESD bleeding occurred within 24 h of ESD, but it can occur as late as two weeks after the procedure<sup>[12,13,27,28]</sup>. Post-ESD bleeding can be controlled by endoscopic hemostasis in most cases (Figure 1), but it sometimes leads to life-threatening conditions that require blood transfusion or emergency surgery<sup>[12,29]</sup>. Therefore, endoscopists should have sufficient knowledge of risk factors for this adverse event and be fully prepared for it.

## RISK FACTORS

When performing gastric ESD, endoscopists should know whether their cases have a high risk of post-ESD bleeding. There have been many reports concerning the risk factors for post-ESD bleeding<sup>[9,12-15,26,27,29-32]</sup>. Although other factors are still controversial, several studies have revealed that antithrombotic agents and resection size are significant risk factors for post-ESD bleeding<sup>[9,14,15,26,27,29,30,33]</sup>.

### Antithrombotic agents

Because the number of patients taking antithrombotic agents has been increasing worldwide<sup>[34,35]</sup>, there will be an increasing necessity to perform ESD for these patients in the future. Endoscopists should pay attention to both the risks of bleeding and thromboembolism when performing ESD in this situation.

Tentative guidelines concerning the continuation and cessation of antithrombotic agents during endoscopy have been published from several societies including the Japan Gastroenterological Endoscopy Society, American Society for Gastrointestinal Endoscopy, and European Society of Gastrointestinal Endoscopy<sup>[36-38]</sup>. ESD for patients taking antithrombotic agents is performed according to these guidelines, but currently data supporting ESD under these guidelines is

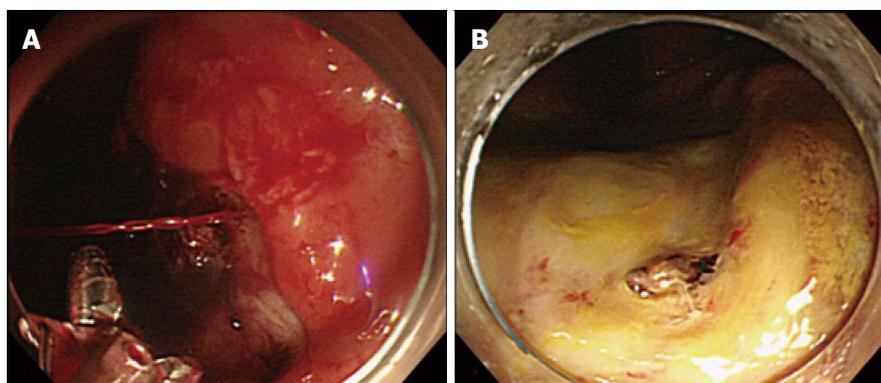
**Table 1** Previous reports of bleeding after gastric endoscopic submucosal dissection

Ref.	Organ	Year	Case No.	Post-ESD bleeding	Perforation	En block resection
Ichiro <i>et al</i> <sup>[13]</sup>	Stomach	2005	1033	6.2%	3.7%	98.0%
Isomoto <i>et al</i> <sup>[17]</sup>	Stomach	2009	589	1.8%	4.5%	94.9%
Chung <i>et al</i> <sup>[9]</sup>	Stomach	2009	1000	15.6%	1.2%	95.3%
Mannen <i>et al</i> <sup>[26]</sup>	Stomach	2009	478	8.2%	3.6%	-
Tsuji <i>et al</i> <sup>[14]</sup>	Stomach	2010	398	5.8%	-	-
Higashiyama <i>et al</i> <sup>[31]</sup>	Stomach	2011	924	3.0%	4.0%	-
Okada <i>et al</i> <sup>[27]</sup>	Stomach	2011	647	4.3%	-	-
Toyokawa <i>et al</i> <sup>[32]</sup>	Stomach	2012	1123	5.0%	2.4%	93.5%
Goto <i>et al</i> <sup>[18]</sup>	Stomach	2012	1814	5.5%	-	-
Lim <i>et al</i> <sup>[16]</sup>	Stomach	2012	1591	5.9%	-	-
Koh <i>et al</i> <sup>[15]</sup>	Stomach	2013	1166	5.3%	-	98.5%

ESD: Endoscopic submucosal dissection.

**Table 2** Previous reports of bleeding after esophageal or colorectal endoscopic submucosal dissection

Ref.	Organ	Year	Case No.	Postoperative bleeding	Perforation	En block resection
Ono <i>et al</i> <sup>[25]</sup>	Esophagus	2009	107	0.0%	4.0%	100.0%
Isomoto <i>et al</i> <sup>[19]</sup>	Esophagus	2013	291	0.7%	0.0%	99.7%
Tsujii <i>et al</i> <sup>[20]</sup>	Esophagus	2015	373	0.0%	5.2%	96.7%
Saito <i>et al</i> <sup>[21]</sup>	Colon	2010	1111	1.5%	4.9%	88.0%
Niimi <i>et al</i> <sup>[79]</sup>	Colon	2010	310	1.6%	4.8%	90.3%
Oka <i>et al</i> <sup>[80]</sup>	Colon	2010	688	1.7%	3.3%	-
Toyonaga <i>et al</i> <sup>[22]</sup>	Colon	2012	1143	1.2%	1.4%	99.3%
Takeuchi <i>et al</i> <sup>[81]</sup>	Colon	2012	348	4.6%	2.3%	91.1%
Lee <i>et al</i> <sup>[24]</sup>	Colon	2013	1000	0.4%	5.3%	97.5%
Nakajima <i>et al</i> <sup>[23]</sup>	Colon	2013	816	2.2%	2.0%	94.5%



**Figure 1** Spurting bleeding from visible vessel on the day after gastric endoscopic submucosal dissection (A) and successful hemostasis by using hemostatic forceps (B).

still insufficient. It is a clinically important, but unsolved question whether antithrombotic agents increase the risk of post-ESD bleeding. Several retrospective studies have shown that antithrombotic agents as a whole are risk factors for post-ESD bleeding<sup>[14,15,33]</sup>. Adversely, there is also data which suggests that antithrombotic agents do not significantly increase post-ESD bleeding<sup>[26,27,29,32]</sup>. However, the types of antithrombotic agents and cessation periods differed among these studies. Each antithrombotic agent has its own mechanism and carries a different risk of bleeding. So the post-ESD bleeding risk for each agent must be analyzed individually.

Aspirin is known to be one of the most commonly administered antiplatelet agents. Initial reports demonstrated the safety of colonoscopic polypectomy in patients taking aspirin<sup>[39-41]</sup>. Similarly the rate of post-ESD bleeding does not significantly increase with the cessation of aspirin from one week before ESD<sup>[16,42]</sup>. Although available data concerning continued aspirin use is still lacking, guidelines permit ESD without aspirin cessation in patients with a high-risk of thromboembolism. Recently, Lim *et al*<sup>[16]</sup>, Matsumura *et al*<sup>[30]</sup> and Sanomura *et al*<sup>[43]</sup> reported that the continued use of aspirin did not increase the risk of bleeding after gastric ESD. However, Cho *et*

*al*<sup>[44]</sup> reported that continued aspirin use increased the risk of bleeding after gastric ESD; post-ESD bleeding occurred at a rate of 21.1% (4 out of 19 continued aspirin users). It is controversial whether the continued use of aspirin is a risk factor of post-ESD bleeding. More accumulation of data on ESD without aspirin cessation is required.

As for thienopyridine, recent guidelines recommend cessation of thienopyridine from at least 5 d before ESD, according to the data that continued use of thienopyridine increased the rate of bleeding after colon polypectomy<sup>[45]</sup>. Although data on thienopyridine monotherapy during the ESD procedure is insufficient, there are two available reports concerning gastric ESD in patients receiving dual antiplatelet therapy. Thienopyridine is principally used in dual antiplatelet therapy (DAPT) in patients undergoing implantation of drug-eluting coronary stents. Tounou *et al*<sup>[46]</sup> reported that DAPT markedly increased the rate of post-ESD bleeding (35.5%). Ono *et al*<sup>[47]</sup> reported a prospective study regarding bleeding after endoscopic procedure including polypectomy, EMR and ESD. Twenty-eight patients continuing aspirin therapy during endoscopic treatment were enrolled in this study, and 7 patients experienced major bleeding events after ESD (stomach: 6, colon: 1). Subanalysis of gastric ESD showed that all the 6 cases of post-ESD bleeding occurred after the resumption of thienopyridine derivatives<sup>[47]</sup>. These reports showed that DAPT is a significant risk factor of bleeding after ESD.

Heparin bridge therapy is commonly performed during cessation of warfarin in patients with a high risk of thromboembolism, but evidence concerning whether heparin bridge therapy can prevent thromboembolism is lacking, and in addition heparin bridge therapy is known to increase the incidence of bleeding events<sup>[48]</sup>. Two retrospective studies showed that post-ESD bleeding in patients undergoing heparin bridge therapy occurred at the rate of 23% to 38%<sup>[30,49]</sup>. Additionally, Douketis *et al*<sup>[50]</sup> reported a randomized trial to evaluate the risks of thromboembolism and bleeding events after operations or other invasive procedures in patients taking warfarin for chronic atrial fibrillation or flutter. This study suggested that forgoing bridging anticoagulation is non-inferior to perioperative heparin bridging for the prevention of arterial thromboembolism and decreases the risk of major bleeding<sup>[50]</sup>. Therefore it may be necessary to reconsider whether bridging is necessary for the management of patients taking warfarin.

Recently direct oral anticoagulant drugs (DOACs) have become increasingly used in clinical practice, and the association between DOACs and the risk of post-ESD bleeding needs to be assessed. However, data about DOACs is still being accumulated and is currently still insufficient. The risk of DOACs for post-ESD bleeding remains to be investigated hereafter.

### Resection size and other factors

There have been several reports that specimen size > 40 mm is a significant risk factor for post-ESD bleeding<sup>[9,15,27,30]</sup>. Owing to the acceptance of expanded indications for larger lesions, there have been increasingly more cases of large ESD in our practices<sup>[51-53]</sup>. The reason why larger resection causes more bleeding is simply considered to derive from the fact that more vessels would be exposed on the ulcer bases after large ESD.

Patients receiving hemodialysis are known to be prone to bleed from gastroduodenal ulcers<sup>[54]</sup>. A few studies showed hemodialysis is a risk factor for post-ESD bleeding<sup>[30,31,55,56]</sup>. Numata *et al*<sup>[55]</sup> reported that two ESD-related deaths occurred among hemodialysis patients in an evaluation of ESD outcomes in 63 patients with chronic kidney disease; post-ESD bleeding triggered femoral infarction in one case, and alveolar hemorrhage occurred in the other case. More careful management after ESD may be required for patients on hemodialysis because post-ESD bleeding may lead to secondary adverse events.

Two studies have also shown that long procedure time is an independent risk factor for post-ESD bleeding<sup>[31,32]</sup>. A longer procedure time was required in these studies when intraoperative bleeding was frequent and difficult to control, which might mean more vessels exist in the submucosal layer in these cases.

As for the location, it has been generally reported that the lower part of the stomach is a risk factor for post-ESD bleeding. Tsuji *et al*<sup>[14]</sup> and Miyahara *et al*<sup>[29]</sup> reported that post-ESD bleeding occurred more frequently in the lower part of the stomach than in the upper or middle part. That may be partly because more careful endoscopic hemostasis is required during the ESD procedure in the upper and middle part of the stomach where intraoperative bleeding frequently occurs, which may ultimately prevent post-ESD bleeding<sup>[13,14,29]</sup>. Although intraoperative bleeding may be associated to submucosal artery diameters, arteries of the upper and middle part of the stomach are known to be thicker in diameter than in the lower part as evaluated in human resected gastric specimens and dog models<sup>[57,58]</sup>. In addition, antral active peristalsis and bile reflux may contribute to a high incidence of post-ESD bleeding in the lower part of stomach<sup>[12,14]</sup>. Adversely, Chung *et al*<sup>[9]</sup> reported that the upper part of the stomach was a risk factor. They performed hemostasis on all vessels likely to bleed regardless of the location<sup>[9]</sup>. Tsuji *et al*<sup>[14]</sup> showed that post-ESD bleeding occurred more often when beginners performed coagulation of the ulcer floor after ESD. These discrepancies might occur due to the amount of remnant exposed vessels on the mucosal defect of ESD.

In summary, according to available evidence,

DAPT and heparin bridge therapy significantly increase post-ESD bleeding, but it is unclear whether other antithrombotic agents are risk factors. In terms of other risk factors for post-ESD bleeding, large resection size would be a reliable risk factor, but there have been an insufficient number of prospective studies and there is not enough well-established data. Large-scale prospective analyses concerning this issue are essential.

## PREVENTIVE METHODS

Massive post-ESD bleeding occasionally leads to a severe condition that requires blood transfusion, such as hemorrhagic shock<sup>[12]</sup>. Therefore, prevention of post-ESD bleeding is imperative. According to previous studies, there are only two well-established effective methods of prevention with supportive evidence: the use of acid secretion inhibitors and preventive coagulation of the ESD-induced ulcer bed.

### Acid secretion inhibitors

Acid secretion inhibitors including proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA) are normally used to facilitate healing of ulcers after gastric ESD. It is still unclear whether PPIs can reduce post-ESD bleeding more effectively than H2RAs although several studies have reported that PPIs may be superior to H2RAs<sup>[59-63]</sup>.

Niimi *et al.*<sup>[64]</sup> reported that 2-wk administration of PPI resulted in 80% of the transitional rate to scarring-stage ulcers at 8 wk after ESD. The study suggested 2-wk administration of a maintenance dosage of PPI may be sufficient in cases without deteriorating factors such as concomitant use of antithrombotic agents or ulcerative findings in the tumor. Further studies are required to determine optimum doses and duration of PPI administration.

### Preventive hemostasis

Endoscopic preventive coagulation or clipping after ESD may prevent post-ESD bleeding. Takizawa *et al.*<sup>[12]</sup> reported that post-ESD coagulation of visible vessels (PEC) prevented post-ESD bleeding (with PEC, 3.1% vs without, 7.1%,  $P < 0.01$ ). Mukai *et al.*<sup>[65]</sup> reported that PEC plus artery-selective clipping may reduce delayed bleeding after gastric ESD (PEC, 4.5% vs PEC plus artery-selective clipping, 1.3%,  $P = 0.17$ ). Uedo *et al.*<sup>[66]</sup> reported that Doppler US may be helpful to search vessels in the post-ESD ulcers.

However, repeated coagulation by hemostatic forceps can lead to coagulation syndrome or delayed perforation<sup>[67]</sup>. A patient with coagulation syndrome presents fever, abdominal pain or leukocytosis as a result of electrocoagulation injury to the gastrointestinal wall. Therefore, endoscopists should take care not to perform excessive coagulation.

### Second-look endoscopy

It was originally reported that a second-look endoscopy (SLE) after the initial endoscopic hemostasis for peptic ulcer bleeding significantly reduces the risk of recurrent bleeding<sup>[68]</sup>. According to such findings, SLE after ESD is performed in many facilities in Japan. However, recent studies have implied that SLE has little influence on the prevention of post-ESD bleeding<sup>[28,69]</sup>. Mochizuki *et al.*<sup>[70]</sup> reported that SLE was not routinely recommended for patients with an average bleeding risk (the incidence of postoperative bleeding of SLE group vs non-SLE groups; 5.4% vs 3.8%). On the other hand, Jung *et al.*<sup>[71]</sup> reported the efficacy of SLE with prophylactic hemostasis.

Nishizawa *et al.*<sup>[72]</sup> systematically evaluated the efficacy of second-look endoscopy for gastric ESD, and they concluded in their systematic review and meta-analysis that second-look endoscopy has no advantage for the prevention of post-ESD bleeding in patients without a high risk of bleeding.

As for patients at low-risk for post-ESD bleeding, it seems that SLE is not routinely recommended. However, there is insufficient data to evaluate the efficacy of SLE in patients with a high risk of post-ESD bleeding.

Even with the above mentioned preventive methods, the rate of postoperative bleeding is still approximately 4.5%<sup>[4]</sup>. Therefore, the development of a novel technique that decreases post-ESD bleeding more effectively is essential.

## NEW METHODS

In order to prevent post-ESD bleeding, methods of closing or shielding the ESD-induced ulcer seem to be promising. As for the closing method, conventional clipping closure is technically difficult in cases where the mucosal defect is large. Lee *et al.*<sup>[73]</sup> reported that mucosal closure with a detachable snare and clips supports earlier healing of ulcers after ESD. Kantsevov *et al.*<sup>[74]</sup> reported that endoscopic suturing closure is a feasible technique which can eliminate the need for hospitalization after the ESD procedure.

Recently, the utility of a shielding method using polyglycolic acid (PGA) sheets and fibrin glue to manage ulcers after ESD procedure has been reported. PGA sheets are widely used in the surgical field as an absorbable material to reinforce suturing. Takimoto *et al.*<sup>[75]</sup> originally reported the efficacy of shielding a mucosal defect after duodenal ESD using PGA sheets and fibrin glue to prevent delayed perforation. Furthermore, Tsuji *et al.*<sup>[76,77]</sup> also reported the possibility of reducing postoperative adverse events, such as post-ESD bleeding or delayed perforation (Figure 2). In addition to PGA shielding, other shielding methods have been reported. There has been a report concerning bio-sheet graft therapy for post-ESD ulcer

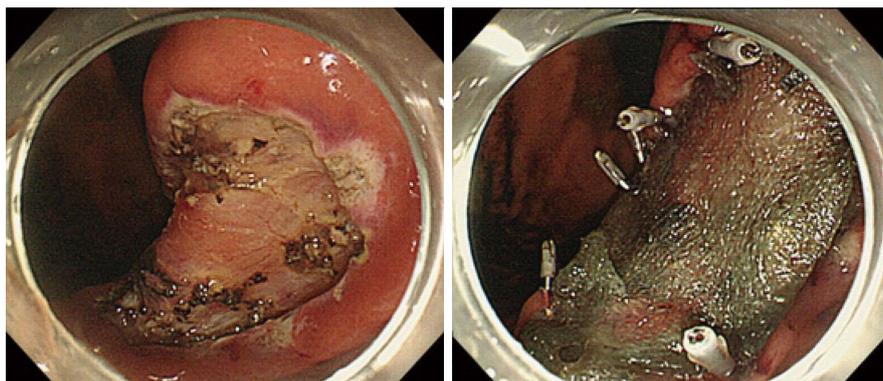


Figure 2 Polyglycolic acid sheets with fibrin glue was applied to the artificial ulcer after gastric endoscopic submucosal dissection by clip and pull method<sup>[82]</sup>.

in an animal experiment<sup>[78]</sup>. According to the study, this bio-sheet graft therapy might be effective in attenuating the degree of inflammation in the ESD-induced ulcers.

However, there has been no randomized controlled trial to investigate the efficacy of these novel methods to prevent postoperative bleeding. Therefore, further research on its efficacy is required.

## CONCLUSION

Although ESD has been established as an excellent method of treatment for superficial gastrointestinal neoplasms, the prevention and management of post-ESD adverse events is an issue still to be solved. Especially, controlling bleeding after ESD should be considered one of the top priorities because its occurrence rate is relatively high and sometimes leads to a severe condition. It is imperative for all endoscopists who perform ESD to get acquainted with the risk factors of post-ESD bleeding. To date, some risk factors, such as antithrombotic drug use and large resection size, have been recognized, but optimum management of these risk factors is still to be clarified. Concerning prevention of post-ESD bleeding, PEC and PPI use are widely established as effective preventive methods, but have not been able to prevent bleeding completely. Currently there are several ongoing studies concerning novel techniques for preventing bleeding with the ultimate goal of achieving zero risk for post-ESD bleeding. Further research is required.

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