Review Article

Bleeding complication after endoscopic submucosal dissection of gastric neoplasm

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A B S T R A C T

Endoscopic submucosal dissection (ESD) is recognized as an effective treatment for superficial gastric neoplasm without metastasis because results of ESD show the high en bloc resection rate and low local recurrence rate. Recently, the indications for ESD have been broadened in the field of therapeutic endoscopy with regard to its safety and efficacy. However, complications can be happened after procedure and post-ESD bleeding is one of the major adverse events which may lead to serious clinical situation of patient. The mechanism of post-ESD ulcer which is made by iatrogenic procedure is different from peptic ulcer which is created under low pH, therefore, the risk factors and treatment methods of post-ESD bleeding is somewhat different from peptic ulcer bleeding. With these reasons, endoscopist should know about the definitions and influencing factors of post-ESD bleeding before and after procedure, and should manage using proper hemostatic methods when post-ESD bleeding is happened. In this review, I try to overview about the post-ESD bleeding and to know the methods of treatment and prevention of bleeding.

Keywords: Endoscopic resection; Hemorrhage; Neoplasm; Stomach

Introduction

Endoscopic resection, which includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is a standard technique for gastric adenoma and early gastric cancer with low risk of lymph node metastasis, and is increasingly being used because it preserves the stomach and is minimally invasive, safe, and convenient. In particular, ESD allows en bloc resection with tumor-free margins, even for large tumors, permits accurate histological assessment, and reduces the risk of local recurrence.1–5

Although the safety of endoscopic resection has been widely confirmed, adverse events such as perforation and bleeding are still a concern. Bleeding after ESD, manifesting as hematemesis or melena, may occur within 24 hours to 1 month from the procedure, can be occurred in approximately 5%.6–9 Even though it is rare, post-ESD bleeding can be one of the most severe adverse events, and may lead to serious hemorrhagic shock requiring blood transfusion, urgent endoscopic treatment, or surgery.

When the bleeding event is happened, it usually can be treated by endoscopic hemostasis or conservative management; however, it sometimes leads to life threatening conditions that require blood transfusion or emergency surgery.9,10 Therefore, in order to manage ESD in gastric tumor properly, knowing about the risk factors, proper treatment of post-ESD bleeding, and prevention of post-ESD bleeding are clinically important issue that needs to be addressed. In this article, we will discuss about the risk factors, proper managements, and preventive methods of post-ESD bleeding.

Definition of Post-ESD Bleeding

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.6,11 Takizawa et al12 reported that 76% of post-ESD bleeding occurred within 24 hours of ESD, but it can occur as late as two weeks after the procedure.

The post-ESD bleeding can be classified as immediate bleeding, early delayed bleeding, and late delayed bleeding according to the timing of bleeding. Even though, there are some differences of definition between articles, immediate bleeding can be defined
as post-endoscopic resection bleeding diagnosed within 24 hours, early delayed bleeding defined as post-endoscopic resection bleeding diagnosed from 24 hours after the EMR/ESD to when the second-look endoscopy was performed, and late delayed bleeding defined as bleeding from the second-look endoscopy to 1 month. Clinically, late delayed bleeding is more important than immediate or early delayed bleeding because it occurs after discharge from hospital and could result in severe adverse events, such as cardiovascular events. To know the definition of post procedural bleeding is important to prepare next step after ESD.

Risk Factors of Post-ESD Bleeding

Various risk factors for post-ESD bleeding such as age, sex, the size of the resected specimen, tumor location, diagnosis, chronic kidney disease (CKD), liver cirrhosis, and the use of antithrombotic (AT) agents have been reported previously; however, most of them are still controversial. Among those risk factors, several studies showed that three factors of tumor resection size, CKD, and AT therapy are significant risk factors for post-ESD bleeding.

Larger ESD specimen size is revealed as a significant risk factor for post-ESD bleeding in various studies. Especially, when the specimen size is larger than 40 mm, the risk of post-ESD bleeding is increased with higher bleeding rates (11.6%–28.6%). Theoretically, a large ulcer has a larger vascular network than a small ulcer, which makes the possibility of bleeding higher. In these days, as indication of gastric ESD is expanded, endoscopists have more chance to meet the large sized tumor. Therefore, we should prepare for the possibility of post-ESD bleeding in larger size case and we try to minimize the chance of bleeding during and after procedure.

Usually, there is concern that complication rates from ESD may be much higher in CKD patients than in non-CKD patients because CKD patients have a tendency for bleeding and more comorbidities such as cardiovascular and cerebrovascular disease. Several previous studies revealed that CKD patients exhibit increased rates (12.3%–13.8%) of post-ESD bleeding compare to non-CKD patients. Even though the bleeding risk posed by renal dysfunction itself has not been studied enough, previous studies showed that stage 4/5 renal dysfunction and hemodialysis are associated with higher bleeding risk than non-CKD patients. Therefore, we should consider that not only CKD patients on dialysis, but also those CKD patients with severe renal dysfunction who do not undergo dialysis, are prone to post-ESD bleeding, and should be carefully observed after ESD.

With the advance of an aging society, we have an increasing opportunity to carry out ESD among aged and comorbid patients receiving AT therapy. AT agents include anticoagulants and antiplatelet agents for the prevention of cardiovascular and cerebrovascular diseases, and the number of patients using oral AT agents has been increasing all over the world. Various studies have been actively carried out on patients taking AT agents to identify delayed bleeding risk and determine the proper timing of drug cessation. In some studies, the delayed bleeding rate of the AT group was higher than that of the control group and the continuous use of AT agents resulted in more delayed bleeding than other groups. These were significant in that they demonstrated the effect and cessation timing of AT therapy on delayed bleeding by calibrating other risk factors in ER patients.

There were conflicting reports as to whether continuing AT

![Fig. 1. Endoscopic findings of post-endoscopic submucosal dissection bleeding and hemostasis. (A) Active oozing bleeding. (B) Active spurting and oozing bleeding. (C) Endoscopic hemostasis by coagulation forceps. (D) Endoscopic hemostasis by hemoclips and coagulation forceps.](image-url)
therapy increases delayed bleeding after gastric ESD, or not.

Among these retrospective observational studies, one study had a control group of non–AT agent users and showed that continuation of AT had a higher incidence of delayed bleeding than their control group.

Heparin bridge therapy (HBT) is often initiated to reduce the risk of thromboembolic events associated with the interruption of oral anticoagulation to achieve better control over bleeding. However, several studies have reported that post-ESD bleeding rate in patients receiving HBT was higher than in those who discontinued AT agents and showed that HBT is a risk factor of post-ESD bleeding. Therefore, we should decide carefully to use AT before and after ESD, especially HBT should be considered in a limited number of patients with a high thromboembolic risk.

### Treatment Methods of Post-ESD Bleeding

In most cases of active bleeding after ESD, endoscopic hemostasis was tried using various methods with hemostatic forceps, hemoclips, fibrin glue, argon plasma coagulation, epinephrine injection, or other materials whenever bleeding was observed (Fig. 1). However, in rare cases, radiologic angiography with embolization or surgical treatment can be performed. Until now, there is no standard treatment method of endoscopic management of post-ESD bleeding and endoscopist should decide to use single or combination hemostatic methods according to the situation in clinical setting.

When the bleeding vessel is seen and endoscopic approach is possible, hemoclip or hemostatic forceps is useful. If the vessel is hidden under blood clots and cannot be found, removal of clots and apply hemostasis to the correct point should be done. However, endoscopist can not find the bleeding vessel due to clot amounting in some case, at that time, injection of fibrin glue to the suspected site can be helpful sometimes. For the oozing bleeding from the small vessels, argon plasma coagulation is effective.

### Preventive Methods of Post-ESD Bleeding

For the prevention of post-ESD bleeding, the using of anti-secretory agents and preventive coagulation of non-bleeding visible vessels after completion of ESD have been shown as effective methods.

Current preventive treatments for post-ESD ulcer mostly rely on potent antisecretory agents, such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RA). Generally, PPIs and H2RA are also used to induce the rapid healing of artificial gastric ulcers after endoscopic resection. PPIs are thought to be more efficient in reducing gastric acid secretion and in significantly accelerating ulcer healing than H2RA in peptic ulcer; however, there are some questions about whether artificial ulcers differ from natural peptic ulcer in healing rates or other factors involved in the healing process remains unknown. Because increased rate of healing in iatrogenic ulcers was associated with the preservation of the muscularis propria layer contraction, which is usually damaged in peptic ulcer. Therefore, even though several studies have reported that PPIs may be superior to H2RAs, it is still unclear whether PPIs can reduce post-ESD bleeding more effectively than other antisecretory agents. After Takizawa et al reported the effectiveness of endoscopic preventive coagulation after ESD for the prevention of post-ESD bleeding, most endoscopists performed preventive coagulation on the visible vessels on the ulcer bed. Other studies also showed that preventive coagulation with/without other methods can reduce the post-ESD bleeding. However, excessive coagulation on the post-ESD ulcer can cause coagulation syndrome or delayed perforation, so endoscopists should be careful to control the degree of coagulation.

Except preventive coagulation on the visible vessels, novel methods such as mucosal closure or shielding have been studied in order to prevent and to reduce the post-ESD bleeding. However, there are not enough data about the effect of these new techniques until now and further studies are needed.

### Conclusions

Post-ESD bleeding is not common complication but very hard to predict and it can lead to severe condition sometimes. Therefore, endoscopist should know the risk factors of bleeding in patients and ready to manage after bleeding happens. In addition, explaining in detail about the possibility and symptoms of post-ESD bleeding to the patient, who can visit the hospital right after symptoms of bleeding develops, is important. To reduce and to eliminate the chance of post-ESD bleeding, further studies about new drugs or new methods are needed.

### Conflicts of Interest

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

### References

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