

Feasibility of a Modified SCC Method With and Without Combining the Use of PGA Sheets and Fibrin Glue for Preventing Delayed Bleeding After Gastric ESD

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Abstract

Background: Some methods have been developed for preventing delayed bleeding (DB) after gastric endoscopic submucosal dissection (GESD). However, none of the methods can completely prevent DB. We hypothesized that DB can be prevented by a modified the search, coagulation, and clipping (MSCC) method for patients at low risk of DB and by combining the use of PGA sheets and fibrin glue with the MSCC method (PMSCC method) for patients at high risk of DB (anti-bleeding [ABI] strategy). In this study, the technical feasibility of this novel strategy was assessed.

Methods: We investigated 123 lesions in 121 consecutive patients who underwent GESD in Kushiro Rosai Hospital between April 2018 and January 2020. The decision for continuation or cessation of antithrombotic agents was based on the Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment.

Results: Oral antithrombotic agents were administered to 28 patients (22.8%). En bloc R0 resection rate was 98.4%. The MSCC method and PMSCC method for preventing were performed in 114 and 9 lesions, respectively. The median time of the MSCC method was 16 min and the median speed was 3.6 cm²/10min. The median time of the PMSCC method was 59 min and the median speed was 1.3 cm²/10min. The only delayed procedural adverse event was DB in one (0.8%) of the 123 lesions.

Conclusions: The ABI strategy is feasible for preventing DB in patients at low risk and high risk of DB after GESD, whereas the PMSCC method may be necessary for reduction of time.

Background

Endoscopic submucosal dissection (ESD) has become a widespread technique for treatment of a gastric tumor. However, post-ESD bleeding is a serious complication after gastric ESD, and the incidence has been reported to be 3–5.5% [1–6]. Post-ESD coagulation (PEC) has been used in many hospitals to prevent post-bleeding [1]. The search, coagulation, and clipping (SCC) method has been reported to be much better than the PEC method for preventing DB after gastric endoscopic submucosal dissection (ESD) [7]. However, the SCC method does not completely prevent post-ESD bleeding. Another approach combines the use of polyglycolic acid (PGA) sheets and fibrin glue to reduce the risk of DB after gastric ESD [8]. However, a multicenter, prospective, randomized controlled study showed that PGA sheets alone were not effective in preventing DB in patients at high risk for such bleeding [9]. Therefore, we have devised a new method by combining the use of PGA sheets and fibrin glue with a modified SCC method for preventing DB after gastric ESD [10]. We hypothesized that DB could be prevented by a modified SCC method (MSCC method) for patients at low risk of DB and by combining the use of PGA sheets and fibrin glue with the MSCC method (PMSCC method) for patients at high risk of DB (anti-bleeding [ABI] strategy). In the current study, we assessed the technical feasibility of this novel strategy.

Methods

Subjects

We investigated 123 lesions in 121 consecutive patients who underwent gastric ESD in the Department of Gastroenterology at Kushiro Rosai Hospital between April 2018 and January 2020. Surgeons of gastric ESD were an endoscopist (S.A.) and some trainees with experience of less than 30 ESD procedures in humans. All of the procedures were tutored by one endoscopist (S.A.). Up until March 2018, ESD was performed in 169 patients (in the pharynx in 1 patient, esophagus in 16 patients, stomach in 128 patients and large intestine in 24 patients) under the

guidance of tutors at other institutions. Perforation and delayed perforation did not occur in any cases, and DB occurred in 4 cases (3.1%, ESD of the stomach). From April 2018, the endoscopist (S.A.) was only a tutor at our institution. Patients at a high risk for DB were defined as patients being administered direct oral anticoagulants (DOAC) or warfarin, patients on dialysis and patients who had received heparin replacement. Other patients were defined as patients at a low risk for DB. We evaluated *en bloc* R0 resection, curative resection, length of the tumor, length of the resected specimen, resection area, resection time, resection speed, method for preventing DB, number of clips used for the MSCC method, time and speed of the PEC, MSCC and PMSCC methods with or without the use of second-look endoscopy and vonoprazan, procedures at the second-look or follow-up endoscopy, and procedural and delayed procedural adverse events including perforation during ESD, delayed perforation, DB and post-ESD stenosis. *En bloc* R0 resection was defined as tumor resection in a single piece with tumor-free lateral and vertical margins. Resection time was the duration from the first injection until achieving complete resection. The resection speed was defined as the resection area divided by resection time (cm^2/h). The resection area was regarded to be approximately oval in shape. The time of the PEC, MSCC and PMSCC methods was defined as the interval from insertion of the first device for the prevention of DB until completion of the method. The speed of the PEC, MSCC and PMSCC methods was defined as the resection area divided by $10 \times$ the time of PEC, MSCC and PMSCC method ($\text{cm}^2/10 \text{ min}$). Perforation was defined as the creation of an immediately recognized hole in the gastric wall. Delayed perforation was defined as the presence of free air on abdominal computed tomography or X-ray after completion of the procedure in patients without perforation during ESD and no symptoms of peritoneal irritation after ESD. DB was defined as bleeding requiring emergency endoscopic hemostasis or transfusion or the presence of hemoglobin loss $\geq 2 \text{ g/dL}$ following ESD [11]. Delayed procedural adverse events were assessed for 30 days post-ESD. Continuation or cessation of antithrombotic agents was determined according to the Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment [12–13]. We examined ABO blood type because it has been reported that blood type O may be less likely to clot than other types [14].

ESD Method And Management After ESD

GIF-H290Z (Olympus Optical, Tokyo, Japan) and a needle knife were used for assessing the lesion margin and marking around the lesion. ESD was performed under conscious sedation using a single-channel gastrointestinal endoscope with a transparent attachment hood fitted to the tip (GIF-Q260J; Olympus Optical). When some difficulties were observed, we used another twin-channel gastrointestinal endoscope (GIF-2TQ260M; Olympus Optical). The GIF-2TQ260M endoscope has a multi-bending and a water jet function. Hyaluronic acid solution was injected into the submucosal layer before mucosal and submucosal cutting. After injection, we mainly performed mucosal cutting with a needle knife and dissection beneath the lesion using an IT knife-2 (Olympus Optical). When some difficulties were observed, we used another knife: hook knife (Olympus Optical), flush knife (Fujifilm Optical) or clutch cutter (Fujifilm Optical). We used a VIO 200D electrosurgical generator (ERBE Elektromedizin, GmbH, Tübingen, Germany). Hemorrhage was controlled using hemostatic forceps such as Coagrasper (Olympus Optical, monopolar hot hemostasis forceps) for the upper digestive tract.

After ESD, a proton-pump inhibitor (omeprazole at 20 mg, twice a day) was intravenously injected. The patient's doctor in the ward rarely instructed a second-look endoscopy to be performed on postoperative day (POD) 1. If there were no problems, oral food intake was started on POD 2. Then an oral proton-pump inhibitor (esomeprazole at 20 mg/day or lansoprazole at 30 mg/day or rabeprazole at 20 mg/day) or vonoprazan (20 mg/day) was administered for a minimum of eight weeks. Sodium alginate (60 ml/day) and aluminum hydroxide gel, magnesium

hydroxide (160 ml/day) were administered for a minimum of three days. Before the patient was discharged from the hospital, follow-up endoscopy was performed on PODs 5–7

Method For Prevention Of Db

We previously described a new method combining the use of PGA sheets and fibrin glue with a modified SCC method for preventing DB after gastric ESD [10]. First, a coagulation procedure was performed after lesion resection, mainly in the vessels at the margin of the ulcer base. Then, perforator vessels emerging between muscle layers were actively sought and clipped using short hemoclips (HX-610-135S, Olympus). Because perforator vessels may also be present in carbonized areas of the ulcer base, clipping was also actively performed in such areas, this constituted the modification of the search, coagulation, and clipping method. For patients at low risk of DB, we ended with this procedure. For patients at high risk of DB, we moved on to the next procedure. In the next procedure, several large and small PGA sheets were placed (based on the size of the ulcer base), using methods proposed by Kobayashi et al. [15] and Takimoto et al. [16], respectively. Finally, fibrin glue was sprayed. All these steps constitute the polyglycolic acid sheets, fibrin glue, and modified search, coagulation, and clipping (PMSCC) method.

Pathological Assessment Of Resected Specimens And Ethics

All resected specimens from the stomach were cut into longitudinal slices of 2–3 mm in width and were embedded in paraffin. Each slice was stained with hematoxylin–eosin and examined microscopically. Curative resection of adenocarcinoma was previously described by the Japanese Gastric Cancer Association. [17].

This study was conducted in accordance with the rules and regulations of the Kushiro Rosai Hospital Institutional Review Board (study registration number: 19233). Written informed consent was obtained from all study subjects. The design of this study is a retrospective case series.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics [18]. Continuous and non-parametric variables were expressed as medians with 25th and 75th percentile values.

Results

The median age of the subjects was 73 (interquartile range [IQR], 69–79) years, and the male/female was 98/25. Oral antithrombotic agents were administered to 28 patients (22.8%). The lesion sites were upper (n = 16), middle (59), lower (48) portion of the stomach. The median length of the long tumor axis was 1.3 (IQR, 0.7–2.0) cm, the median resected specimen length was 3.0 (IQR, 2.5–4.1) cm, and the median resection area was 5.5 (IQR, 3.5–9.4) cm² (Table 1). En bloc R0 resection rate was 98.4% and curative resection rate was 87.0%. The median resection time was 91 (IQR, 55–137) min and the median resection speed was 4.5 (IQR: 2.5–5.4) cm²/h. The MSCC and PMSCC method for the preventing DB were performed in 114 and 9 lesion, respectively. The median time of the MSCC method was 16 (IQR, 8–23) min and the median speed was 3.6 (IQR, 2.8–4.1) cm²/10 min. The median time

of the PMSCC method was 59 (IQR, 44–63) min and the median speed was 1.3 (IQR, 1.2–2.4) cm²/10 min. The only delayed procedural adverse was DB in one (0.8%) of the 123 lesions (Table 2).

Table 1
Characteristics of the patients and lesions

Characteristics		Values
Age	median (IQR), y	73 (69–79)
Sex	male/female	98/25
Oral antithrombotic agents, n (%)		
	None	95 (77.2)
	Warfarin	3 (2.4)
	DOAC	3 (2.4)
	DAPT	1 (0.8)
	Clopidogrel	3 (2.4)
	Aspirin	7 (5.7)
	Aspirin + others	1 (0.8)
	Cilostazol	2 (1.6)
	Others	8 (6.5)
Dialysis, n (%)		2 (1.6)
Heparin placement, n (%)		1 (0.8)
Lesion site, n (%)		
	Upper	16 (13.0)
	Middle	59 (48.0)
	Lower	48 (39.0)
Length of resected specimen	median (IQR), cm	3.0 (2.5–4.1)
Resection area	median (IQR), cm ²	5.5 (3.5–9.4)
Length of tumor	median (IQR), cm	1.3 (0.7–2.0)
Pathological diagnosis, n (%)		
	Adenocarcinoma	106 (86.2)
	Adenoma	14 (11.4)
	Others	3 (2.4)
Depth, n (%)		
	Intramucosa	99 (80.5)
	Submucosa	24 (19.5)

IQR, interquartile range; DOAC, direct oral anticoagulants; DAPT, dual antiplatelet therapy

Characteristics		Values
Macroscopic type, n (%)		
	Depressed	52 (42.3)
	Non-depressed	71 (57.7)
Submucosal fibrosis, n (%)		
	Negative	107 (87.0)
	Positive	16 (13.0)
Blood type, n (%)		
	O	40 (32.5)
	A	37 (30.1)
	B	35 (28.5)
	AB	11 (8.9)
IQR, interquartile range; DOAC, direct oral anticoagulants; DAPT, dual antiplatelet therapy		

Table 2
Results and clinical course of gastric ESD

Characteristics		Values
<i>En bloc</i> R0 resection, n (%)		121/123 (98.4)
VM1, n (%)		2 (1.6)
HM1, n (%)		0 (0)
Curative resection, n (%)		107/123 (87.0)
Resection time	median (IQR), min	91 (55–137)
Resection speed	median (IQR), cm ² /h	4.5 (2.6–6.2)
Surgeon	S.A. alone/others	84/39
Method for prevention of DB	MSCC/PMSCC	114/9
Time of PEC method	median (IQR), min	7 (5–11)
Speed of PEC method	median (IQR), cm ² /10 min	7.5 (4.9–12.4)
Time of MSCC method	median (IQR), min	16 (8–23)
Speed of MSCC method	median (IQR), cm ² /10 min	4.0 (2.7–7.1)
Number of clips used for MSCC method	median (IQR), n	4 (1–7)
Time of PMSCC method*	median (IQR), min	59 (44–63)
Speed of PMSCC method*	median (IQR), cm ² /10 min	1.3 (1.2–2.4)
Second-look endoscopy, n (%)		15 (12.9)
Vonoprazan, n (%)		99 (80.5)
Perforation during ESD, n (%)		0 (0)
Delayed perforation, n (%)		0 (0)
Delayed bleeding, n (%)		1 (0.8)
Post-ESD stenosis, n (%)		0 (0)
*Only nine patients in whom PMSCC method was performed are included.		
PEC, post-ESD coagulation		

Table 3 shows details of the 9 patients in whom the PMSCC method was used. The PMSCC method was used in 9 patients at high risk of DB for the following reasons: heparin substitution (one patient), hemodialysis (two patients), direct oral anticoagulant administration (three patients), and oral warfarin administration (three patients). DB did not occur in any of the nine patients (Table 3). Table 4 shows details of the patient with DB (Table 4).

Table 3
Details of the 9 patients in whom the PMSCC method was used

Patient	Age	Sex	Lesion site	Length of resected specimen	Oral antithrombotic agents	Dialysis	Heparin placement	Vonoprazan	Blood type
1	78	M	Lower	4.3 cm	Aspirin	-	+	+	A
2	85	M	Lower	4.3 cm	Nicorandil	+	-	+	B
3	72	M	Middle	2.2 cm	Warfarin	-	-	+	A
4	74	M	Middle	4.8 cm	DOAC	-	-	+	A
5	66	M	Upper	4.1 cm	DOAC	-	-	+	A
6	66	M	Middle	7.0 cm	-	+	-	+	O
7	70	M	Middle	1.9 cm	Warfarin	-	-	+	O
8	74	M	Middle	4.0 cm	Warfarin	-	-	+	B
9	61	M	Middle	3.1 cm	DOAC + others	-	-	+	B

Table 4
Details of the patient with DB

Method	Timing of DB	Transfusion	Lesion site	Length of resected specimen	Oral antithrombotic agents	Vonoprazan	Blood type
MSCC	Day 5	-	posterior wall lesser curvature middle body	5.3 cm	Aspirin + limaprost	+	B

Discussion

In this study, we investigated the technical feasibility of this novel strategy and found that (1) DB occurred in only one patient, (2) the time of the MSCC method was acceptable, (3) the use of the PMSCC method prevented DB in patients at high risk of DB after gastric ESD, and (4) the time of the PMSCC method was not acceptable.

The incidence of DB after gastric ESD has been reported to be 3-5.5% [1–6] and the incidence of DB in patients receiving antithrombotic therapy has been reported to be 21–38% [19–22]. In this study, the incidence of DB in all of the patients was 0.8% and the incidence of DB in patients receiving antithrombotic therapy was 3.6%. Thus, the ABL strategy may be useful for preventing DB in patients after gastric ESD.

In recent years, attempts have been made to endoscopic suture the ulcer base for prevention of DB in patients after gastric ESD. However, the stomach has a thick wall, and it is difficult for the sutures to be retained. It seems that the suture can only be maintained for a few days [23]. The latest article reported that the suture was gradually improved, however, the incidence of DB was 10% [24]. In the current endoscopic technique, complete suture of the ulcer base in

the stomach seems to be difficult. Therefore, the ABI strategy is reasonable for preventing DB in patients after gastric ESD.

A region in which bleeding occurs in ESD is often carbonized. When a region becomes carbonized, it is difficult to recognize exposed blood vessels, and subsequent DB prevention measures might be neglected. In our method, clipping was actively performed at carbonized sites. If bleeding does not occur during ESD, exposed blood vessels can be easily recognized and that may be important for preventing DB.

Although bleeding may be observed from perforator vessels in areas where PGA sheets are peeled off [9], we believe that if perforator vessels at the base of ulcers are clipped in advance then such DB may be prevented.

DOAC are associated with gastrointestinal (GI) bleeding, and it has been hypothesized that non-absorbed, active anticoagulant agents within the GI tract induce bleeding of fragile mucosal defects [25]. In this study, fragile mucosal defects were protected by PGA sheets. Prevention of DOAC-related DB might be possible by the PMSCC method.

It is not practical to use the complicated PMSCC method in all patients. The simple MSCC method should be used in low-risk patients, and the complicated PMSCC method should only be used in high-risk patients. In the future, we may decide which method to use depending on the number of DB risk factors.

The time of the PMSCC method was not acceptable. However, we are now developing a new technique to shorten the procedure time of PMSCC. We hope to report results soon.

Our study has three main limitations: the main surgeon is single, the small sample size and the retrospective study design. Future prospective studies with larger sample sizes and randomized controlled trials are needed to evaluate the utility of our method.

Conclusions

The ABI strategy is feasible for preventing DB in patients at low risk and high risk of DB after gastric ESD, whereas the PMSCC method may be necessary for reduction of time.

Abbreviations

DB, delayed bleeding; GESD, gastric endoscopic submucosal dissection; MSCC, modified the search, coagulation, and clipping; ABI, anti-bleeding; PEC, Post-ESD coagulation; SCC, search, coagulation, and clipping; ESD, endoscopic submucosal dissection; PGA, polyglycolic acid; POD, postoperative day; IQR, interquartile range; GI, gastrointestinal

Declarations

Ethics approval and consent to participate

The study was approved by the local ethic review board of the Kushiro Rosai Hospital. Written informed consent was obtained from all study subjects.

Consent for publication

Written consent for the publication of personal/clinical data was obtained from all study subjects.

Availability of data and material

From the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

SA wrote the manuscript. SO, AM, AS, SY, AY, KH, NK, IS, HO and TM edited the manuscript. SA is the article guarantor. All Authors read and approved the manuscript.

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