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EDITORIAL

Management of bleeding and artificial gastric ulcers associated with endoscopic submucosal dissection

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Abstract

Endoscopic submucosal dissection (ESD), an endoscopic procedure for the treatment of gastric epithelial neoplasia without lymph node metastases, spread rapidly, primarily in Japan, starting in the late 1990s. ESD enables en bloc resection of lesions that are difficult to resect using conventional endoscopic mucosal resection (EMR). However, in comparison to EMR, ESD requires a high level of endoscopic competence and a longer resection time. Thus, ESD is associated with a higher risk of adverse events, including intraoperative and postoperative bleeding and gastrointestinal perforation. In particular, because of a higher incidence of intraoperative bleeding with mucosal incision and submucosal dissection, which are distinctive endoscopic procedures in ESD, a strategy for endoscopic hemostasis, mainly by thermo-coagulation hemostasis using hemostatic forceps, is important. In addition, because of iatrogenic artificial ulcers that always form after ESD, endoscopic hemostasis and appropriate pharmacotherapy during the healing process are essential.

Key words: Artificial ulcer; Endoscopic hemostasis; Endoscopic submucosal dissection; Gastric epithelial neoplasia; Hemostatic forceps

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is a novel endoscopic procedure developed in the 1990s[1,2], and is characterized by the use of electrosurgical knives for mucosal incision and submucosal dissection[3-15]. In ESD, the resected size and shape of tumors can be controlled, and even lesions difficult to resect by endoscopic mucosal resection (EMR) can be resected en bloc by ESD. As this technique permits en bloc resection of tumors, ESD has the advantages of enabling accurate pathological assessment and reducing the risk of local recurrence[2,16-19].

However, ESD requires a higher level of endoscopic competence than EMR. In addition, as a result of ESD being used to treat larger lesions and lesions with ulcerative findings, operation time is longer, with a higher risk

of adverse events such as bleeding and gastrointestinal perforation[20-29]. The incidence of procedure-related bleeding is higher with ESD than with EMR, and to permit safe completion of ESD, control of bleeding is very important. In this article, we discuss the characteristics of ESD-related bleeding (intraoperative and postoperative bleeding) and endoscopic hemostasis. Furthermore, to prevent postoperative bleeding, we also discuss the pharmacotherapy of artificial ulcers after ESD.

ENDOSCOPIC HEMOSTASIS USING HEMOSTATIC FORCEPS

Endoscopic hemostatic methods for peptic ulcers include various techniques, such as local injection of hypertonic saline-epinephrine (HSE) and ethanol, mechanical hemostasis using endoscopic hemoclips, and thermo-coagulation hemostasis[30,31]. Local injection of HSE alone is inferior to combination therapy with other hemostatic methods, but the clear superiority of any one method has not been definitively established[32]. Thermo-coagulation devices include contact thermal devices such as heater probes and hemostatic forceps, and non-contact thermal devices such as an argon plasma coagulator[33,34].

For hemostasis of ESD intraoperative bleeding, Enomoto *et al*[35] reported the usefulness of a method of thermo-coagulation hemostasis using monopolar hemostatic forceps in combination with an endoscope equipped with a water-jet system. Hemostatic technique in ESD, which differs from hemostasis for usual gastrointestinal bleeding, is often characterized by the need for repeated hemostasis during both mucosal incision and submucosal dissection. In addition, precise hemostatic maneuvers are required, in order not to interfere with the subsequent procedure after hemostatic treatment[36,37]. Therefore, hemostatic forceps, which enable reliable hemostasis when, with re-holding of the ruptured vessels permissible several times before coagulation, bleeding points can be accurately grasped, are useful for hemostasis in ESD-related bleeding[38,39] (Figure 1).

With wider use of ESD, hemostasis using hemostatic forceps has become routine at medical centers, and its usefulness for bleeding from exposed vessels at the base of peptic ulcers has also been reported[40,41]. Moreover, the usefulness not only of monopolar, but also of bipolar hemostatic forceps, has been reported[42].

MANAGEMENT OF BLEEDING DURING AND AFTER ESD

ESD-related bleeding includes intraoperative bleeding associated with procedures such as mucosal incision and submucosal dissection, and delayed bleeding, which occurs postoperatively from exposed vessels at ulcer bases. Appropriate management of each type of bleeding is required.

Endoscopic hemostasis for intraoperative bleeding

In ESD, the incidence of intraoperative bleeding, which is to some degree unavoidable given the nature of techniques such as incision and dissection, is as high as 22.6%[16]. In particular, with ESD for lesions in the upper third of the stomach, because of abundant vessels in the submucosa, the incidence of intraoperative bleeding is relatively high[43]. To predict intraoperative bleeding, identification of the submucosal vascular structure by preoperative endoscopic ultrasonography can be useful[44].

Of the series of techniques in ESD, bleeding is inevitable with submucosal local injection and mucosal incision because they are blind procedures in the vascular-rich submucosal tissue. To produce higher hemostatic ability, a small amount of epinephrine to a concentration of 0.0005% is added to the submucosal cushion (glyceol, Chugai Pharmaceutical Co., Tokyo Japan). On the other hand, during submucosal dissection, bleeding can be avoided at all sites by making every effort to visually identify vessels and not perform dissection blindly. Oyama *et al*[45] noted that identification of vessels prior to submucosal dissection and prophylactic thermo-coagulation are most important in preventing ESD intraoperative bleeding. Toyonaga *et al*[13,46] stated that knowing the correct layer of the submucosa containing fewer vessels and existing fibrous tissue, is important in reducing ESD intraoperative bleeding.

When bleeding occurs during ESD, by washing out the blood with the water-jet system and using a transparent attachment hood, a clear visual field can be maintained, and bleeding points can be rapidly identified[35]. For bleeding from vessels smaller than the electrosurgical knife tip or arm, hemostasis by thermo-coagulation with the knife is usually possible. For bleeding from vessels larger than the electrosurgical knife tip or arm, or bleeding for which hemostasis with the knife is difficult, hemostatic forceps are used (Figure 2). Fujishiro *et al*[47] reported that hemostatic forceps for vessels smaller than 2 mm in diameter, and hot biopsy forceps for vessels larger than 2 mm in diameter, are useful. When hemostasis by thermo-coagulation cannot be achieved, hemostasis using endoscopic hemoclips is necessary, so that subsequent procedures are not hindered.

Hemostasis for delayed bleeding

Delayed bleeding after ESD occurs in 0%-9% of cases[6,16,18,28,48-54] (Table 1). For resected lesions located in the middle and lower third of the stomach, the incidence is higher. Bleeding occurs when vessels at ulcer bases rupture due to physical stimulation by peristalsis or due to chemical stimulation, for example, by bile reflux[48]. Delayed bleeding often occurs within 24 h postoperatively and is related to lesion location, size, and ulcer-findings[48,55]. For delayed bleeding, in almost all cases, hemostasis is achieved with urgent endoscopic hemostasis[56]. However, cases requiring vascular embolization because endoscopic hemostasis could not be achieved[57], and cases complicated by disseminated intravascular coagulation the day after delayed bleeding[58] have been reported, so caution is necessary.

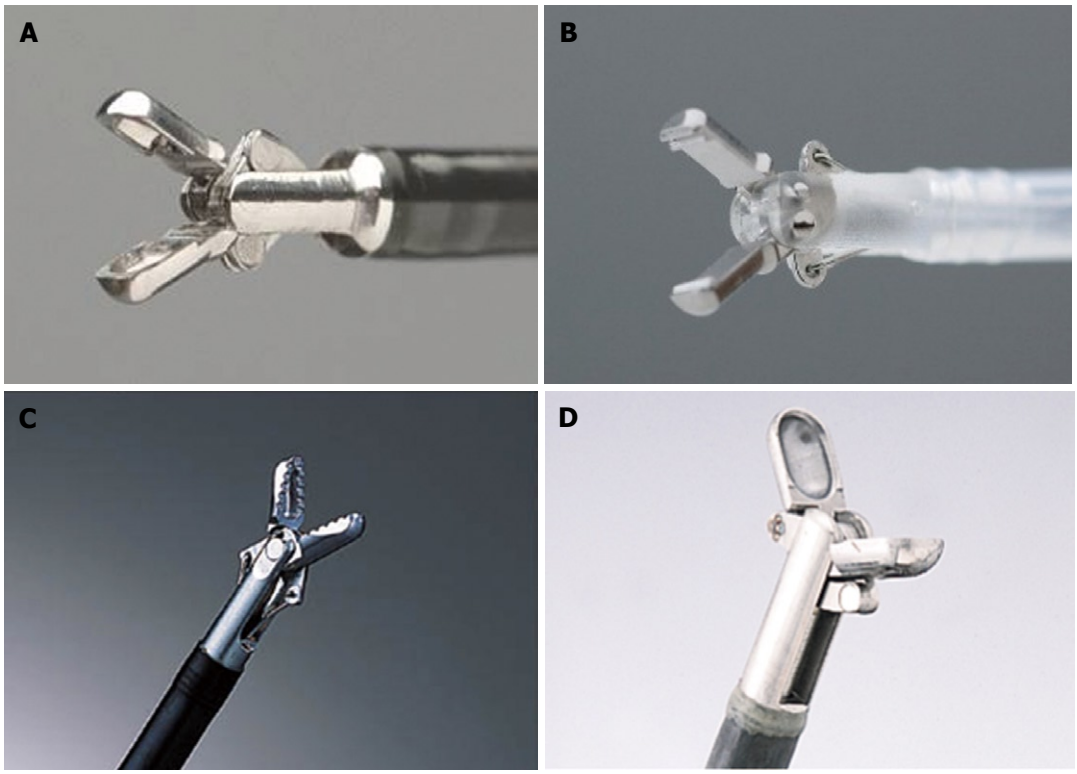

Figure 1 Hemostatic forceps tips. A: Monopolar hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan); B: Bipolar hemostaticforceps (H-S2518; Pentax, Tokyo, Japan); C: Hemostatic forceps (Coagrasper: FD-410LR; Olympus, Tokyo, Japan); D: Hot biopsy forceps (FD-1L-1; Olympus, Tokyo, Japan).

Table 1 Delayed bleeding rate of endoscopic submucosal dissection for gastric epithelial neoplasia

Author	Year	Total cases	Delayed bleeding (%)	En bloc resection rate (%)
Oda *et al*[48]	2005	945	6	93
Kakushima *et al*[49]	2006	383	3.4	91
Imagawa *et al*[18]	2006	196	0	93
Onozato *et al*[50]	2006	171	7.6	94
Oka *et al*[16]	2006	195	6.2	83
Hirasaki *et al*[51]	2007	112	7.1	96
Ono *et al*[6]	2008	161	8.7	99
Hoteya *et al*[52]	2009	572	4.9	95
Isomoto *et al*[53]	2009	510	1.8	95
Tsuji *et al*[54]	2010	398	5.8	NA
Akasaka *et al*[28]	2011	1188	3.1	95

NA: Not analyzed.

To prevent delayed bleeding, prophylactic coagulation of exposed vessels at the bases of artificial ulcers that occur after ESD lesion resection is very useful. According to Takizawa *et al*[59], the cause of delayed bleeding is due more to insufficient prophylactic thermo-coagulation than insufficient primary hemostasis during ESD[60], because the site of delayed bleeding is not the site of endoscopic hemostasis during surgery. In addition, a study has been conducted on the prevention of delayed bleeding by evaluation of blood flow at ulcer bases using endoscopic Doppler ultrasound (US). Uedo *et al*[61], based on blood flow detected using Doppler US, reported that, by coagulation of vessels seen at artificial ulcer bases after ESD lesion resection, delayed bleeding is reduced, and unnecessary thermo-coagulation of vessels without blood flow can be avoided. On the other hand, Choi *et al*[62] reported that prophylactic closure of gastric EMR-induced ulcers with metal hemoclips prevent delayed bleeding.

In 2008, a survey of treatment methods for peptic and artificial ulcer bleeding was conducted at nine departments of high-volume center hospitals in Japan[63]. For endoscopic hemostasis of peptic ulcer bleeding, the number one method used was clipping (32.9%), followed by coagulation forceps (23.5%). In contrast, for artificial ulcer bleeding, coagulation forceps (77.8%) were used significantly more. In addition, the proportion of patients who underwent second-look endoscopy, compared to peptic ulcers, was significantly lower for artificial ulcers (86% and 71%, respectively).

The effectiveness of second-look endoscopy after hemostasis of peptic ulcer bleeding has previously been shown[64,65]. However, according to Goto *et al*[66], for artificial ulcers, no significant difference in the incidence of delayed bleeding before and after second-look endoscopy was found. This suggests that delayed bleeding after ESD, irrespective of whether second-look endoscopy is performed, may develop. However, for artificial ulcers located in the lower third of the stomach, compared to ulcers located in the upper and middle third of the stomach, because delayed bleeding occurs earlier, careful follow-up observation or early second-look endoscopy may be useful[54,66].

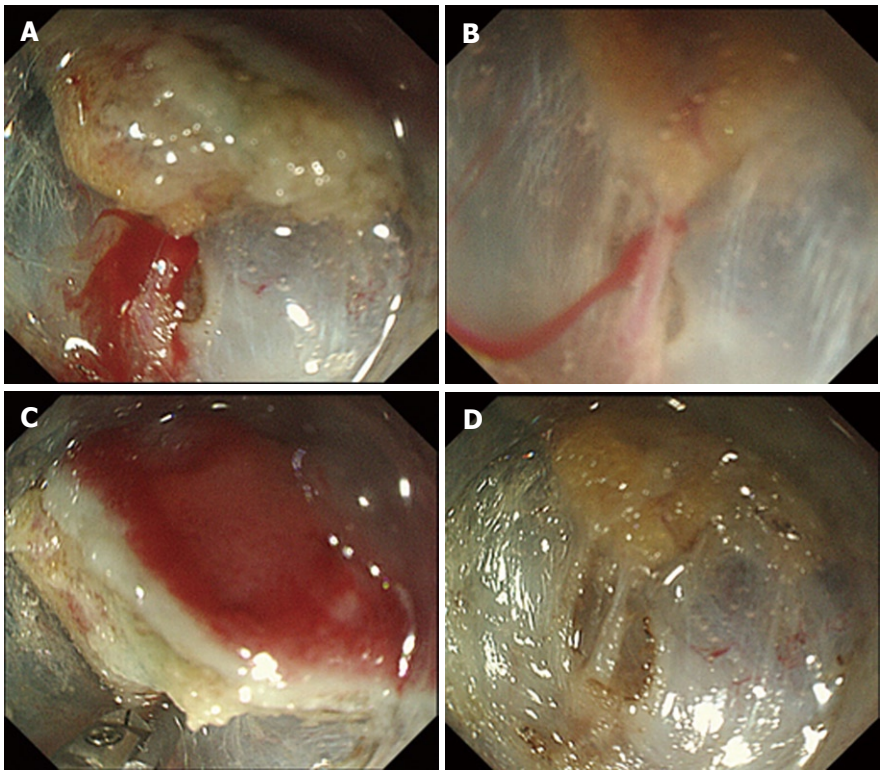

Figure 2 Hemostatic procedure for endoscopic submucosal dissectionintraoperative bleeding using hemostatic forceps. A: Pulsatile bleeding is observed during submucosal dissection; B: By filling the tip attachment with water, the bleeding point can be pinpointed and identified; C: After identifying the bleeding point, the vessel is securely grasped by hemostatic forceps, and thermo-coagulation is performed; D: Complete hemostasis is achieved, without excessive coagulation.

MANAGEMENT OF ARTIFICAL GASTRIC ULCERS AFTER ESD

Pharmacotherapy of artificial ulcers that develop after ESD lesion resection is also important to prevent delayed bleeding. However, management must take into account the differences in etiology between peptic ulcers and artificial ulcers after ESD.

Comparison of peptic ulcers and artificial ulcers

Currently, proton pump inhibitors (PPIs) are the drugs of first choice for treatment of peptic ulcers, and when a PPI cannot be used, an H2-receptor antagonist (H2RA) is selected. Treatment is generally for 8 wk. A meta-analysis of ulcer healing rates reported significantly higher ulcer healing rates with PPIs than with H2RAs[67,68]. In addition, in a meta-analysis of the efficacy of preventing recurrence of bleeding gastric ulcers, no differences in rebleeding rates, surgical intervention rates, or mortality rates between the two classes of drugs were reported[69].

The etiology of artificial ulcers after gastric ESD and peptic ulcers also differs greatly[70]. First, peptic ulcers develop, at least in part, due to hyperacidity, whereas artificial ulcers form in a hypoacidic environment in which there is severe mucosal atrophy. Second, peptic ulcers develop at sites where there is breakdown of gastric mucosal defense mechanisms, whereas artificial ulcers occur iatrogenically at sites where mucosal defense mechanisms are intact. Third, peptic ulcers include ulcers deeper than the submucosa, and inflammation spreads in the ulcer periphery, whereas artificial ulcers, because they basically occur due to submucosal dissection, are relatively shallow ulcers down to the submucosa, and the inflammation is localized. Despite these differences, treatment of an artificial ulcer after gastric ESD, based on treatment for a peptic ulcer, is empiric, with an anti-acid drug for 8 wk[63] (Table 2).

Anti-acid drugs for artificial ulcers

For artificial ulcers that develop after ESD for gastric mucosal lesions without preoperative ulcer findings, Kakushima *et al*[71] reported that healing occurred within 8 wk with PPI administration for 8 wk, irrespective of ulcer size or location. In addition, factors that influence artificial ulcer healing such as artificial ulcer size, location, *Helicobacter pylori* infection status, and extent of gastric mucosal atrophy had no effect. However, with fibrosis deeper than the submucosa of lesions prior to ESD, healing may be delayed[72,73]. According to Huang *et al*[74], although the recurrence rate of ESD artificial ulcers is lower than that of peptic ulcers, *Helicobacterpylori* infection and lesion ulcer findings are risk factors for recurrence. In contrast, Oh *et al*[75] reported that, because the extent of healing of artificial ulcers 4 wk after ESD is determined by the size of the ulcer initially formed, the duration of PPI treatment should be decided based on this parameter.

For artificial ulcers after EMR, Lee *et al*[76] compared PPIs in 1-wk and 4-wk treatment groups. They found that, after 4 wk, ulcer size, stage, subjective symptoms, and use of other mucosal-protective antiulcer drugs did not significantly differ between the groups. Niimi *et al*[77] reported that administration of PPI for 2-wk for artificial ulcers after ESD may be sufficient to help them heal. These results suggest that, for artificial ulcers, unlike peptic ulcers, the importance of acid secretion inhibition

Table 2 Healing process of gastric artificial ulcers after endoscopic submucosal dissection

Author	Year	Total cases	Drugs administration	Weeks	Ulcer healing rate (%)		Average ulcer size	
					4 wk	8 wk	Maximal diameter (mm)	Resected area (mm^2)
Kakushima *et al*[71]	2004	70	PPI + sucralfate	8	NA	100	34.7	NA
Lee *et al*[76]	2004	26	OPZ 20 mg	1	12	NA	NA	503
		34	OPZ 20 mg	4	15	NA	NA	575
Yamaguchi *et al*[78]	2005	29	OPZ 20 mg	8	NA	NA	27.8	NA
		28	Famotidine 40 mg	8	NA	NA	22.4	NA
Uedo *et al*[79]	2007	73	RPZ 20 mg	8	NA	83	41	NA
		70	Cimetidinde 800 mg	8	NA	89	40.5	NA
Asakuma *et al*[80]	2009	28	RPZ 20 mg + ES 3.0 g	8	40.7	96.3	NA	1306
		28	RPZ 20 mg	8	11.5	76.9	NA	1274
Kato *et al*[81]	2010	31	RPZ 10 mg + rebamipide 300 mg	4	68	NA	35	NA
		31	RPZ 10 mg	4	35	NA	31	NA
Fujiwara *et al*[82]	2011	30	RPZ 20 mg + rebamipide 300 mg	8	NA	86.7	41	1453
		31	RPZ 20 mg	8	NA	54.8	42.8	1521
Niimi *et al*[77]	2011	55	RPZ 10 mg	2	NA	80.0	32.7	NA

NA: Not analyzed; PPI: Proton pump inhibitor; OPZ: Omeprazole; RPZ: Rabeprazole; ES: Ecabet sodium.

in the ulcer healing process may be low.

Yamaguchi *et al*[78] compared PPI-treatment and H2RA-treatment groups in patients with artificial ulcers after EMR. They reported no differences in the incidence of delayed bleeding or ulcer size at 30 d and 60 d postoperatively. They did state that artificial ulcers healed more easily than peptic ulcers, and they concluded that, for artificial ulcers with severe bleeding within 24 h after surgery, treatment with H2RA drugs, whose onset of inhibition of gastric acid secretion is more rapid than that with PPIs, is appropriate.

Uedo *et al*[79] compared PPI-treatment and H2RA-treatment groups in patients with artificial ulcers after ESD. There were no differences in the incidence of delayed bleeding or ulcer healing rates between the groups. However, the cumulative non-bleeding rate using the Kaplan-Meier method was significantly higher in the PPI group. Moreover, on multivariate analysis, PPI treatment was an independent factor in reducing the rate of delayed bleeding. Their results suggested that PPIs are more effective than H2RAs for preventing ESD delayed bleeding.

For post-EMR ulcers and post-ESD ulcers, in terms of formation by endoscopic resection, with the exception of size, the pathophysiology is the same. However, in studies to date, with regard to ulcer healing and prevention of delayed bleeding when artificial ulcers are treated with acid secretion inhibitors, there is no agreement in the results. Regarding the need for and duration of treatment with acid secretion inhibitors for artificial ulcers, there is still room for debate.

Mucosal-protective antiulcer drugs in artificial ulcers

In the treatment of peptic ulcers, there is no evidence that combined therapy with a PPI and a mucosal-protective antiulcer drug is superior to a PPI alone. However, in artificial ulcers, an additive effect of mucosal-protective antiulcer drugs has been reported (Table 2). Asakuma *et al*[80] compared combined therapy with a PPI (rabeprazole 20 mg/d) and ecabet sodium (3.0 g/d) *vs* the PPI alone for artificial ulcers after ESD. At 4 wk and 8 wk, ulcer healing rates were significantly higher in the combined treatment group. In addition, Kato *et al*[81] compared combined therapy with a PPI (rabeprazole 10 mg/d) and rebamipide (300 mg/d) *vs* the PPI alone for artificial ulcers after ESD. At 4 wk, the ulcer scarring rate was significantly higher in the combined treatment group. Similarly, Fujiwara *et al*[82] compared combined therapy with a PPI (rabeprazole 20 mg/d) and rebamipide (300 mg/d) *vs* the PPI alone for artificial ulcers after ESD. At 8 wk, the ulcer scarring rate was significantly higher in the combined treatment group.

Thus, among the mucosal-protective antiulcer drugs, there are drugs that accelerate ulcer healing. This may be attributable to differences in the etiology between artificial ulcers and peptic ulcers, as previously mentioned, but further evidence must be accumulated.

CONCLUSION

With the increasing use of ESD for gastric epithelial neoplasia, management of ESD-related bleeding and artificial ulcers after lesion resection has become an important issue not only in Japan, but throughout the world. Therefore, more effective endoscopic hemostatic methods and appropriate pharmacotherapy of artificial ulcers, taking into account their etiology, are becoming increasingly important. Moreover, safer and more reliable ESD techniques must be developed.

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