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Author(s)	Ogiyama, Hideharu; Kato, Minoru; Yamaguchi, Shinjiro et al.
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Original Article

Efficacy of prophylactic clip closure in reducing the risk of delayed bleeding after colorectal endoscopic submucosal dissection in patients on anticoagulant therapy: Multicenter prospective study

Hideharu Ogiyama,^{1,4} Minoru Kato,⁵ Shinjiro Yamaguchi,² Takashi Kanesaka,⁶ Takuya Yamada,⁷ Masashi Yamamoto,⁸ Masato Komori,³ Koji Nagaike,⁹ Masanori Nakahara,⁴ Shusaku Tsutsui,¹ Yoshiki Tsujii,⁵ Ryotaro Saita,¹⁰ Hideki Iijima,⁵ Yoshito Hayashi⁵ and Tetsuo Takehara⁵

¹Department of Gastroenterology and Hepatology, Itami City Hospital, ²Department of Gastroenterology, Kansai Rosai Hospital, ³Department of Gastroenterology, Hyogo Prefectural Nishinomiya Hospital, Hyogo, ⁴Department of Gastroenterology and Hepatology, Ikeda Municipal Hospital, ⁵Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, ⁶Department of Gastrointestinal Oncology, Osaka International Cancer Institute, ⁷Department of Gastroenterology and Hepatology, Osaka Rosai Hospital, ⁸Department of Gastroenterology, Toyonaka Municipal Hospital, ⁹Department of Gastroenterology and Hepatology, Suita Municipal Hospital and ¹⁰Department of Medical Innovation, Osaka University Hospital, Osaka, Japan

Objectives: The high rate of delayed bleeding after colorectal endoscopic submucosal dissection (ESD) in patients undergoing anticoagulant therapy remains a problem. Whether prophylactic clip closure reduces the rate of delayed bleeding in these patients is unclear. This study aimed to evaluate the efficacy of prophylactic clip closure in patients receiving anticoagulants.

Methods: This multicenter prospective interventional trial was conducted at nine referral centers in Japan. Patients regularly taking anticoagulants, including warfarin potassium or direct oral anticoagulants, and undergoing ESD for colorectal neoplasms were enrolled. The discontinuation of anticoagulants was minimized according to recent guidelines. After the ESD, post-ESD ulcers were prophylactically closed using endoclips. The primary end-point was the incidence of delayed bleeding. The sample size was 45 lesions, and prophylactic clip closure was considered effective when the upper limit of the 90% confidence interval (CI) for delayed bleeding did not exceed 20%.

Results: Forty-five lesions were used, and three were excluded. Complete closure was achieved in 41/42 lesions (97.6%). The overall delayed bleeding rate was low, at 4.9% (2/41; 90% [CI] 0.8–14.5), which was significantly lower than that at the prespecified threshold of 20% ($P = 0.007$). The median closure procedure time was 17 min, and the median number of clips was nine. No massive delayed bleeding requiring transfusion, interventional radiology, or surgery was observed, and no thromboembolic events were observed.

Conclusion: Prophylactic clip closure may reduce the risk of delayed bleeding following colorectal ESD in patients receiving anticoagulants.

Trial registration: UMIN Clinical Trial Registry (UMIN000036734).

Key words: anticoagulant therapy, antithrombotic drug, colorectal endoscopic submucosal dissection, delayed bleeding, prophylactic clip closure

INTRODUCTION

ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) is a minimally invasive procedure that facilitates

en bloc resection of colorectal neoplasms and accurate histological evaluation. Delayed bleeding is a common adverse event in colorectal ESD, with a frequency of 1–5% reported in previous multicenter studies.^{1–4}

Due to the increase in the older adult population, the number of patients undergoing antithrombotic therapy with anticoagulants has also increased worldwide. In colorectal ESD, our multicenter study and several single-center studies revealed that among patients taking anticoagulants, the risk of delayed bleeding after colorectal ESD was high, at

Corresponding: Tetsuo Takehara, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan. Email: takehara@gh.med.osaka-u.ac.jp

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15–25%.^{5–8} Delayed bleeding can cause a situation requiring a blood transfusion, repeat endoscopy, prolonged hospital stay, or rehospitalization, leading to increased medical costs.

Prophylactic clip closure can prevent delayed bleeding in colonic polypectomies of lesions that are 20 mm or larger and located in a proximal location.^{9–11} In colorectal ESD, only a few studies have reported that prophylactic clip closure contributes to a reduction in the rate of delayed bleeding.^{12–15} These reports were retrospective studies, and except for one meta-analysis, they were conducted at a single center. Therefore, no consensus has been reached on whether prophylactic clip closure reduces delayed bleeding in patients taking anticoagulants.

Thromboembolic events, such as cerebrocardiovascular events, can occur during the discontinuation of anticoagulant therapy and can result in critical situations, including fatal clinical outcomes. To reduce the risk of thromboembolic events, the duration of the interruption of antithrombotic drugs should be minimized during the periendoscopic period, even in high-risk procedures.¹⁶

Radaelli *et al.*¹⁷ reported that in high-risk procedures that contain ESD, bleeding tended to increase when direct oral anticoagulant (DOAC) was administered earlier. The shorter the duration of antithrombotic drug interruption, the greater the risk of delayed bleeding.

Therefore, this study aimed to evaluate the efficacy of prophylactic clip closure for post-ESD ulcers in patients receiving anticoagulant therapy who are at a high risk of delayed bleeding.

METHODS

Study design

THIS MULTICENTER PROSPECTIVE study was performed at one academic and eight tertiary hospitals that participated in the Osaka Gut Forum (OGF1914) between June 2019 and May 2023. This study was approved by the Institutional Review Boards of all participating institutions and registered in the UMIN Clinical Trial Registry (UMIN000036734). This study was conducted in accordance with the 2013 revision of the Declaration of Helsinki. Written informed consent was obtained from all enrolled patients.

Patients

The inclusion criteria were: (i) patients with colorectal neoplasms who met the Japan Gastroenterological Endoscopy Society's (JGES) colorectal ESD indications^{18,19}; (ii) patients taking anticoagulants such as warfarin potassium and DOACs (dabigatran, rivaroxaban, apixaban, and

edoxaban); (iii) tumor diameter of ≤ 5 cm assessed by preoperative endoscopy; (iv) age ≥ 20 years; (v) performance status ≤ 2 ; and (vi) normal primary organ function.

The exclusion criteria were: (i) colorectal neoplasms that spread to the ileum or anal canal; (ii) patients scheduled to receive concurrent endoscopic treatment for a colorectal lesion within the previous 28 days; (iii) patients scheduled to receive chemotherapy, radiotherapy, or surgery within the previous 28 days; (iv) patients diagnosed with any psychiatric illness; and (v) patients who have a metal allergy.

Management of anticoagulant and antiplatelet agents

Perioperative administration of anticoagulant was performed following the JGES guidelines,^{16,20} and the duration of the interruption of antithrombotic drugs was minimized.

Warfarin users were managed with heparin bridge therapy (HBT), continued warfarin therapy, or a temporary switch to DOAC (DOAC replacement). In HBT, warfarin was suspended for 3–5 days before ESD, and unfractionated heparin was administered as an intravenous infusion. Heparin sodium was withheld for at least 3 h before ESD. On the day after ESD, both heparin sodium and warfarin were restarted after confirming the absence of hematochezia. Heparin sodium was discontinued when the international normalized ratio of prothrombin time (PT-INR) reached the therapeutic range.¹⁶

Direct oral anticoagulant users were managed with or without HBT. In patients taking DOAC without HBT, DOAC was only withheld on the day of ESD. In patients taking DOAC with HBT, heparin was administered until the resumption of DOAC treatment on the morning after ESD.²⁰ In patients at a high risk of thromboembolism, ESD was performed on antiplatelet monotherapy with aspirin or cilostazol without discontinuation.²⁰

ESD and prophylactic clip closure procedures

Endoscopic submucosal dissection was performed using the standard protocol. Intraoperative bleeding was coagulated using electrosurgical knives or hemostatic forceps, as appropriate. The degree of submucosal fibrosis was classified into three types (F0–2), as described previously.²¹ Any bleeding in the post-ESD ulcer was coagulated using electrosurgical knives or hemostatic forceps, or stopped by clipping. If blood vessels were observed in the post-ESD ulcer, hemostatic procedures were allowed.

Finally, a prophylactic clip closure was performed until the ulcer base was completely covered by the surrounding

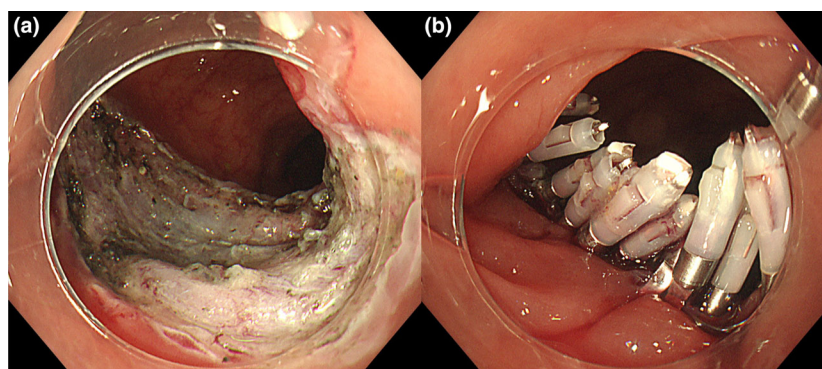


Figure 1 Prophylactic clip closure after colorectal endoscopic submucosal dissection (ESD). (a) Post-ESD ulcer. (b) Complete prophylactic clip closure of the post-ESD ulcer.

mucosa (Fig. 1). Complete closure was considered successful when the ulcer base could not be visualized. Endoscopic images after clip closure were evaluated by central review.

Many closure techniques, including mucosal incision and line-assisted complete closure (LACC), have been previously reported,^{22,23} and each physician selects their preferred closure method. The mucosal incision approach involves making small incisions encircling the ulcer with an ESD knife and closing the incisions with clips.²² The LACC procedure entails collecting both sides of the mucosal defect with a clip attached to a nylon line and placing additional clips to achieve full closure.²³

Study end-points

The primary end-point was a delayed bleeding rate in colorectal ESD within 28 days of the procedure. Delayed bleeding was defined as hematochezia showing stigmata of recent hemorrhage (active bleeding, nonbleeding visible vessel, or adherent clot) on colonoscopy and required hemostasis.²⁴

The secondary end-points included: (i) delayed bleeding severity that necessitated blood transfusion, surgical intervention, or interventional radiology; (ii) onset of delayed bleeding; (iii) prevalence of cardiovascular, cerebral, and systemic thromboembolic events within 28 days after ESD; (iv) prophylactic clip closure time, number of clips, and the rate of lesions that could not achieve complete closure; (v) incidence rate of post-ESD coagulation syndrome (PECS); (vi) length of hospitalization; (vii) rate of delayed perforation; and (viii) ESD-associated or any other adverse events.

Sample size

Combining the data from three previous reports published before study commencement, the point estimate of delayed

bleeding rate after colorectal ESD in patients taking anticoagulants was 20% (13/65 cases),^{6–8} which was set as the null hypothesis. The expected bleeding rate after prophylactic clip closure was set as 5%, which was deemed acceptable in clinical practice. A sample size of 37 cases is required for a one-sample exact test of proportions at a one-sided significance level of 5% and a power of 80%. Considering dropouts and cases in which lesions did not achieve complete closure, the target sample size was set at 45.

Statistical analysis

Continuous variables were presented as medians and ranges, and categorical variables were presented as numbers and proportions. The primary end-point was evaluated using a one-sided exact binomial test. The confidence interval (CI) was based on the Clopper–Pearson method. The per-protocol set (PPS) was defined as all lesions that achieved complete closure and was used in the primary analysis. The full analysis set (FAS) included all lesions, including those that failed to achieve complete closure. The one-sided significance level was set at $P < 0.05$. Statistical analyses were performed using JMP software (version 12.2.0; SAS Institute, Cary, NC, USA).

RESULTS

Background characteristics of patients

FORTY-FOUR PATIENTS WITH 45 lesions were enrolled (Fig. 2). Three lesions were excluded (resected by underwater endoscopic mucosal resection [$n = 1$], no prophylactic clip closure [$n = 1$], and warfarin discontinuation without HBT [$n = 1$]). One lesion did not achieve complete closure, and 41 lesions were analyzed using the PPS dataset.

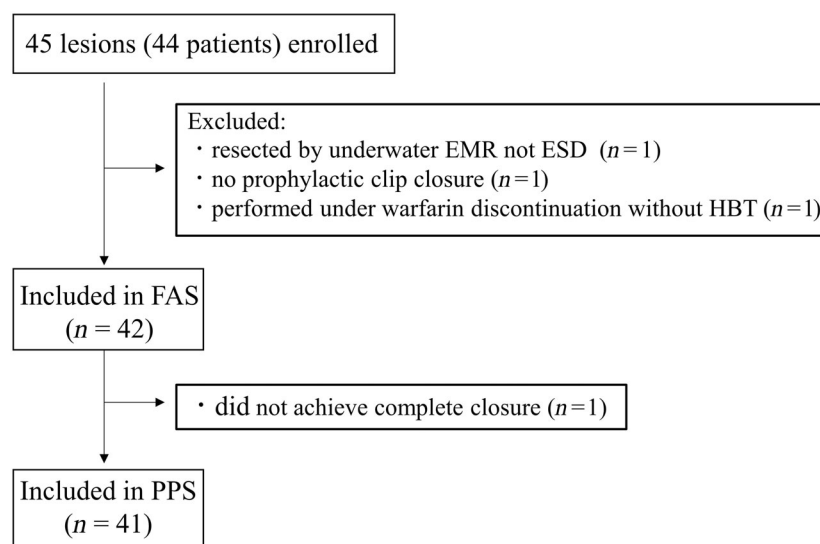


Figure 2 Study flowchart. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FAS, full analysis set; HBT, heparin bridge therapy; PPS, per-protocol set.

Table 1 shows the clinical characteristics of all the included patients and lesions. The median age was 75 years, and 28 patients (68%) were men. Nine patients (22%) received antiplatelet therapy. Regarding anticoagulant therapies, 33 patients were DOAC users and eight were warfarin users. HBT was administered to three patients: two warfarin users and one DOAC user. Perioperative warfarin management included HBT ($n = 2$), warfarin continuation ($n = 5$), and DOAC replacement ($n = 1$). DOAC was discontinued after 1 day with ($n = 1$) and without HBT ($n = 32$).

Table 2 shows the outcomes of ESD and prophylactic clip closure. No intraoperative perforations were observed. En bloc resection was achieved for 41 lesions (97.6%). The median procedure time except closure time was 66 min, and the median diameter of the resected specimens and tumors was 33 and 25 mm, respectively. Only one lesion of 95 mm exceeded 5 cm due to pre-ESD endoscopic underestimation, while the resected tumor diameter of the other lesions was ≤ 5 cm. The hemostatic procedure of post-ESD ulcer just before clip closure was performed in 20 lesions (63%).

Complete closure was achieved in 41/42 (97.6%) lesions. The median closure procedure time was 17 min, and the number of clips was nine (4–23). For the closure method, the numbers of conventional, mucosal incisions, and LACC were 27, 9, and 6, respectively. Complete closure failed in one case in the lower rectum with a mucosal defect size of 30 mm. When the LACC method was performed, however, a thick wall of the lower rectum could not be appropriately gathered by pulling the line (Fig. S1).

Study end-points

Only two patients experienced delayed bleeding in this study (Table 3). In the PPS analysis, the overall delayed bleeding rate was low at 4.9% (2/41; 90% CI 0.8–14.5), which was lower than that at the prespecified threshold of 20% ($P = 0.007$). In FAS analysis, the overall delayed bleeding rate was low, at 4.8% (2/42; 90% CI 0.8–14.2).

Table 4 shows the characteristics and outcomes of the delayed bleeding cases. One bleeding lesion was located in the cecum, and clip closure was performed using a conventional method. Delayed bleeding increased from the gap between the clips (Fig. S2) and occurred three times. Another bleeding lesion was located in the transverse colon, underlying the semilunar fold with fold convergence. The lesion was closed using the mucosal incision method. Colonoscopy at the time of bleeding showed that some clips were detached, and delayed bleeding occurred from a vessel located in an uncovered ulcer. One of the two bleeding lesions had undergone a preventive hemostatic procedure.

No massive delayed bleeding requiring transfusion, interventional radiology, or surgery was observed, and no thromboembolic events were observed in this study. The onset from ESD to delayed bleeding was 3, 8, and 14 days in one case and 1 day in the other. We performed endoscopies to manage delayed bleeding each time and achieved hemostasis by coagulation or clipping. The anticoagulants used in the two patients with bleeding were DOACs (dabigatran and rivaroxaban). In addition to

Table 1 Characteristics of the patients and lesions (full analysis set)

	Total 42 lesions (41 patients)
Age (years), median (range)	75 (53–88)
Sex, men/women	28/13
PS, 0/1/2	26/11/4
Anticoagulants, <i>n</i> (%)	
Warfarin	8 (20)
DOAC	33 (80)
Dabigatran	3 (7)
Apixaban	9 (22)
Edoxaban	11 (27)
Rivaroxaban	10 (24)
Reasons for anticoagulant use, <i>n</i> (%)	
Atrial fibrillation	28 (68)
Deep vein thrombosis	3 (7)
Cardiac valve disease	3 (7)
Ischemic heart disease	1 (2)
Other	6 (15)
Antiplatelet drugs, <i>n</i> (%)	9 (22)
Aspirin	6 (15)
Thienopyridine derivatives	1 (2)
Other	2 (5)
Platelet ($\times 10^4$), median (range)	20.1 (10.1–38.8)
eGFR (mL/min/1.73 m ²), median (range)	56.0 (24.5–92.8)
PT-INR, median (range)	1.26 (0.91–4.30)
APTT (s), median (range)	34.0 (27.9–60.8)
Tumor location, C/A/T/D/S/R	4/13/12/1/5/7
Macroscopic features, LST-G/LST-NG/protruded	14/23/5
Endoscopic fold conversion, <i>n</i> (%)	4 (9)
Management strategy of warfarin	
Heparin bridge therapy, <i>n</i> (%)	2 (25)
Warfarin continuation, <i>n</i> (%)	5 (63)
DOAC replacement, <i>n</i> (%)	1 (13)
Management strategy of DOAC	
Heparin bridge therapy, <i>n</i> (%)	1 (3)

A, ascending colon; APTT, activated partial thromboplastin time; C, cecum; D, descending colon; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; LST-G, laterally spreading tumors, granular type; LST-NG, laterally spreading tumors, non-granular type; PS, performance status; PT-INR, prothrombin time international normalized ratio; R, rectum; S, sigmoid colon; T, transverse colon.

endoscopy, antithrombotic agents were withdrawn for 14 and 2 days, respectively. The median length of hospitalization was 7 days, and in bleeding cases, the lengths of hospitalization were 25 and 8 days. The incidence rate of PECS was 2.3% (1/42). No delayed perforation or other adverse events were observed.

Table 2 Outcomes of endoscopic submucosal dissection (ESD) and prophylactic clip closure (full analysis set)

	Total (<i>n</i> = 42)
Electrosurgical knives	
Flush knife BT/Dual Knife J/Proknife/endosaber/IT nano/SB knife	24/12/2/3/1/1
Electrosurgical generator, VIO3/VIO300D	26/16
Use of hemostatic forceps, <i>n</i> (%)	29 (69.0)
Procedure time (min), median (range)	66 (24–193)
En bloc resection, <i>n</i> (%)	41 (97.6)
Fibrosis (F0/F1/F2) [†]	21/19/2
Resected specimen size (mm), median (range)	33 (23–100)
Resected tumor size (mm), median (range)	25 (15–95)
Histology, adenoma/SSL/adenocarcinoma	21/1/20
Invasion depth of cancer, M/SM1/SM2	17/2/1
Intraoperative perforation	0 (0.0)
Hemostatic procedure of post-ESD ulcer, <i>n</i> (%)	20 (63.0)
Closure procedure time (min), median (range)	17 (3–54)
Number of clips, median (range)	9 (4–23)
Closure method, conventional/mucosal incision/line-assisted complete closure	27/9/6
Complete closure rate, <i>n</i> (%)	41 (97.6)
Delayed bleeding, <i>n</i> (%)	2 (4.8)
Delayed bleeding with endoscopic hemostasis, <i>n</i> (%)	2 (4.8)
Transfusion, <i>n</i> (%)	0 (0.0)
PECS, <i>n</i> (%)	1 (2.3)
Delayed perforation, <i>n</i> (%)	0 (0.0)
Thromboembolism, <i>n</i> (%)	0 (0.0)
Length of hospitalization (days), median (range)	7 (5–25)

[†]The degree of submucosal fibrosis was classified into three types (F0–2), as described previously.²³

M, mucosal; PECS, post-ESD coagulation syndrome; SM, submucosal; SSL, sessile serrated lesion.

Table 3 The incidence rate of delayed bleeding (per-protocol set)

	Delayed bleeding	90% CI
Total, <i>n</i> (%)	2 (4.9)	0.8–14.5%
Antithrombotic drug		
DOAC, <i>n</i> (%)	2 (5.9)	1.1–17.4%
Warfarin, <i>n</i> (%)	0 (0.0)	0.0–34.8%
Antiplatelet drug		
Presence, <i>n</i> (%)	0 (0.0)	0.0–28.3%
Absence, <i>n</i> (%)	2 (6.3)	1.1–18.4%

CI, confidence interval; DOAC, direct oral anticoagulant.

DISCUSSION

TO OUR KNOWLEDGE, this is the first prospective study to reveal the efficacy of prophylactic clip closure

Table 4 Characteristics and outcomes of delayed bleeding cases

No.	Sex	Age (years)	Anticoagulant agents	Heparin bridge therapy	Antiplatelet agents	Location	Macroscopic features	Resected specimen size (mm)	Procedure time (min)	Hemostatic procedure of post-ESD ulcer	Closure method	Number of clips	Closure time (min)	Histology	Blood transfusion	Length of hospitalization (days)	Time from ESD to bleeding (days)
1	M	80	Dabigatran	No	—	Cecum	LST-NG	25	66	Yes	Conventional	5	11	Adenoma	None	25	3, 8, 14
2	M	76	Rivaroxaban	No	—	Transverse	LST-NG	37	55	No	Mucosal incision	7	10	MCa	None	8	1

ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumor, nongranular type; M, male; MCa, mucosal cancer.

in reducing the risk of delayed bleeding after colorectal ESD in patients receiving anticoagulants. The rate of delayed bleeding was 4.9% (90% CI 0.8–14.5), which was lower than that in three previous reports (20%).^{6–8} In this study, the duration of anticoagulant withdrawal was minimized, and no thrombotic events occurred.

A higher rate of delayed bleeding after the endoscopic removal of gastrointestinal neoplasms has been reported in patients taking antithrombotic agents.^{25–28} In particular, among patients on antithrombotic therapy, anticoagulants exert a greater influence on delayed bleeding after ESD than antiplatelets.²⁵ In colorectal ESD, previous studies, including our multicenter study, have shown that patients taking anticoagulants have a higher risk of delayed bleeding (15–25%).^{5–8} Delayed bleeding can cause serious complications requiring emergency endoscopy and transfusions, which increase medical costs in clinical practice. In gastric ESD, preventive coagulation therapy of visible vessels in post-ESD ulcers using hemostatic forceps may reduce the risk of delayed bleeding.²⁹ However, the muscularis propria of the colon is much thinner than that of the stomach; therefore, in colorectal ESD, preventive coagulation may cause excessive damage to the muscularis propria, leading to delayed perforation. Therefore, prophylactic clip closure is a promising procedure to minimize the risk of delayed bleeding.

Delayed bleeding occurred in two cases. One reason for delayed bleeding is that closure of only the mucosa creates a submucosal dead space between the mucosa and muscular layer,³⁰ which makes it difficult to completely close the remaining vessels in the post-ESD ulcer. Another reason is that patients receiving anticoagulants may experience oozing from small vessels besides the penetrating vessels. This bleeding can occur in small areas that cannot be covered by clip closure and, therefore, may not be prevented by clip closure.

In this study we achieved prophylactic clip closure using a conventional method, the mucosal incision method, or LACC method. However, complete closure was not achieved in one patient with a lesion in the rectum. The reason is as follows: the rectum had a thick mucosa and muscularis, similar to those of the stomach,³⁰ making endoscopic closure difficult. Incomplete closure may weaken the effectiveness of decreasing delayed bleeding.

Endoscopic closure of large mucosal defects after ESD is sometimes difficult using conventional clip closure. To address this problem, many endoclip-based techniques, such as the mucosal incision method or the LACC method (which were used in this study), have been developed. However, in some cases, it is difficult to perform complete closure using these techniques. We reported that the failed

prophylactic closure rate in colorectal ESD was 8/103 (7.8%) due to the larger resected specimen/tumor size and a longer procedure time.¹⁴ Yamasaki *et al.*²³ reported that LACC is difficult for lesions located at the flexure. Nomura *et al.*³⁰ described the difficulty of clip closure because the muscularis layer forms the haustra of the colon, and the mucosa and muscularis layers of the rectum are as thick as those of the stomach. In addition to endoclip-based techniques, other closure techniques require special devices, such as the over-the-scope clip,³¹ Overstitch (Apollo Endosurgery, Austin, Texas, USA),³² endoscopic hand-suturing (EHS),³³ and the helix tacking system (X-tack).³⁴ These methods may achieve a more thorough closure than that using endoclip-based techniques. However, they are expensive and time-consuming, especially EHS, and methods other than X-tack require the reinsertion of an endoscope. Overstitch requires a double channel scope and is difficult to perform for proximal colonic lesions; therefore, it is difficult to use these methods in clinical practice. Therefore, a closure method that increases the ratio of complete closures and is more convenient in clinical practice is required.

This study had several limitations. First, we were unable to conduct a randomized study. The delayed bleeding rate after colorectal ESD in patients receiving anticoagulants is reported to be influenced by several factors, including the type of anticoagulants, rectal lesions, HBT, and the procedure time.^{5,35} A recent multicenter study reported a lower bleeding rate, ranging from 7.2% to 18.3%, depending on the anticoagulant, than the estimated rate of 20% in our study.³⁵ This multicenter study contains about 20% of cases with prophylactic clip closure and participating institutions mostly consist of academic centers and cancer specialty facilities, which are considered to be high-volume centers that are reported to have lower bleeding rates.⁴ It is plausible that these points contribute to the lower bleeding rate. To confirm this, a randomized trial should be conducted. However, a small number of patients taking anticoagulants underwent colorectal ESD; therefore, it is difficult to secure the required sample size for a randomized trial. Second, we excluded lesions >5 cm in the preoperative diagnosis and those that spread to the ileum or anal canal, as these lesions can be difficult to close completely. However, the relationship between lesion size and risk of delayed bleeding is controversial.^{36,37}

In conclusion, our study revealed that prophylactic clip closure may reduce the risk of delayed bleeding after colorectal ESD in patients receiving anticoagulants. To confirm the effectiveness of reduced delayed bleeding by prophylactic clip closure, a randomized controlled trial is needed. To make prophylactic clip closures more

effective and acceptable, simpler closure methods should be developed.

CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

FUNDING INFORMATION

NONE.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Figure S1 (a) Postendoscopic submucosal dissection ulcer in the lower rectum with a mucosal defect size of 30 mm. (b) Despite attempting closure with line-assisted complete closure and the conventional method, complete closure could not be achieved for the ulcer.

Figure S2 (a) Complete prophylactic clip closure was performed after endoscopic submucosal dissection. (b) Emergency endoscopy at the bleeding event showed that

the clips remained, and bleeding was not observed initially. (c) Bleeding occurred in the gap between the clips after washing the ulcer with water.