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Comparison of endoscopic closure versus non-closure for post-gastric endoscopic submucosal dissection artificial floor in antithrombotic therapy: a propensity score-matched analysis

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Abstract

Background The management of delayed bleeding after gastric endoscopic submucosal dissection (ESD) is currently an important issue because of recent increases in the number of patients on antithrombotic therapy. Artificial ulcer closure has been shown to prevent delayed complications in the duodenum and colon. However, its effectiveness in cases involving the stomach remains unclear. In this study, we aimed to determine whether endoscopic closure reduces post-ESD bleeding in patients undergoing antithrombotic therapy.

Methods We retrospectively analyzed 114 patients who had undergone gastric ESD while on antithrombotic therapy. The patients were allocated to one of 2 groups: a closure group (n=44) and a non-closure group (n=70). Endoscopic closure had been performed using multiple hemoclips or using the endoscopic ligation with O-ring closure method after coagulation of exposed vessels on the artificial floor. Propensity score matching resulted in 32 pairs of patients (closure vs. non-closure 32:32). The primary outcome was post-ESD bleeding.

Results The post-ESD bleeding rate was significantly lower in the closure group (0%) than in the non-closure group (15.6%) (P=0.0264). There were no significant differences between the 2 groups regarding white blood cell count, C-reactive protein, maximum body temperature, or scores on a verbal rating scale that assesses the degree of abdominal pain.

Conclusion Endoscopic closure may contribute to decreasing the incidence of post-ESD gastric bleeding in patients undergoing antithrombotic therapy.

Keywords Gastric endoscopic submucosal dissection, endoscopic closure, delayed bleeding, antithrombotic therapy, early gastric cancer

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Conflict of Interest: None

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Introduction

Endoscopic submucosal dissection (ESD), a minimally invasive procedure, has become a standard means of managing superficial gastric tumors without risk of lymph node metastasis [1,2]. However, complications such as post-ESD bleeding and perforation have been reported in a certain percentage of patients, especially those on antithrombotic therapy, and their management is important [3,4].

Previous studies have shown that proton pump inhibitors (PPIs) [5] and preventive coagulation of blood vessels exposed by performing ESD [6] are effective in preventing post-ESD bleeding. Vonoprazan, a potassium-competitive acid blocker, is reportedly more effective than PPIs in reducing the risk of post-ESD bleeding [7]. However, a meta-analysis found that none of these antacid medicines significantly reduces the incidence of post-ESD bleeding [8].

Shielding using polyglycolic acid (PGA) sheets and fibrin glue has been developed as a means of preventing post-ESD

complications [9]; this includes the PGA sheet delivery method [10-14]. However, since there is insufficient evidence for the effectiveness of applying PGA sheets to prevent post-ESD gastric bleeding [15,16], further research is needed.

To date, endoscopic closure has been shown to prevent post-ESD complications in the duodenum and colon [17-20]. Although several endoscopic closure methods involving creation of an artificial gastric floor to prevent post-ESD bleeding have been attempted [21-25], there are too few data to determine the efficacy of closure in patients taking antithrombotic agents. In this study, we aimed to examine the effectiveness of prophylactic endoscopic closure by comparing closure and non-closure groups of patients at high risk of post-ESD bleeding because they were undergoing antithrombotic therapy.

Patients and methods

Study design

This retrospective comparative study was conducted at a single center, approved by the Clinical Ethics Committee of Kagawa University Hospital (Registration No. 2021-149), and conformed to the requirements of the Declaration of Helsinki. The study cohort comprised 114 patients who had undergone ESD for gastric neoplasms while taking antithrombotic agents in our department between January 2016 and March 2021. ESD had been performed to treat adenomas or early gastric carcinomas, with an expected depth of invasion of no more than slightly (500 μm) into the submucosa and a minimal likelihood of lymph node metastasis, in accordance with Japanese ESD criteria [2]. Antithrombotic agents were stopped before ESD in accordance with the current guidelines [26]. In cases of post-ESD bleeding, emergency endoscopy was performed and hemostasis was applied. Antithrombotic drugs were temporarily discontinued and resumed after the absence of bleeding was confirmed by endoscopy the next day. The study patients were allocated to 2 groups for retrospective analysis: 44 who had undergone post-ESD defect closure (closure group), and 70 cases who had not (non-closure group). Complete closure of the artificial defect without exposure of the muscle layer had been achieved in all 44 patients in the closure group. The exclusion criteria were 2 or more neoplasms, and lesions located in the cardia or pyloric ring (because of the risk of endoluminal stenosis after closure). Patients in whom closure had been attempted but left incomplete were assigned to the non-closure group.

All patients had provided written informed consent for the procedure and their participation in the study. The present study was approved by the Clinical Ethics Committee of Kagawa University Hospital (Registration No. 2021-149) and was conducted in accordance with the principles of the Declaration of Helsinki. This study is reported according to the STROBE checklist. All patients provided their written informed consent to undergo the procedures and participate in the study.

All procedures were performed by 5 endoscopists (NK, HK, NN, TC and TY), each of whom had successfully performed more than 100 gastric ESDs.

ESD procedure

All study patients had undergone gastric ESD under deep sedation with propofol or general anesthesia. The procedures were performed using a single-channel endoscope (GIF-H260Z or GIF-Q260J; Olympus Medical, Tokyo, Japan) and an electrosurgical unit (VIO 300D; ERBE, Elektromedizin, Tübingen, Germany). Carbon dioxide was insufflated during the procedures.

The ESD protocol was as follows: 1) marking dots were placed circumferentially approximately 5 mm beyond the lesion, using a DualKnife (KD-441Q; Olympus Medical); 2) a mixture of 0.4% hyaluronate sodium solution (MucoUp; Johnson & Johnson K.K., Tokyo, Japan) and glycerol (Chugai Pharmaceutical, Tokyo, Japan) was injected into the submucosa; 3) the mucosa was then incised circumferentially and submucosal dissection performed using a DualJnife and an ITknife2, respectively (KD-611L; Olympus Medical). After *en-bloc* resection, visible vessels were coagulated using hemostatic forceps (Coagrasper; FD-411QR; Olympus Medical). Resection time was defined as the time from the start of submucosal injection to the resection of the lesion.

Endoscopic closure procedure

Endoscopic closure was attempted at the discretion of the individual endoscopist after consideration of the patient's age and comorbidities. After *en-bloc* resection and preventive coagulation of visible vessels, one of the following 2 closure procedures was performed: conventional clip closure, or the endoscopic ligation with O-ring closure (E-LOC) method [21].

Conventional clip closures were performed in an endoscopic forward direction (Fig. 1A). The first hemoclip (HX-610-090; Olympus Medical) was used to fix the distal edge of the artificial defect (Fig. 1B). Additional clips were placed sequentially from the distal side to achieve complete closure of the defect (Fig. 1C,D).

The E-LOC procedure was performed as follows: First, a 3–0 surgical nylon loop, 2 cm in diameter, was positioned around the defect, and 2 hemoclips (HX-610-090; Olympus Medical) were used to anchor the loop on both edges of the defect (Fig. 2A), while another was applied to the muscle layer (Fig. 2B). Next, hemostatic forceps were used to grasp the loop and pull it into the cap of an endoscopic variceal ligation device (MD-48720U; Sumius, Tokyo, Japan) (Fig. 2C). The deployed hemoclips were then pulled into the cap (Fig. 2D). An O-ring was fired around the hemoclips to close the proximal side of the defect (Fig. 2E). This procedure was repeated toward the distal side, eventually achieving complete closure of the whole defect (Fig. 2F) [21]. While we performed conventional clip closure between January 2016 and March 2019, we mainly performed the newly developed E-LOC closure method between April 2019 and March 2021 to improve the technical aspects, which enabled closure of large defects after gastric ESD.

In this study, complete closure was defined as successful closure of a defect without exposure of the submucosal or muscle layer.

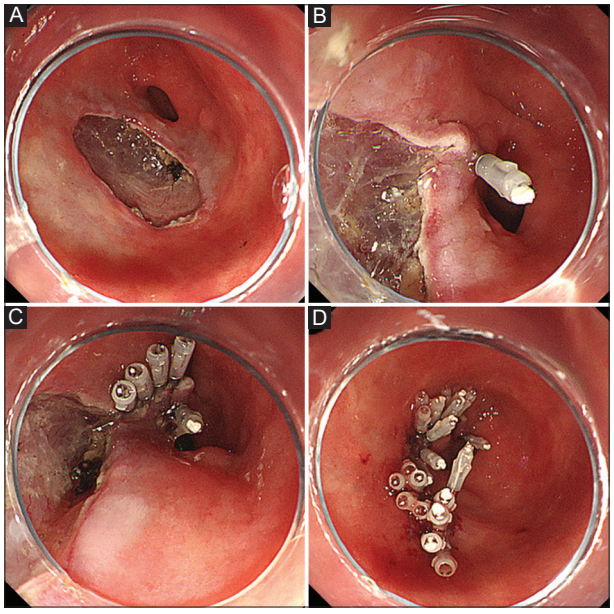

Figure 1 Conventional clip closure performed in a post- endoscopic submucosal dissection artificial defect 30 mm in diameter in the anterior wall of the antrum. (A) Closure was performed in an endoscopic forward direction. (B) The first hemoclip was used to fix the distal edge of the artificial defect. (C) Additional clips were placed sequentially from the distal side. (D) Complete closure of the defect

Follow up after ESD

Oral intake of food and liquid was prohibited from postoperative day (POD) 0 until the morning of POD 1. Patients took 20 mg PPI orally for 56 days from POD 1. Relevant laboratory tests were performed on POD 1 and second-look endoscopy on POD 1-3. Additionally, the patients were checked daily for fever or abdominal pain during their hospital stay. They were discharged when they were asymptomatic, generally on POD 12-14. Two months after ESD, a follow-up endoscopy was performed to confirm scarring of the post-ESD defect.

Outcome measures

The primary outcome was post-ESD bleeding rate, post-ESD bleeding being defined as a requirement for hemostasis on urgent endoscopic examination. The secondary outcomes were rate of delayed perforation, abdominal pain according to an initial verbal rating scale (VRS), and increases in white blood cell count, C-reactive protein (CRP) concentrations, and maximum body temperature.

We compared the 2 groups using the VRS on POD 1. VRS, also known as verbal pain scores and verbal descriptor scales, are tools used to assess the experience of pain, being self-reports that consist of several statements designed to describe pain intensity and duration. VRS scores are on a scale of 0-3, with 0 equal to no pain and 3 equal to the worse pain imaginable [27].

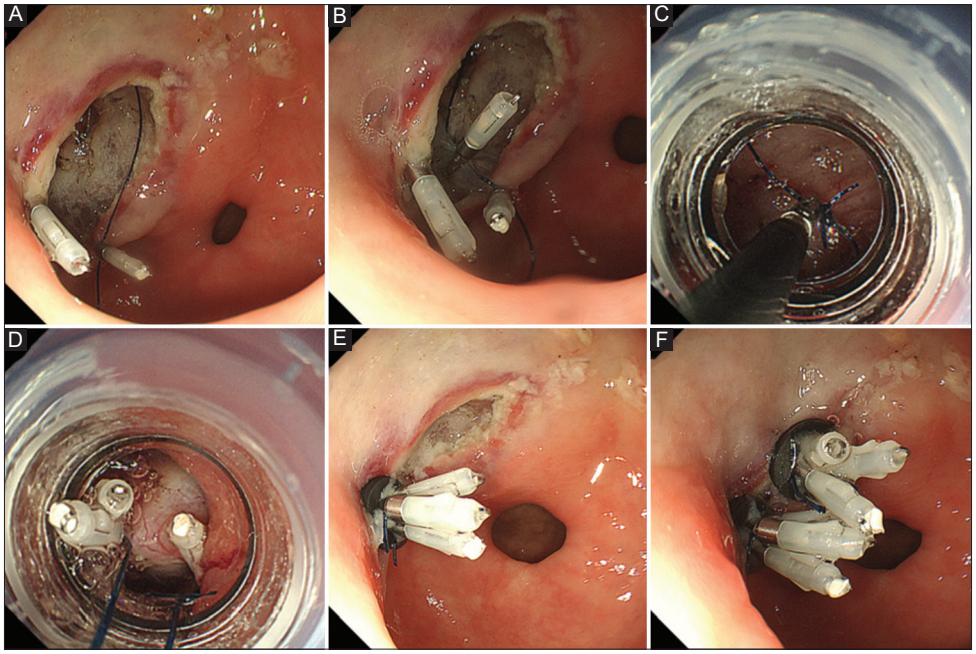

Figure 2 Endoscopic ligation with O-ring closure performed in a post- endoscopic submucosal dissection artificial defect 45 mm in diameter in the lesser curvature of the antrum. (A) A 3–0 surgical nylon loop, 2-cm in diameter, was positioned around the defect, and 2 hemoclips were used to anchor the loop on both edges of the defect. (B) Another hemoclip was applied to the muscle layer. (C) Hemostatic forceps were used to grasp the loop and pull it into the cap of an endoscopic variceal ligation device. (D) The deployed hemoclips were then pulled into the cap. (E) An O-ring was fired around the hemoclips to close the proximal side of the defect. (F) Complete closure of the whole defect

Statistical analysis

Continuous variables are summarized as medians and 25^{th}-75^{th} percentiles, reported as P25-P75, and were compared using the χ^2 test and Fisher's exact test. Propensity scores were calculated using a logistic regression model with the variables of age, sex, antithrombotic agent, heparin bridging, chronic kidney disease with hemodialysis, white blood cell count before ESD, CRP before ESD, location of lesion, tumor size, resection size, resection time, *en-bloc* resection rate, curative resection rate, intraoperative perforation, and pathology findings (histological type, carcinoma depth, and indicators of invasion). After the propensity scores had been estimated, one-to-one matching was performed using the nearest-neighbor method with the caliper set at 0.2. Furthermore, P-values of <0.05 were considered to denote statistical significance. All analyses were performed using JMP Pro 15 software (SAS Institute, Cary, NC, USA).

Results

Clinicopathological characteristics according to the closure and non-closure groups are summarized in Table 1. A total of 114 patients were enrolled: 44 in the closure group and 70 in the non-closure group. Resection time, curative resection rate, and pathological type differed significantly between the 2 groups. Propensity score matching created 32 matched pairs of patients between the 2 groups; these patients' characteristics are summarized in Table 1. The baseline characteristics of the 32 pairs of propensity score-matched patients were comparable.

Outcomes of patient response and measurements before and after propensity analysis are summarized in Table 2. The post-ESD bleeding rate was significantly lower in the closure group than in the non-closure group (0% and 15.6%, respectively; P=0.0264). No delayed perforations occurred in either group. There were no significant differences between the 2 groups regarding white blood cell count, CRP, maximum body temperature, or VRS scores representing the degree of abdominal pain.

The results of closure are shown in Table 3. In the closure group of 44 cases, conventional clip closure and E-LOC were performed in 24 and 20 cases, respectively. The median time (P25-P75) to closure was 24 (range: 14-36) min and the median total procedure time was 51 (range: 35-87.75) min. There were no closure-associated complications such as perforation, bleeding, or stenosis.

Discussion

In this retrospective study, we compared gastric post-ESD bleeding between the closure and non-closure groups of patients receiving antithrombotic agents. There was no post-ESD bleeding in the closure group, compared with a rate of 15.6% in the non-closure group (P=0.0264). Thus, we found that defect closure is efficacious in preventing post-ESD gastric bleeding.

Previous studies have found that antithrombotic therapy poses an elevated risk of post-ESD gastric bleeding, reporting extremely high rates of 11.1-45.4% in patients taking multiple antithrombotic agents [28]. Only a few studies have reported the efficacy of closure after gastric ESD [17,24,25], which is why the main purpose of this study was to clarify whether endoscopic defect closure contributes to the prevention of post-ESD bleeding. In this study, 2 different closure procedures were performed: conventional clip closure and E-LOC. It is often difficult to close large defects after gastric ESD by the conventional clip closure method, because the gastric walls are thick and hard. Kinoshita *et al* reported achieving complete closure of the artificial floor after gastric ESD in 68.2% of patients (15/22) [29]. In the present study, the conventional clip closure group did have some limitations: we excluded patients in whom clip closure was attempted but was unsuccessful. Abe *et al* reported an endoscopic technique for closing large gastric defects with an endoloop and hemoclips [24]. However, this procedure requires a double-channel endoscope. We therefore developed the E-LOC method, which enables closure of large defects after gastric ESD [21]. The E-LOC method was the one mainly used for defect closure after it was devised, at the endoscopists' discretion. Although this procedure requires an endoscopic variceal ligation device, it is novel in that it can be performed with a single-channel endoscope.

Several studies have demonstrated the usefulness of defect closure after ESD in the colon and duodenum. Fujihara *et al* reported that prophylactic closure is effective in reducing inflammatory reactions and abdominal symptoms after ESD for large superficial colorectal neoplasms, without increasing adverse events [19]. Kato *et al* reported that defect closure after duodenal ESD reduces inflammatory reactions, as reflected by serum CRP concentration [30]. In the present study, we found no significant differences between the closure and non-closure groups in the secondary outcomes we selected: namely, increases in white blood cell count, CRP concentration, and maximum body temperature. Larger studies are needed to accurately determine whether such differences exist.

The number of patients undergoing ESD while receiving antithrombotic therapy has recently been increasing, in parallel with the diagnosis of metabolic syndrome. Several studies have shown an association between antithrombotic therapy and an increased risk of post-ESD bleeding [4,9]. Recently, Hatta *et al* reported a model for predicting post-ESD bleeding in patients with early gastric cancer (BEST-J score: Bleeding after ESD Trend from Japan) [31]. This model comprises 10 variables (warfarin, direct oral anticoagulants, chronic kidney disease with hemodialysis, P2Y12 receptor antagonist, aspirin, cilostazol, tumor size >30 mm, tumor located in the lower-third of the stomach, presence of multiple tumors, and interruption of any type of antithrombotic agent). We were not able to analyze all of these factors in the present study; however, we minimized differences between the 2 groups by performing propensity score-matching analysis. There were 5 cases of post-ESD bleeding in the non-closure group after propensity score matching, 1 patient being at intermediate-risk and 4 at high-risk according to BEST-J scores. These results are consistent with those previously reported.

This study has some limitations. First, it was a relatively small, single-center, retrospective study. Second, there were

Table 1 Clinicopathological characteristics of the patients who underwent gastric ESD

Characteristics	Before matching			After matching		
	Closure	Non-closure	P-value	Closure	Non-closure	P-value
	n=44	n=70		n=32	n=32	
Age (years), median (P25-P75)	78 (74 to 84)	77 (72 to 84)	0.5031	79.5 (74.25 to 84)	77.5 (70.5 to 83)	0.4578
Men/women, nTI	39/5	55/15	0.1587	27/5	26/6	0.7403
Antithrombotic therapy						
Aspirin, n (%)	20 (45.5)	27 (38.6)	0.4679	13 (40.6)	16 (50)	0.4509
P2Y12RA, n (%)	6 (13.6)	11 (15.7)	0.7606	5 (15.6)	5 (15.6)	>0.99
Cilostazol, n (%)	7 (15.9)	12 (17.1)	0.8631	5 (15.6)	4 (12.5)	>0.99
Warfarin, n (%)	3 (6.8)	8 (11.4)	0.5258	2 (6.3)	4 (12.5)	0.6719
DOAC, n (%)	7 (15.9)	11 (15.7)	0.9779	6 (18.8)	5 (15.6)	>0.99
DAPT, n (%)	1 (2.3)	2 (2.9)	>0.99	0 (0)	1 (3.1)	>0.99
Heparin bridging, n (%)	0 (0)	5 (7.1)	0.1546	0 (0)	1 (3.1)	>0.99
CKD with hemodialysis, n (%)	3 (6.8)	3 (4.3)	0.6748	1 (3.1)	1 (3.1)	>0.99
WBC count before ESD, median (P25-P75)	5725 (4930-7605)	5350 (4730-6935)	0.5554	5295 (4239-6238)	5500 (4720-6915)	0.3378
CRP before ESD, median (P25-P75)	0.11 (0.04-0.29)	0.09 (0.04-0.23)	0.2188	0.13 (0.05-0.41)	0.105 (0.04-0.21)	0.2718
Lesion location, long axis, n (%)						
Fornix	0 (0)	3 (4.3)	0.2276	0 (0)	2 (6.3)	0.2460
Upper body	5 (11.4)	10 (14.3)	0.4412	4 (12.5)	5 (15.6)	0.5000
Middle body	5 (11.4)	7 (10)	0.7108	3 (9.4)	2 (6.3)	0.8227
Lower body	8 (18.2)	13 (18.6)	0.9583	6 (18.8)	9 (28.1)	0.3747
Angle	8 (18.1)	9 (12.9)	0.4412	6 (18.8)	5 (15.6)	0.7403
Antrum	18 (40.9)	28 (40)	0.9233	13 (40.6)	9 (28.1)	0.2915
Lesion location, short axis, n (%)						
Lesser curvature	20 (45.5)	29 (41.4)	0.6727	17 (53.1)	12 (37.5)	0.2083
Greater curvature	10 (22.7)	17 (24.3)	0.8486	6 (18.8)	8 (25)	0.5448
Anterior wall	9 (20.5)	10 (14.3)	0.3937	5 (15.6)	7 (21.9)	0.7500
Posterior wall	5 (11.4)	14 (20)	0.3047	4 (12.5)	5 (15.6)	>0.99
Tumor size, mean (SD), mm	16.7 (1.7)	16.6 (1.3)	0.9593	16.7 (1.9)	15.0 (1.9)	0.5473
Outcomes associated with ESD						
Resection size, mean (SD), mm	30.1 (2.0)	34.6 (1.6)	0.0706	32.0 (2.0)	30.0 (2.0)	0.4645
Resection time, mean (SD), min	42.0 (41.4)	66.2 (50.7)	0.0093	47.3 (7.4)	48.1 (7.4)	0.9452
En bloc resection, n (%)	44 (100)	70 (100)	>0.99	32 (100)	32 (100)	>0.99
Curative resection, n (%)	44 (100)	64 (91.4)	0.0138	32 (100)	32 (100)	>0.99
Intraoperative perforation, n (%)	1 (2.3)	2 (2.9)	>0.99	0 (0)	1 (3.1)	>0.99
Pathology results						
Histological type, n						
Adenoma	5	0	0.0074	2	0	0.4921
Differentiated carcinoma	36	68	0.0050	27	31	0.0742
Undifferentiated carcinoma	3	0	0.0551	3	0	0.2381
Other	0	2	0.5218	0	1	>0.99
Carcinoma depth, n						
M	43	63	0.0899	31	31	>0.99
SM1	1	2	>0.99	1	0	>0.99
SM2	0	3	0.2827	0	1	>0.99
Indicators of invasion, n						
Lymphatic invasion	0	2	0.5227	0	0	>0.99
Vascular invasion	0	5	0.1544	0	0	>0.99

ESD, endoscopic submucosal dissection; P2Y12RA, P2Y12 receptor antagonist; DOAC, direct oral anticoagulant; DAPT, dual antiplatelet therapy; CKD, chronic kidney disease; WBC, white blood cells; CRP, C-reactive protein; M, mucosal invasion; SM1, submucosal invasion <500 μm from the muscularis mucosa; SM2, submucosal invasion ≥500 μm from the muscularis mucosa; SD, standard deviation

several possible sources of bias in the closure group, including tumor size, because only patients in whom closure had been successful were included. We used propensity score matching to adjust for these factors, which reduced the number of participants even further. A prospective randomized study is needed to confirm the efficacy and safety of closure of post-

Table 2 Outcomes of patient response and measurements

Outcomes	Before matching			After matching		
	Closure	Non-closure	P-value	Closure	Non-closure	P-value
	n=44	n=70		n=32	n=32	
Post-ESD bleeding, n (%)	0 (0)	10 (14.3)	0.0066	0 (0)	5 (15.6)	0.0264
Delayed perforation, n (%)	0 (0)	0 (0)	>0.99	0 (0)	0 (0)	>0.99
WBC count (POD1), median (P25-P75)	7925 (6702.5-9887.5)	7765 (6597.5-9225)	0.4507	7725 (6572.5-8752.5)	7720 (6700-9360)	0.5752
WBC count (POD4), median (P25-P75)	5465 (4852.5-6460)	5840 (4760-7345)	0.6116	5365 (4800-6022.5)	5870 (5095-7242.5)	0.1539
CRP (POD1), median (P25-P75)	0.85 (0.54-1.425)	0.795 (0.4125-1.1425)	0.5202	0.925 (0.6075-1.425)	0.92 (0.52-1.155)	0.8934
CRP (POD4), median (P25-P75)	0.865 (0.5025-1.985)	1.24 (0.8575-2.4825)	0.1433	0.905 (0.6425-1.985)	1.01 (0.76-1.52)	0.3777
Maximum body temperature, median (P25-P75), ℃	37.1 (36.825-37.375)	37.1 (36.875-37.4)	0.8178	37.1 (36.825-37.375)	37.15 (36.8-37.375)	0.8786
Abdominal pain, VRS, median (range)	0 (0-1)	0 (0-2)	0.7786	0 (0-1)	0 (0-2)	0.7325

ESD, endoscopic submucosal dissection; WBC, white blood cells; CRP, C-reactive protein; POD, postoperative day; VRS, verbal rating scale

Table 3 Results of closure technique

Parameters	n=44
Closure technique, conventional clips: E-LOC	24:20
Closure procedure time, median (P25-P75), min	24 (14-36)
Total procedure time, median (P25-P75), min	51 (35-87.75)
Complication rate associated with closure, n (%)	
Perforation	0 (0)
Bleeding	0 (0)
Stenosis	0 (0)

E-LOC, endoscopic ligation with O-ring closure

ESD defects. The VRS had several limitations, one being that the interpretation of descriptors may have been influenced by various factors, such as age, sex and education, which could have led to under- or over-estimation of the patients' experience of pain. Another disadvantage is the limited number of choices (compared with those on numeric and visual analog scales), which may have affected the scale's precision and sensitivity.

In conclusion, endoscopic closure may contribute to decreasing post-ESD gastric bleeding in patients undergoing antithrombotic therapy.

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Summary Box

What is already known:

- Antithrombotic therapy poses an increased risk of gastric bleeding after endoscopic submucosal dissection (ESD)
- Artificial ulcer closure has been shown to prevent delayed complications in the duodenum and colon
- Proton pump inhibitors are effective in preventing delayed bleeding
- Preventive coagulation of blood vessels exposed by performing ESD is effective in preventing delayed bleeding

What the new findings are:

- Endoscopic closure may contribute to decreasing the delayed bleeding after gastric ESD
- We developed the endoscopic ligation with O-ring closure method, which enables closure of large defects after gastric ESD
- We found no significant differences between the closure and non-closure groups in increases in white blood cell count, C-reactive protein concentrations, or maximum body temperature

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