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Original research

Prophylactic clip closure after endoscopic submucosal dissection of large flat and sessile colorectal polyps: a multicentre randomised controlled trial (EPOC trial)

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ABSTRACT

Background Prophylactic clip closure after endoscopic mucosal resection reduces delayed bleeding in large and proximal colon lesions; however, evidence regarding its effectiveness in colorectal endoscopic submucosal dissection (ESD) is lacking.

Objective To compare clinically significant delayed bleeding rates between a clip closure and a control group for flat and sessile 20–50 mm colorectal polyps following ESD.

Design A multicentre randomised controlled trial conducted at four Japanese institutions randomly assigned patients to closure or non-closure groups. Significant postprocedural bleeding (haematochezia) was classified as severe (requiring endoscopic haemostasis or blood transfusion in patients with haemoglobin levels <70 g/L or haemorrhagic shock) or mild.

Results The closure and control groups comprised 150 and 149 cases in the intention-to-treat (ITT) analysis and 142 and 141 cases in the per-protocol (PP) analysis, respectively. Rates of complete clip closure were 88.7% (ITT) and 93.0% (PP). The ITT analysis revealed delayed bleeding rates of 6.7% and 20.1% (OR: 0.28; 95% CI: 0.13 to 0.60; p<0.001; absolute risk difference (ARD): 13.5%; 95% CI: 5.6% to 20.9%) and severe delayed bleeding rates of 1.3% and 8.7% (OR: 0.14; 95% CI: 0.03 to 0.64; p=0.003; ARD: 7.4%; 95% CI: 2.2% to 12.4%) in the closure and control groups, respectively. These differences were confirmed in the PP analysis. Delayed perforation was not observed, and the post-ESD coagulation syndrome rate was not significantly different between the two groups. Multivariate logistic regression analyses identified prophylactic clip closure as a significant independent preventive factor for both delayed bleeding (OR: 0.22; 95% CI: 0.08 to 0.50; p<0.001) and severe delayed bleeding (OR: 0.22; 95% CI: 0.05 to 0.76; p=0.015).

Conclusions Prophylactic clip closure, successfully achieved in approximately 90% of cases, reduced the delayed bleeding rate after resection of colorectal polyps measuring 20–50 mm.

Trial registration number UMIN000043675.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prophylactic clip closure after endoscopic mucosal resection has been shown to reduce the delayed bleeding rate in large and proximal colon lesions. However, evidence regarding its effectiveness in colorectal endoscopic submucosal dissection (ESD) remains limited.

WHAT THIS STUDY ADDS

⇒ In this randomised controlled trial, the prophylactic clip closure after ESD reduces the delayed bleeding rate compared with the control group. Additionally, multivariate logistic regression analyses identified prophylactic clip closure as a considerable independent preventive factor of delayed bleeding.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Prophylactic clip closure should be recommended following colorectal ESD as it decreases the delayed bleeding rate.

INTRODUCTION

Colorectal endoscopic submucosal dissection (ESD) has been increasingly used for en bloc resection of colorectal superficial neoplasms of ≥20 mm in size; however, issues regarding complication measures due to the high degree of difficulty and adverse event rates persisted.[1] Delayed bleeding is one of the most frequent and serious adverse events in colorectal ESD, with a reported incidence of 1.5%–11.9%.[2] Therefore, reducing delayed bleeding is a crucial challenge for safe colorectal ESD.

Recently, four randomised controlled trials (RCTs) regarding endoscopic mucosal resection (EMR) revealed that prophylactic clip closure decreased delayed bleeding in large and proximal colon lesions.[3–6] Colorectal ESD is indicated for large lesions, and prophylactic clip closure may be beneficial, as it is in EMR for large lesions. Therefore, prophylactic clip closure after colorectal ESD potentially protects against delayed bleeding; however, some studies regarding colorectal ESD have not revealed that prophylactic clip closure

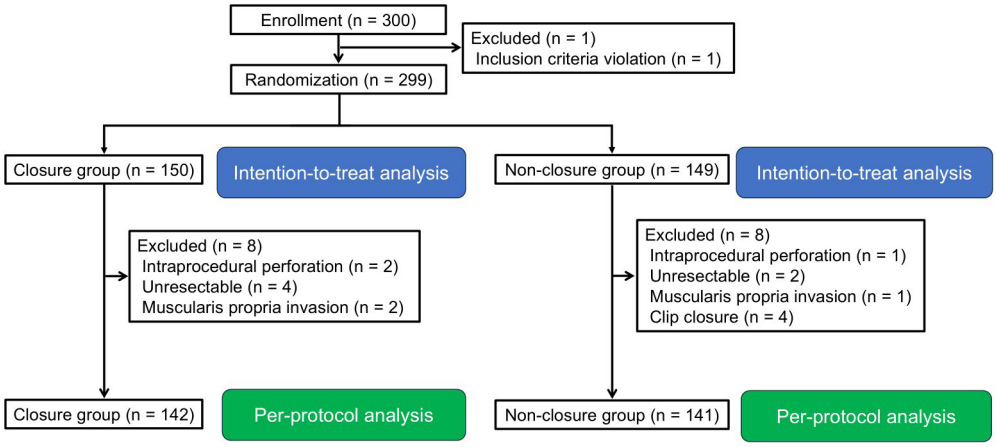

Figure 1 Patient enrolment and randomisation flow chart.

Table 1 Characteristics of patients and lesions in the closure and non-closure groups

	Intention-to-treat		Per-protocol	
	Closure group (n=150)	Non-closure group (n=149)	Closure group (n=142)	Non-closure group (n=141)
Age, mean (SD), years	70.3 (10.6)	70.6 (10.8)	70.4 (10.5)	70.4 (10.8)
Gender, male, n (%)	101 (67.3)	89 (59.7)	96 (67.6)	86 (61.0)
Performance status, n (%)				
0	143 (95.3)	135 (90.6)	136 (95.8)	127 (90.1)
1	6 (4.0)	12 (8.1)	6 (4.2)	12 (8.5)
2	1 (0.7)	2 (1.3)	0 (0.0)	2 (1.4)
Hypertension, n (%)	78 (52.0)	79 (53.0)	73 (51.4)	72 (51.1)
Hyperlipidaemia, n (%)	63 (42.0)	72 (48.3)	58 (40.8)	68 (48.2)
Diabetes mellitus, n (%)	30 (20.0)	34 (22.8)	28 (19.7)	33 (23.4)
Haemodialysis, n (%)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
Antiplatelet agent users, n (%)	15 (10.0)	18 (12.1)	14 (9.9)	17 (12.1)
Anticoagulants users, n (%)	10 (6.7)	5 (3.4)	10 (7.0)	5 (3.5)
Location, n (%)				
Cecum	18 (12.0)	27 (18.1)	17 (12.0)	26 (18.4)
Ascending colon	27 (18.0)	27 (18.1)	27 (19.0)	24 (17.0)
Transverse colon	39 (26.0)	33 (22.2)	38 (26.7)	32 (22.7)
Descending colon	16 (10.7)	7 (4.7)	16 (11.3)	7 (5.0)
Sigmoid colon	27 (18.0)	23 (15.4)	23 (16.2)	22 (15.6)
Rectum	23 (15.3)	32 (21.5)	21 (14.8)	30 (21.3)
Macroscopic type, n (%)				
LST-G	44 (29.3)	45 (30.2)	42 (29.6)	43 (30.5)
LST-NG	78 (52.0)	73 (49.0)	77 (54.2)	70 (49.6)
Sessile lesion	28 (18.7)	31 (20.8)	23 (16.2)	28 (19.9)

LST-G, laterally spreading tumour granular; LST-NG, LST non-granular.

decreases delayed bleeding.[7–9] As mentioned above, the efficacy of prophylactic clip closure after colorectal ESD has been controversial, and no RCTs have set the delayed bleeding rate as the primary endpoint.

Therefore, we conducted the first RCT in which the delayed bleeding rate was set as the primary endpoint to investigate the efficacy of prophylactic clip closure after colorectal ESD.

MATERIALS AND METHODS

Trial design

This prospective, multicentre, parallel two-arm, open-label RCT was conducted at four Japanese institutions between June 2021 and October 2023. This RCT was registered with the University Hospital Medical Information Network Center in Japan (UMIN000043675). Written informed consent for trial participation was obtained from all patients prior to enrolment. The manuscript was prepared under the Consolidated Standards of Reporting Trials guidelines.

Patient involvement

Patients and their families were not involved in setting the research question or the outcome measures; however, they were intimately involved in the design and implementation of the intervention. They also played a central role in disseminating the baseline information, which helped motivate community involvement during and beyond the study.

Inclusion and exclusion criteria of patients

This study screened patients aged ≥20 years, with colorectal neoplasms of 20–50 mm in size that are considered challenging to remove en bloc using EMR, and with an Eastern Cooperative Oncology Group performance status range of 0–2 for inclusion. The exclusion criteria were (1) preoperative endoscopic diagnosis of tumour submucosal invasion depth ≥1000 µm, (2) lesions of local recurrence after endoscopic resection, (3) familial adenomatous polyposis or inflammatory bowel disease, (4) thrombocytopenia, coagulation disorder or bleeding tendency and (5) confirmed or possible pregnancy.

ESD procedure

Six board-certified fellows of the Japan Gastroenterological Endoscopy Society (JGES) and one trainee at four institutions performed all procedures during inpatient management. A colonoscope (PCF-H290TI, PCF-H290ZI, GIF-H290T, GIF-Q260J; Olympus Medical Systems, Tokyo, Japan) that was attached to a transparent soft hood was used with carbon dioxide insufflation. Then, 0.4% sodium hyaluronate (MucoUp; Boston Scientific Japan, Tokyo, Japan) or 0.6% sodium alginate (LiftalK;

Table 2 Clinicopathological characteristics of resected lesions in the closure and non-closure groups

	Intention-to-treat			Per-protocol		
	Closure group (n=150)	Non-closure group (n=149)	P value	Closure group (n=142)	Non-closure group (n=141)	P value
Tumour size, mean (SD), mm	30.0 (11.1)	30.1 (9.4)	0.892	30.0 (11.2)	30.2 (9.5)	0.881
Specimen size, mean (SD), mm	38.9 (11.1)	40.1 (10.5)	0.371	38.9 (11.2)	40.0 (10.7)	0.418
Severe fibrosis, n (%)	25 (16.7)	17 (11.4)	0.244	18 (12.7)	13 (9.2)	0.447
Pathology, n (%)*			0.437			0.287
SSL	16 (11.0)	13 (8.8)		15 (10.6)	12 (8.5)	
LGIN	60 (41.1)	60 (40.8)		60 (42.2)	58 (41.1)	
HGIN	36 (24.6)	52 (35.4)		36 (25.4)	52 (36.9)	
Adenocarcinoma						
T1 (SM<1000 µm)	12 (8.2)	8 (5.4)		12 (8.4)	7 (5.0)	
T1 (SM≥1000 µm)	18 (12.3)	12 (8.2)		17 (12.0)	11 (7.8)	
T2	2 (1.4)	1 (0.7)		—	—	
Other	2 (1.4)	1 (0.7)		2 (1.4)	1 (0.7)	

*In the intention-to-treat analysis, four cases in the closure group and two cases in the non-closure group were missing because the endoscopic submucosal dissections performed were incomplete.
HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia; SM, submucosa; SSL, sessile serrated lesion; T1, submucosal superficial invasive carcinoma; T2, muscularis propria invasive carcinoma.

Kaigen Pharma Co., Osaka, Japan), with small amounts of indigo carmine and epinephrine, were injected into the submucosal layer. Scissor-type knives (SB Knife Jr, SB Knife Jr2; SB-KAWASUMI LABORATORIES, Kawasaki, Japan) or needle knives (DualKnife J; Olympus Medical Systems, ORISE ProKnife; Boston Scientific Japan or TechKnife; MC Medical, Tokyo, Japan) were used for circumferential incision and dissection. The scissor-type and needle knives, as well as haemostatic forceps (Coagrasper; Olympus Medical Systems or RAICHO2; Kaneka Medix Corporation, Osaka, Japan), were used for vessel coagulation as required in continuous intraprocedural bleeding situations. A high-frequency generator (VIO3, VIO300D; Erbe Elektromedizin, Tübingen, Germany) was used to pass current during the procedure. Sedatives and antibiotics were not routinely used. The decision to continue or discontinue treatment for patients undergoing antithrombotic treatment was made based on the guidelines proposed by the JGES.[10 11]

Clip closure

Endoclips (EZ Clip; Olympus Medical Systems, SureClip; MC Medica. or Zeoclip; Zeon Medical, Tokyo, Japan) were used for prophylactic clip closure. The clip closure was initiated from the lateral side of the post-ESD ulcer. Then, additional clips were gradually placed toward the contralateral side. Depending on the situation, the traction device such as endoclip with an attached thread was used to pull the normal mucosa, reducing the ulcer and facilitating easy closure. Complete closure was defined as an ESD ulcer that was not exposed to the lumen. Occasionally, visible vessels on the defect were prophylactically coagulated.

Randomisation and masking

Randomisation was stratified based on lesion location (proximal or distal) and antithrombotic medication history. Proximal location indicated the cecum to the transverse colon, whereas distal location indicated the descending colon to the rectum. Furthermore, an electronic data capture system (University Hospital Medical Information Network Internet Data and Information System for Clinical and Epidemiological Research, Cloud version) was used to randomly assign eligible participants in a 1:1 ratio to the closure or non-closure group through the minimisation method. The operators and assistants were aware of the participant's study arm assignment before the procedure, whereas the participants were not. Endoclips were used for the prophylactic closure of mucosal defects after colorectal ESD in the closure group. Conversely, the post-ESD ulcer was left open in the non-closure group; however, clipping was allowed in cases

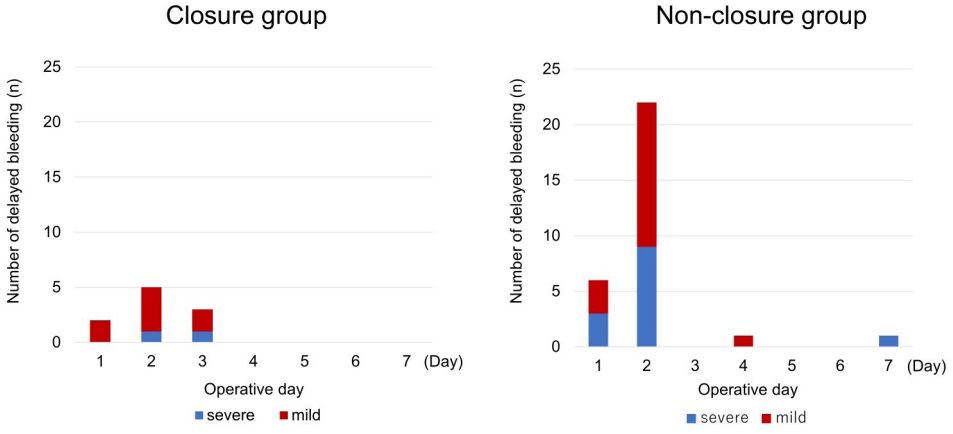

Figure 2 Time-to-event analysis of delayed bleeding in the closure versus non-closure groups.

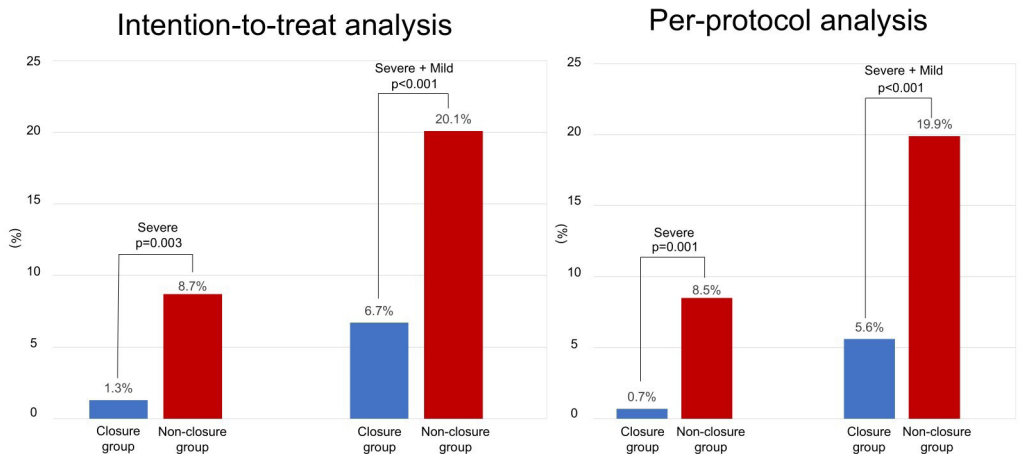

Figure 3 Comparison of delayed bleeding rates in the closure versus non-closure groups.

of uncontrollable bleeding or a high risk of delayed perforation as judged by operators.

Endpoint definitions

The primary endpoint was the delayed bleeding rate 30 days postprocedure, which was categorised into severe and mild delayed bleeding. Severe delayed bleeding was characterised by haematochesia, which required endoscopic haemostasis or blood transfusion, whereas mild delayed bleeding was haematochesia, which required no haemostasis or blood transfusion. The presence of haematochezia, which comprised residual blood, was categorised as mild delayed bleeding. Emergency endoscopy was considered in patients with repeated haematochezia and blood transfusion was considered in patients with haemoglobin levels <70 g/L or haemorrhagic shock.

The secondary endpoints included delayed perforation rate, post-ESD coagulation syndrome (PECS) rate, clip closure time and the number of clips used. As previously reported, PECS was determined based on either of the following findings post-ESD: Visual Analogue Scale (VAS) ≥30 mm or an increase in VAS ≥20 mm from baseline; body temperature ≥37.5°C; and white cell count ≥0.01×10^9/L without extraluminal air.[9] Histopathological diagnosis was performed following the JGES guidelines for colorectal ESD and the Japanese Society for Cancer of the Colon and Rectum guidelines 2019 for colorectal cancer treatment.[1 12] R0 resection was defined as an en bloc resection with negative horizontal and vertical margins. Curative resection was defined as an R0 resection and fulfilment of all of the following characteristics: (1) differentiated or papillary carcinoma; (2) no lymphovascular invasion; (3) submucosal invasion depth <1000 µm and (4) grade 1 budding. Adverse events were reported by each institution and ultimately approved through a central review. All patients were required to attend outpatient follow-up to monitor for adverse events like delayed bleeding.

Statistical analyses

Sample size was based on the delayed bleeding rate. Our retrospective study revealed 2.2% and 5.9% delayed bleeding rates in the closure and non-closure groups, respectively.[13] Furthermore, a previous study showed a 1.5%–11.9% delayed bleeding rate.[2] Therefore, we hypothesised that the prophylactic clip closure after colorectal ESD was adequate under the delayed bleeding rate of 1% and 8% in the closure and non-closure groups, respectively. We estimated that 270 participants would be required to detect a significant difference between the groups with a significance level of two-sided alpha of 0.05 and a power of 80%.

Table 3 Endoscopic submucosal dissection-related outcomes of the closure and non-closure groups

	Intention-to-treat			Per-protocol		
	Closure group (n=150)	Non-closure group (n=149)	P value	Closure group (n=142)	Non-closure group (n=141)	P value
Procedure time, mean (SD), min	47.4 (39.2)	48.2 (29.4)	0.830	46.6 (39.1)	46.0 (25.0)	0.887
En bloc resection, n (%)	145 (96.7)	147 (98.7)	0.448	142 (100.0)	141 (100.0)	
R0 resection, n (%)	140 (93.3)	141 (94.6)	0.809	138 (97.2)	136 (96.5)	0.750
Curative resection, n (%)	122 (81.3)	131 (87.9)	0.149	121 (85.2)	127 (90.1)	0.279
Closure time, mean (SD), min	15.3 (8.8)	—		15.3 (8.8)	—	
Complete closure, n (%)	133 (88.7)	—		132 (93.0)	—	
Number of clips, mean (SD)	15.3 (9.1)	—		15.5 (9.1)	—	
Adverse events, n (%)						
Delayed bleeding	10 (6.7)	30 (20.1)	<0.001	8 (5.6)	28 (19.9)	<0.001
Severe delayed bleeding	2 (1.3)	13 (8.7)	0.003	1 (0.7)	12 (8.5)	0.001
PECS	30 (20.0)	30 (20.1)	1.000	27 (19.0)	27 (19.1)	1.000
Intraprocedural perforation	2 (1.3)	1 (0.7)	1.000	—	—	
Delayed perforation	0 (0)	0 (0)		0 (0)	0 (0)	

PECS, postendoscopic submucosal dissection coagulation syndrome.

Table 4 Predictors of delayed bleeding after colorectal endoscopic submucosal dissection

	Mild and severe delayed bleeding				Severe delayed bleeding			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age >72 years	0.68 (0.35 to 1.34)	0.309	0.53 (0.23 to 1.17)	0.118	0.94 (0.33 to 2.66)	1.000		
Male sex	1.22 (0.60 to 2.48)	0.724			1.61 (0.50 to 5.19)	0.584		
Hypertension	1.81 (0.91 to 3.63)	0.125	1.80 (0.75 to 4.44)	0.188	3.83 (1.06 to 13.88)	0.034		
Hyperlipidaemia	1.25 (0.64 to 2.44)	0.609			5.24 (1.45 to 18.96)	0.007	3.88 (1.08 to 18.46)	0.037
Diabetes mellitus	1.96 (0.95 to 4.07)	0.095			4.65 (1.62 to 13.37)	0.005	3.08 (0.96 to 10.17)	0.060
Haemodialysis	6.61 (0.41 to 107.94)	0.250			20.21 (1.20 to 340.24)	0.098		
Antithrombotic medicine users	1.94 (0.88 to 4.29)	0.107	2.21 (0.81 to 5.91)	0.120	2.80 (0.91 to 8.60)	0.074	1.84 (0.49 to 6.25)	0.351
Tumour location, rectum	7.31 (3.57 to 14.99)	<0.001	7.48 (3.35 to 17.19)	<0.001	2.34 (0.77 to 7.14)	0.164	2.40 (0.66 to 7.93)	0.173
Tumour morphology, LST	0.60 (0.28 to 1.28)	0.201			0.66 (0.20 to 2.15)	0.507		
Pathology, Invasive cancer	2.16 (1.02 to 4.59)	0.049			1.67 (0.51 to 5.44)	0.490		
En bloc resection	0.92 (0.11 to 7.89)	1.000			0.30 (0.03 to 2.68)	0.305		
Fibrosis, severe	2.79 (1.27 to 6.14)	0.014	2.63 (0.94 to 7.10)	0.065	1.57 (0.42 to 5.82)	0.451		
Clip closure	0.31 (0.15 to 0.65)	0.002	0.22 (0.08 to 0.50)	<0.001	0.22 (0.06 to 0.81)	0.016	0.22 (0.05 to 0.76)	0.015
Specimen size >870 mm^2	2.53 (1.23 to 5.22)	0.015	2.38 (1.08 to 5.52)	0.032	2.61 (0.80 to 8.52)	0.169		
Procedure time >39 min	1.69 (0.86 to 3.33)	0.173			2.18 (0.73 to 6.54)	0.190	2.34 (0.76 to 8.19)	0.142

LST, laterally spreading tumour.

Finally, we calculated that 300 patients were required, considering approximately 10% for protocol deviations and dropouts.

All assigned patients were included in the intention-to-treat (ITT) analysis. The per-protocol (PP) analysis excluded the following cases from the ITT analysis: intraprocedural perforation, incomplete ESD, invasion of the muscularis propria and clip closure at the operator's discretion in the non-closure group.

Continuous variables were presented as the mean±SD and compared using the Student's t-test. The Fisher's exact test was used to analyse differences in the categorical variables. Univariate and multivariate logistic regression analyses were conducted to determine the risk factors of delayed bleeding after colorectal ESD. A stepwise method was used to select items for multivariate analysis. A two-sided $p<0.05$ indicated statistical significance. The JMP V.16.1.0 software (SAS Institute Japan, Tokyo, Japan) was used for all statistical analyses.

RESULTS

Baseline characteristics of the enrolled patients and their lesions

This study enrolled 300 patients; however, one was excluded for not meeting the inclusion criteria (figure 1). The patients were randomly assigned to one of two groups: the closure group (n=150) or the non-closure group (n=149) and were analysed using the ITT method. A total of eight cases were excluded from the ITT analysis in both groups. Therefore, the PP analysis included 142 cases in the closure group and 141 cases in the non-closure group. Four patients in the non-closure group experienced intraprocedural muscle layer injury, and prophylactic clip closure was performed to prevent delayed perforation. In two patients, clipping was limited to the injured muscle layer, whereas in the remaining two, complete clip closure was applied to the entire post-ESD ulcer.

Table 1 shows the characteristics of patients and their lesions, whereas table 2 shows the clinicopathological characteristics of the resected lesions. Patient characteristics, lesion factors and clinicopathological characteristics of resected lesions were well-balanced between both groups (tables 1 and 2).

Delayed bleeding rates and other ESD-related outcomes

In the ITT analyses, 19/40 delayed bleeding cases underwent emergency endoscopies. Of the 19 emergent endoscopy cases, 15 required haemostasis and were classified as severe delayed bleeding. In the PP analyses, 17/36 cases with delayed bleeding underwent emergent endoscopies. Among these, 13 required haemostasis and were classified as severe delayed bleeding. All cases requiring haemostasis were treated using clips, and none required blood transfusion. Figure 2 depicts the time-to-event analysis of severe and mild delayed bleeding. The ITT analysis revealed significantly lower delayed bleeding rates in the closure group than in the non-closure group (6.7% (10 cases) vs 20.1% (30 cases); OR: 0.28; 95% CI: 0.13 to 0.60; $p<0.001$, absolute risk difference (ARD): 13.5%; 95% CI: 5.6% to 20.9%) (figure 3, table 3). Furthermore, severe delayed bleeding rates were significantly lower in the closure group than in the non-closure group (1.3% (2 cases) vs 8.7% (13 cases); OR: 0.14; 95% CI: 0.03 to 0.64; $p=0.003$, ARD: 7.4%; 95% CI: 2.2% to 12.4%). The PP analyses also revealed significantly lower delayed and severe delayed bleeding rates in the closure group than in the non-closure group. In the closure group, delayed bleeding tended to decrease regardless of the lesion's location and size (online supplemental table 1). The proportions of complete closure in the ITT and PP analyses were 88.7% and 93.0%, respectively.

PECS and intraprocedural perforation were not significantly different between the groups, and both groups did not demonstrate delayed perforation.

Predictors of delayed bleeding after colorectal ESD

Table 4 shows the predictors of delayed bleeding after colorectal ESD. The multivariate logistic regression analyses identified the prophylactic clip closure as a significant independent preventive factor of delayed bleeding and severe delayed bleeding. Conversely, the rectal lesion and specimen size of >870 mm^2 were determined as significant independent risk factors of delayed bleeding, whereas hyperlipidaemia was determined as a significant independent risk factor of severe delayed bleeding.

DISCUSSION

This multicentre RCT revealed that the severe delayed bleeding rate and overall delayed bleeding rate were significantly lower in the clip closure group compared with the non-closure group after colorectal ESD. Additionally, after conducting multivariate logistic regression analyses, prophylactic clip closure was found to significantly decrease the risk of delayed and severe delayed bleeding. Furthermore, rectal and large lesions emerged as significant independent risk factors for delayed bleeding, whereas hyperlipidaemia was found to be a significant independent risk factor for severe delayed bleeding.

The primary endpoint, delayed bleeding rate, was significantly reduced using prophylactic clip closure after colorectal ESD. To date, several RCTs and meta-analyses regarding EMR revealed the efficacy of prophylactic clip closure in large proximal colon lesions.[3–6 14–19] However, precoagulation and prophylactic haemostasis can be performed intraoperatively in colorectal ESD, potentially preventing delayed bleeding without clip closure compared with EMR. In actual fact, three RCTs validated the efficacy of prophylactic clip closure after colorectal ESD, and no significant difference was noted in delayed bleeding rate.[7–9] However, the delayed bleeding rate was a secondary endpoint in these reports, and the sample size was insufficient for validation. We have retrospectively reported prophylactic clip closure as an independent factor for decreasing delayed bleeding rate.[13] In our current RCT, we conducted an adequate sample size calculation and set the delayed bleeding rate as the primary endpoint based on our and other previous reports and revealed the efficacy of prophylactic clip closure for delayed bleeding. Concerning severe delayed bleeding, which is clinically more important, a similar reduction in delayed bleeding rate was observed. The complete closure rate of this study was 88.7% in the ITT analysis and 93.0% in the PP analysis. These rates are relatively higher than those reported in previous studies.[3–6] The use of novel clips and closure techniques may have contributed to the high complete closure rate, leading to better outcomes for the closure group.[20 21] In this study, the severe and overall delayed bleeding rates were significantly lower in the complete closure group (136 cases) than in the other group (partial/non-closure; 163 cases) (0.7% (1/136 case) vs 8.6% (14/163 cases); $p=0.002$ and 3.7% (5/136 cases) vs 21.5% (35/163 cases); $p<0.001$, respectively). Furthermore, the multivariate logistic regression analyses identified the prophylactic clip closure as a significant independent preventive factor of delayed bleeding. Delayed bleeding tended to decrease in the closure group, regardless of the lesion's location and size. These results strongly confirm the efficacy of prophylactic clip closure, and we highly recommend clip closure to prevent delayed bleeding after colorectal ESD.

The multivariate analysis of current study identified rectal and large lesions as significant independent risk factors for delayed bleeding. Although large and proximal colon lesions related to EMR are associated with a high risk of delayed bleeding and prophylactic clip closure is considered effective, previous colorectal ESD reports showed a higher rate of delayed bleeding in rectal or rectosigmoid lesions. This disparity led to the development of a risk-scoring model that emphasises the importance of these locations.[22 23] Furthermore, Pohl *et al* considered potential explanations for clip failure in rectal lesions, including poorer clipping quality and shorter clip retention time. The latter factor could relate to the thicker wall of the distal colon relative to the proximal colon.[3] Here, the high complete closure rate of the closure group while using 15.3±9.1 clips may have reinforced the wound and prevented delayed bleeding when placed in the thick-walled rectum and large lesions. Increasing the complete closure rate is an urgent issue because previous RCTs regarding clip closure in EMRs with lesions ≥20 mm reported a 57.1%–71.1% successful complete closure rate.[3–6] Currently, various suture techniques have been reported, and establishing more reliable methods for large lesions is anticipated.[20 21]

On multivariate logistic regression analysis, hyperlipidaemia emerged as a significant independent risk factor for severe delayed bleeding. Previous studies found cardiovascular disease increases the risk of delayed bleeding after EMR and polypectomy, leading to the development of a risk-scoring model that emphasises certain comorbidities.[24 25] For example, vascular fragility from comorbid cardiovascular disease can trigger delayed bleeding. In fact, although no significant difference was observed in the current study, there was a tendency suggesting that diabetes mellitus could be a potential risk factor. Similarly, hyperlipidaemia may also be a risk factor for delayed bleeding after ESD.

No significant difference was found between the closure and non-closure groups concerning PECS, which was expected to be prevented by clip closure. A previous RCT revealed that PECS was rather higher in the closure group; however, the study was terminated during its course.[9] Although the PECS criteria of the current study adhered to strict criteria similar to those of the previous study, and the sample size was larger and seemed to have a higher impact, the PECS diagnostic criteria and onset mechanism are not yet completely elucidated.[9] Therefore, based on the current findings, it is difficult to conclude that clip closure is not recommended for PECS prevention, and further investigations are needed.

Although we recommend prophylactic clip closure after colorectal ESD, we require additional information on the cost-effectiveness and labour intensity of this method. Despite using an average of 15.3±8.8 min and 15.3±9.1 clips, no severe delayed bleeding cases were fatal, and haemostasis was successfully established using endoscopy. While four cases underwent prophylactic clip closure at the operator's discretion, our non-closure group had no instances of delayed perforation. Therefore, concerning labour intensity, further validation is warranted to determine the necessity of clip closure for all cases or the superiority of selecting high-risk lesions. One such option could involve limiting clip closure attempts to rectal or large lesions and to patients with hyperlipidaemia as these were also identified as high-risk factors for delayed bleeding via the logistic regression analysis. Other options might include scoring systems. For example, the application of the risk-scoring model proposed by Seo *et al*, which identifies rectosigmoid lesions, lesions measuring ≥30 mm, and antiplatelet agent use, revealed the effectiveness of prophylactic clip closure in high-risk groups during this study's subgroup analyses (online supplemental table 2).[22] Applying this risk-scoring model to the present participants, we found that the specificity and negative predictive value were favourable, making it an effective tool for predicting delayed bleeding. In the future, it may be possible to use such scoring to firmly select high-risk cases that require prophylactic clip closure.

This study has several limitations. First, although inpatient management staff was blinded, the operators were not blinded to the group allocation, raising concerns about potential biases. We cannot rule out the possibility that this design influenced decisions regarding emergency endoscopy and blood transfusion. However, the current study design did not allow for a blinded analysis. Second, the details of treatment strategies, such as suture method, knife selection and high-frequency generator setting, are left to each institution's discretion. However, these are standardised at each facility, and their impact was minimal. On the contrary, the multicentre nature of this study enables the results to be universal, which is the strength of the current study. Third, only Japanese institutions

validated the current study, and the applicability of these favourable outcomes to other countries or races is limited. Therefore, planning multicentre RCT at the global level and meta-analyses is anticipated. Finally, the clip closure-related adverse events, such as stenosis, were unclear due to the unverified long-term clinical outcomes. Thus, long-term case observation is desirable in this study.

In conclusion, we performed the first RCT that set delayed bleeding rate as the primary endpoint to investigate the efficacy of prophylactic clip closure after colorectal ESD, which revealed a decreased delayed bleeding rate. Therefore, we strongly recommend prophylactic clip closure following colorectal ESD to protect against delayed bleeding.

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