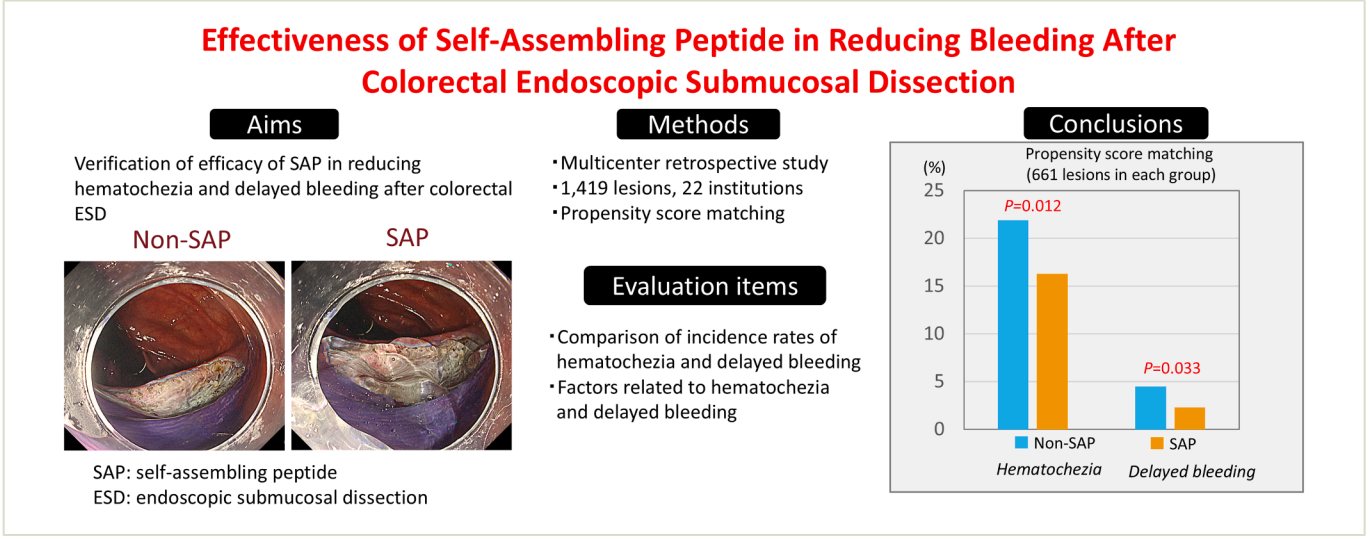
ORIGINAL ARTICLE

Effectiveness of self-assembling peptide in reducing bleeding after colorectal endoscopic submucosal dissection

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GRAPHICAL ABSTRACT



Background and Aims: The newly developed self-assembling peptide (SAP) is expected to exert hemostatic effects on the gastrointestinal tract and promote ulcer healing. However, its efficacy in preventing postprocedural hemorrhage after colorectal endoscopic submucosal dissection (ESD) remains uncertain. This study aimed to determine whether SAP could reduce hematochezia, including delayed bleeding (DB), and prevent its occurrence after colorectal ESD.

Methods: This multicenter retrospective study included 1597 patients with 1654 colorectal ESD-related lesions treated between January 2017 and July 2024. Initially, 1419 lesions were analyzed and categorized into non-SAP and SAP groups. Subsequently, the differences between lesions with and without postprocedural hematochezia and DB were explored. Factors associated with hematochezia and DB were examined using univariate and multivariate logistic regression analyses.

Results: A total of 719 and 700 lesions were assigned to the non-SAP and SAP groups, respectively. The use of SAP was associated with a significant reduction in hematochezia. In addition, SAP significantly reduced DB. SAP was identified as a significant factor in the prevention of hematochezia and DB after colorectal ESD.

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Conclusions: The application of SAP significantly reduced the occurrence of hematochezia and DB after colorectal ESD. Furthermore, SAP was a significant factor associated with the reduction of hematochezia and DB. Therefore, SAP may be appropriate for the prevention of post-ESD bleeding in the colon. (Gastrointest Endosc 2025;■:1-13.)

INTRODUCTION AND BACKGROUND

Colorectal endoscopic submucosal dissection (ESD) has been widely used as a treatment that enables the en bloc resection of early-stage colorectal tumors.[1-4] However, postprocedural adverse events, such as perforation, bleeding, and post-ESD electrocoagulation syndrome, have been reported. Delayed bleeding (DB) is a potentially serious postprocedural adverse event that warrants careful consideration, with an incidence rate of 1.5% to 8.1% reported in clinical studies.[1,2,5-8] In addition, some patients experienced obscure hematochezia or melena that did not fulfill the criteria for DB after ESD. A previous study reported hematochezia in 25% of patients after colorectal ESD.[9] The presence of blood in the stool increases the burden on both patients and medical staff because of the need for frequent monitoring. Consequently, minimizing the occurrence of hematochezia after ESD is strongly desirable.

The newly developed self-assembling peptide (SAP) is expected to exert hemostatic effects on the gastrointestinal tract and promote ulcer healing. Previous studies have demonstrated the hemostatic efficacy of SAP in various conditions, including acute gastrointestinal bleeding[10,11] and intraprocedural bleeding associated with endoscopic procedures.[12] A randomized controlled trial (RCT) evaluating the effect of SAP on intraprocedural bleeding during esophageal, gastric, and colorectal ESD reported a significant reduction in coagulation requirements for intraprocedural hemostasis with SAP application.[12,13] A recent meta-analysis further confirmed that SAP is a safe and effective treatment for gastrointestinal bleeding.[14,15] In addition, SAP has been reported to promote ulcer healing in gastric ulcers,[16] rectal ulcers,[17] and post-ESD ulcers in the colon.[12] Although SAP is recommended for the prevention of postprocedural hemorrhage in Europe and the United States, evidence supporting its effectiveness in preventing DB after endoscopic resection in the colon remains limited.[18]

Therefore, this study primarily focused on hemostatic and ulcer-healing effects of SAP, hypothesizing that its application to colorectal ESD-related ulcers would reduce the incidence of postprocedural bleeding. This study aimed to determine whether the application of SAP could both reduce hematochezia and prevent its occurrence after colorectal ESD.

METHODS

Study patients

This multicenter retrospective study enrolled patients who underwent colorectal ESD between January 2017 and July 2024 at 22 institutions, including academic centers and general hospitals. The patients were divided into the non-SAP group, which comprised patients who did not use SAP, and the SAP group, which consisted of patients who used SAP. As SAP was approved for insurance coverage in Japan in December 2021, patients in the SAP group were enrolled from December 2021, whereas those in the non-SAP group were enrolled from January 2017. To minimize confounding factors affecting DB, patients who could not undergo complete en bloc resection, those who had their ulcers sutured, and those who had insufficient spraying of SAP were excluded. In addition, patients with multiple ESDs performed in the same colon were excluded because it was difficult to identify the specific lesion causing postprocedural bleeding.

This study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki. Furthermore, this study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine (approval number 2023-0025) and was subsequently confirmed and approved by the ethics committees of all participating institutions.

Sample size

At our hospital, the incidence of hematochezia after colorectal ESD was 21%. On the basis of this, the sample size was calculated with the expectation of a 5% to 7% reduction in hematochezia with SAP application. Assuming a statistical power of 0.80, a 2-sided significance level of 0.05, and an α error of 2.5%, the minimum required sample size was estimated to be 588 lesions per group. Data collection began in April 2022, with data on new cases gathered from each facility every 3 months until the number of cases exceeded 600 in each group.

Management of anticoagulants and antithrombotic agents

The cessation and resumption of anticoagulant and antithrombotic agents for ESD were performed in accordance with the guidelines of the Japan Gastroenterological

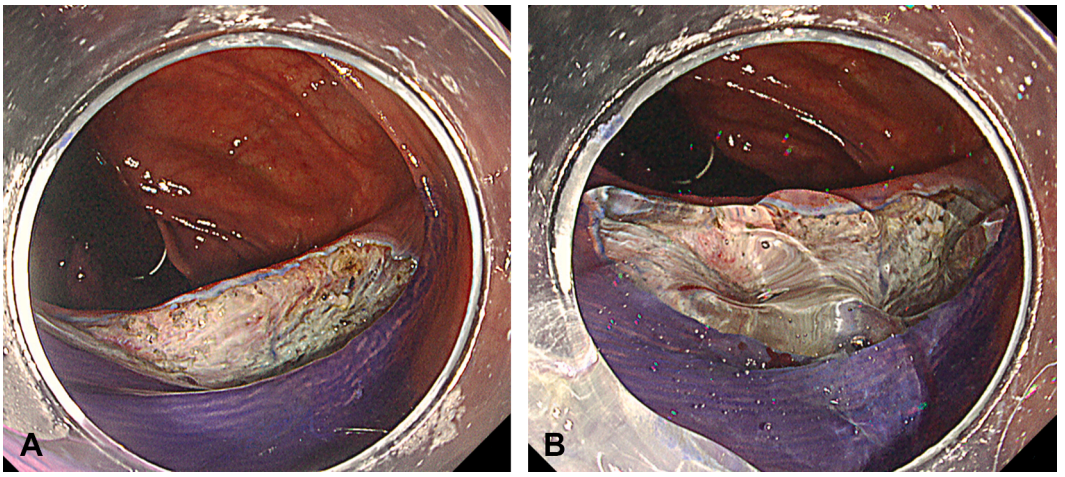


Figure 1. Endoscopic images after colorectal endoscopic submucosal dissection (ESD). **A,** A 30-mm postprocedural ulcer was observed after ESD. **B,** Ulcer covered with self-assembling peptide after ESD.

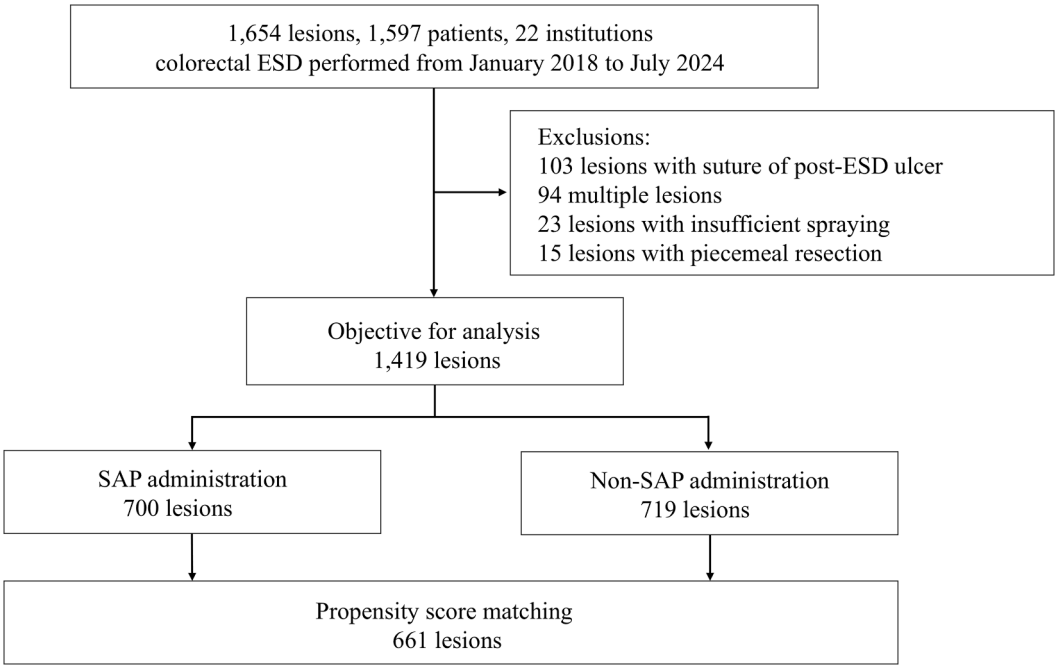


Figure 2. Flowchart of the study design and patient selection. *ESD*, Endoscopic submucosal dissection; *SAP*, self-assembling peptide.

Endoscopy Society (JGES).[19,20] When confirmation was obtained from the prescribing physician regarding the possibility of discontinuing the medication, the agents were withheld following the recommended protocol. For antiplatelet therapy, aspirin was continued or discontinued for 3 to 5 days before ESD. Similarly, cilostazol was continued or discontinued for 1 to 3 days before ESD. Thienopyridine was discontinued 5 to 7 days before ESD. All antiplatelet agents were restarted 1 to 2 days before ESD. For anticoagulant therapy, warfarin was discontinued for 3 to 5 days before ESD, with heparin bridging maintained until the morning of the procedure. Heparin was discontinued for at least 3 hours before ESD. Heparin and warfarin were resumed on day 1 after ESD, with warfarin continued, provided that the prothrombin time/international normalized ratio (PT-INR) remained within the therapeutic range. Direct oral anticoagulants (DOACs) were discontinued 24 to 48 hours before ESD with heparin bridging therapy (HBT). DOACs were restarted on day 1 after ESD. After the 2017 JGES guidelines[20] were published, warfarin was

TABLE 1. Patient-, lesion-, and procedure-related characteristics

Patient	Non-SAP group (*N* = 719)	SAP group (*N* = 700)	*P* value
Age, y (IQR)	72.0 (63.0-77.5)	71.0 (61.0-77.0)	.301
Sex (M/F)	408/311	423/277	.162
Hemoglobin, mg/dL (IQR)			
Pre-ESD	13.3 (12.1-14.4)	13.4 (12.3-14.6)	.016
Post-ESD on POD1	12.8 (11.8-14.0)	13.1 (11.9-14.2)	.010
Comorbidity, *n* (%)			
Cardiovascular disease	97 (13.5)	68 (9.7)	.031
Liver disease	14 (1.9)	10 (1.4)	.539
Chronic kidney disease	25 (3.5)	27 (3.9)	.778
Use of antithrombotic/antiplatelet agents, *n* (%)	108 (15.0)	91 (13.0)	.285
Aspirin	51 (7.1)	35 (5.0)	.099
Antiplatelet agents other than aspirin	24 (3.3)	28 (4.0)	.507
Warfarin	11 (1.5)	4 (0.6)	.078
DOAC	32 (4.5)	28 (4.0)	.673
No. of antithrombotic/antiplatelet agents			
Single/double	99/9	87/4	N/A
Heparin replacement, *n* (%)	11 (1.5)	1 (0.1)	.004
Lesion			
Location			
Right-side colon, *n* (%)	384 (53.4)	366 (52.3)	.672
Left-side colon, *n* (%)	335 (46.6)	334 (47.7)	
Sigmoid colon/rectum, *n* (%)	94/208 (42.0)	92/210 (43.1)	.668
Morphologic type, *n* (%)			
Polypoid	326 (45.3)	276 (39.4)	.028
Nonpolypoid	393 (54.7)	424 (60.6)	
Histology, *n* (%)			<.001
Adenoma	550 (76.5)	455 (65.0)	
Carcinoma (≥T1)	107 (14.9)	175 (25)	
SSL, SSLD	36 (5.0)	42 (6)	
Others	26 (3.6)	28 (4)	
Lesion size, mm (IQR)	28 (20-40)	28 (21-37)	.736
Lesion size ≥40 mm, *n* (%)	190 (26.4)	150 (21.4)	.030
Severe fibrosis, *n* (%)	111 (15.4)	99 (14.1)	.502
Procedure			
En bloc resection, *n* (%)	719 (100)	700 (100)	N/A
Procedure time, min (IQR)	76 (46-120)	79 (50-115)	.629
Intraoperative perforation, *n* (%)	46 (6.4)	31 (4.4)	.115
Hematochezia, *n* (%)	164 (22.8)	114 (16.3)	.002
Mild	129 (17.9)	90 (12.9)	.954
Moderate/severe	27/8 (4.9)	20/4 (3.5)	
Time to first hematochezia, *n* (%)			
<24 h	134 (18.6)	84 (12.0)	.138
≥24 h	30 (4.2)	30 (4.3)	

(*continued on the next page*)

TABLE 1. Continued

Patient	Non-SAP group ($N = 719$)	SAP group ($N = 700$)	*P* value
Day to first hematochezia, d (IQR, range)	1 (1-1, 1-13)	1 (1-2, 1-13)	.125
Hemoglobin >2 mg/dL decrease or blood transfusion, *n* (%)	4 (0.6)	4 (0.6)	.970
Delayed bleeding, *n* (%)	32 (4.5)	16 (2.3)	.027
Endoscopic hemostasis, *n* (%)	28 (3.9)	12 (1.7)	.013

DOAC, Direct oral anticoagulants; *ESD*, endoscopic submucosal dissection; *N/A*, not applicable; *POD*, postoperative day; *SAP*, self-assembling peptide; *SSL*, sessile serrated lesion; *SSLD*, sessile serrated lesion with dysplasia.

continued if the PT-INR was within the therapeutic range. DOACs were discontinued only on the day of ESD, and HBT was not recommended.

Colorectal ESD

The indications for colorectal ESD were determined based on the JGES guideline.[2] Prophylactic vascular coagulation was first performed using an ESD knife. When bleeding could not be stopped, the endoscopists used SAP spraying or hemostatic forceps during the procedure. Injuries to the muscle propria or perforations were managed using clip closure at the discretion of the endoscopist. The degree of submucosal fibrosis was determined as follows: F0, no fibrosis; F1, mild fibrosis; and F2, severe fibrosis characterized by a white, wall-like appearance.[21] In this study, F2 fibrosis was defined as severe fibrosis. Procedure time was defined as the interval from the start of incision to the completion of resection. Blood tests (complete blood count and biochemical parameters) were performed on the following day. Symptoms, including abdominal pain, tenderness, and defecation (eg, hematochezia and melena) along with vital signs, were monitored from the day of ESD.

Definition of hematochezia and DB

Hematochezia was defined as the presence of blood in the stool after colorectal ESD. In cases of bleeding, photographs of the toilet were taken at facilities where objective evaluation was possible. Hematochezia was assessed by nurses and medical doctors at the time of occurrence. The severity of hematochezia was classified as mild, moderate, or severe based on the color of the water in the toilet bowl, following the criteria from a previous study.[9] The classifications were as follows: mild, with clear or slightly pink water around the stool; moderate, with entirely reddish water but a clear bottom; and severe, with reddish water and an unclear bottom. When multiple episodes of hematochezia occurred, the most prominent degree of severity was recorded. DB after colorectal ESD was defined as marked hemorrhage resulting in a decrease in hemoglobin levels by >2 g/dL or requiring endoscopic hemostasis within a specific period after treatment. Hemorrhage occurring within 14 days of ESD was considered either hemorrhage or DB.

Use of SAP

SAP (PuraStat; 3-D Matrix Ltd, Caluire-et-Cuire, France) was used for intraprocedural hemostasis in all cases, following the adaptation protocol in Japan. A single bottle of SAP (3 mL) was used in each case. Residual SAP from the hemostatic procedure was subsequently applied to the bottom of the ulcer after ESD (Fig. 1). In this study, the SAP group was defined as possessing lesions in which >80% of the post-ESD ulcer bed was covered with SAP. The endoscopists determined whether the SAP was sprayed onto more than 80% of the ulcer bed.

Statistical analyses

Continuous variables are expressed as medians with IQRs and were compared using a Mann-Whitney *U* test or a Kruskal-Wallis test. Categorical variables are expressed as proportions and percentages and were compared using the Fisher exact probability test. Univariate and multivariate logistic regression analyses were performed. A P value <.05 was considered significant for all analyses. Propensity score matching was used to match patients, based on the location of the lesion (sigmoid colon/rectal lesions or not), use of anticoagulants and antithrombotic agents, heparin replacement, and lesion size (≥40 mm), all of which have been previously identified as risk factors for DB. All statistical analyses were performed using IBM SPSS Statistics 26 version 29.0.1.0 (171) (IBM Corp, Armonk, NY, USA) software, or EZR, version 1.61 software, which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient flow

Data from 1597 patients with 1654 colorectal ESD lesions were collected during the study period. After applying the exclusion criteria, 235 lesions (103 with post-ESD ulcer sutures, 94 with multiple lesions, 23 with insufficient SAP application, and 15 with piecemeal resection) were excluded. Ultimately, 719 lesions in the non-SAP group and 700 lesions in the SAP group were included in the analysis (Fig. 2).

Baseline patient-, lesion-, and procedure-related characteristics

The baseline characteristics of the patients, lesions, and procedures are summarized in Table 1. A significant difference was observed in the rate of cardiovascular disease as a

TABLE 2. Patient-, lesion-, and procedure-related characteristics after propensity score matching

Patient	Non-SAP group (*N* = 661)	SAP group (*N* = 661)	*P* value
Age, y (IQR)	71 (62-71)	71 (61-77)	.365
Sex (M/F)	380/281	398/263	.342
Hemoglobin, mg/dL (IQR)			
Pre-ESD	13.3 (12.1-14.4)	13.4 (12.3-14.6)	.116
Post-ESD on POD1	12.9 (11.8-14.1)	13.1 (11.9-14.2)	.071
Comorbidity, *n* (%)			
Cardiovascular disease	77 (11.6)	65 (9.8)	.329
Liver disease	12 (1.8)	8 (1.2)	.500
Chronic kidney disease	21 (3.2)	26 (3.9)	.553
Use of antithrombotic/antiplatelet agents, *n* (%)	82 (12.4)	85 (12.9)	.869
Aspirin	41 (6.2)	34 (5.1)	.405
Antiplatelet agents other than aspirin	21 (3.2)	23 (3.5)	.759
Warfarin	3 (0.5)	4 (0.6)	.705
DOAC	23 (3.5)	28 (4.2)	.475
No. of antithrombotic/antiplatelet drug			
Single/double	77/5	81/4	N/A
Heparin replacement, *n* (%)	1 (0.2)	1 (0.2)	1.000
Lesion			
Location			
Right-side colon, *n* (%)	352 (53.3)	349 (52.8)	.869
Left-side colon, *n* (%)	309 (46.7)	312 (47.2)	
Sigmoid colon/rectum, *n* (%)	89/189 (42.1)	84/197 (42.5)	.991
Morphologic type, *n* (%)			
Polypoid	291 (44.0)	262 (39.6)	.118
Nonpolypoid	370 (56.0)	399 (60.4)	
Histology, *n* (%)			<.001
Adenoma	506 (76.6)	428 (64.8)	
Carcinoma (≥T1)	94 (14.2)	168 (25.4)	
SSL, SSLD	36 (5.4)	40 (6.1)	
Others	25 (3.8)	25 (3.8)	
Lesion size, mm (IQR)	27.0 (20.0-37.0)	29.0 (21.0-38.0)	.036
Lesion size ≥40 mm, *n* (%)	150 (22.7)	150 (22.7)	1.000
Severe fibrosis, *n* (%)	94 (14.2)	93 (14.1)	1.000
Procedure			
En bloc resection, *n* (%)	661 (100)	661 (100)	.937
Procedure time, min (IQR)	74 (45-118)	80 (51-117)	.060
Intraoperative perforation, *n* (%)	43 (6.5)	31 (4.7)	.188
Hematochezia, *n* (%)	145 (21.9)	108 (16.3)	.012
Mild	112 (16.9)	85 (12.9)	.782
Moderate/severe	25/8 (5.0)	19/4 (3.5)	
Time to first hematochezia, *n* (%)			
<24 h	118 (17.9)	79 (12.0)	.128
≥24 h	27 (4.1)	29 (4.4)	
Day to first hematochezia, d (IQR, range)	1 (1-1, 1-11)	1 (1-2, 1-13)	.130
Hemoglobin >2 mg/dL decrease or blood transfusion, *n* (%)	4 (0.6)	4 (0.6)	1.000

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TABLE 2. Continued

Patient	Non-SAP group (N = 661)	SAP group (N = 661)	P value
Delayed bleeding, *n* (%)	30 (4.5)	15 (2.3)	.033
Endoscopic hemostasis, *n* (%)	26 (3.9)	11 (1.7)	.012

DOAC, Direct oral anticoagulants; *ESD*, endoscopic submucosal dissection; *N/A*, not applicable; *POD*, postoperative day; *SAP*, self-assembling peptide; *SSL*, sessile serrated lesion; *SSLD*, sessile serrated lesion with dysplasia.

comorbidity between the 2 groups (non-SAP group: 13.5% vs SAP group: 9.7%; P = .031). No significant differences were observed in the proportion of patients taking antiplatelet or anticoagulant agents and the location of lesions in the sigmoid colon/rectum, which are areas prone to post-ESD bleeding. The proportion of lesions ≥40 mm was significantly higher in the non-SAP group (non-SAP group: 26.4% vs SAP group: 21.4%, P = .030). The incidence of hematochezia was significantly lower in the SAP group (non-SAP group: 22.8% vs SAP group: 16.3%, P = .002), and the incidence of DB was also lower in the SAP group (non-SAP group: 4.5% vs SAP group: 2.3%, P = .027). In addition, the rate of endoscopic hemostasis was significantly lower in the SAP group (1.7%) than in the non-SAP group (3.9%) (P = .013). No differences were found in the degree of bleeding or the time to first hematochezia among patients who experienced hematochezia.

Baseline characteristics after propensity score matching

Propensity score matching was performed to adjust for the characteristics influencing hemorrhage after colorectal ESD and to reduce bias in the analysis (Table 2). After matching, 661 lesions from each group were included. Hematochezia was significantly lower in the SAP group (16.3%) than in the non-SAP group (21.9%) (P = .012). The incidence of DB was also significantly lower in the SAP group (2.3%) than in the non-SAP group (4.5%) (P = .033). There was no difference in the degree of hematochezia or the time to the initial occurrence of hematochezia between the 2 groups.

Hematochezia

After ESD, the patients were divided into hematochezia and nonhematochezia groups (H and NH groups, respectively). The characteristics of both groups are shown in Table 3. Overall, 19.6% (278/1419) of the patients experienced hematochezia. No significant differences in comorbidities or antithrombotic/antiplatelet agent use were observed between the H and NH groups. Regarding lesion-related factors, the H group had a higher proportion of lesions located in the sigmoid colon/rectum (P < .001), polypoid lesions (P < .001), and lesions measuring ≥40 mm (P < .001). ESD-related factors also differed between the groups, with the H group showing a higher percentage of severe fibrosis (P < .001) and longer procedure times (P < .001). When analyzing SAP use, the NH group had a significantly higher percentage of patients who received SAP (51.4%) than the H group (41.0%) (P = .002). Colonoscopy for hemostasis was performed in 13.3% of patients with hematochezia. Univariate and multivariate logistic regression analyses were conducted to identify the significant factors associated with hematochezia (Table 4). The univariate analysis revealed location (sigmoid colon/rectum) (odds ratio [OR], 5.464; 95% CI, 4.065-7.344; P < .001), polypoid lesions (OR, 2.535; 95% CI, 1.938-3.317; P < .001), a lesion size of ≥40 mm (OR, 2.199; 95% CI, 1.657-2.917; P < .001), severe fibrosis (OR, 1.981; 95% CI, 1.425-2.756; P < .001), procedure time (OR, 1.005; 95% CI, 1.004-1.007; P < .001), and SAP use (OR, 0.658; 95% CI, 0.505-0.859; P < .001) as significant factors. The multivariate analysis identified the use of antiplatelet or anticoagulant agents (OR, 1.492; 95% CI, 1.016-2.192; P = .041), location (OR, 5.028; 95% CI, 3.646-6.933; P < .001), a lesion size of ≥40 mm (OR, 1.723; 95% CI, 1.208-2.456; P = .003), and procedure time (OR, 1.003; 95% CI, 1.001-1.005; P = .006) as significant factors. Conversely, SAP use (OR, 0.637; 95% CI, 0.478-0.850; P = .002) was the only factor significantly associated with a reduction in the incidence of hematochezia.

Delayed bleeding

In the study cohort, DB occurred in 3.4% (48/1419) of patients. Patients were divided into DB and non-DB groups (Table 5). The DB group had a significantly higher use of antiplatelet or anticoagulant agents (P = .004), a higher proportion of lesions located in the sigmoid colon/rectum (P = .017), a significantly longer procedure time (P < .001), and a significantly lower rate of SAP use (P = .027). Risk factors for DB were analyzed using univariate and multivariate analyses (Table 6). Univariate analysis identified cardiovascular disease (OR, 2.065; 95% CI, 1.009-4.226; P = .047), use of antiplatelet or anticoagulant agents (OR, 2.111; 95% CI, 1.079-4.130; P = .029), location (OR, 2.113; 95% CI, 1.173-3.805; P = .013), procedure time (OR, 1.006; 95% CI, 1.003-1.008; P < .001), and SAP use (OR, 0.502; 95% CI, 0.273-0.924; P = .027) as significant factors. In the multivariate analysis, location (OR, 1.939; 95% CI, 1.063-3.537; P = .031) and procedure time (OR, 1.005; 95% CI, 1.002-1.009; P < .001) remained significant predictors of DB. SAP (OR, 0.516; 95% CI, 0.278-0.957; P = .036) was also determined to be a significant factor associated with a reduction in DB.

TABLE 3. Comparison of characteristics between patients with and without hematochezia

Patient	Nonhematochezia group ($N = 1141$)	Hematochezia group ($N = 278$)	*P* value
Age, y (IQR)	71 (62-77)	72 (60-78)	.815
Sex (M/F)	670/471	161/117	.839
Hemoglobin, mg/dL (IQR)			
Pre-ESD	13.4 (12.2-14.5)	12.2 (12.2-14.4)	.797
Post-ESD on POD1	13.0 (11.9-14.1)	12.9 (11.8-14.0)	.645
Comorbidity, *n* (%)			
Cardiovascular disease	130 (11.4)	35 (12.6)	.602
Liver disease	22 (1.9)	2 (0.7)	.201
Chronic kidney disease	42 (3.7)	10 (3.6)	1.000
Use of antithrombotic/antiplatelet agents, *n* (%)	150 (13.1)	49 (17.6)	.067
Aspirin	67 (5.9)	19 (6.8)	.546
Antiplatelet agents other than aspirin	37 (3.2)	15 (5.4)	.087
Warfarin	7 (0.6)	8 (2.9)	.001
DOAC	48 (4.2)	12 (4.3)	.935
No. of antithrombotic/antiplatelet drugs			
Single/double	143/7	43/6	N/A
Heparin replacement, *n* (%)	8 (0.7)	4 (1.4)	.228
Lesion			
Location			
Right-side colon, *n* (%)	685 (60.0)	65 (23.4)	<.001
Left-side colon, *n* (%)	456 (40.0)	213 (76.6)	
Sigmoid colon/rectum, *n* (%)	154/243 (34.8)	32/175 (74.5)	<.001
Morphologic type, *n* (%)			
Polypoid	433 (37.9)	169 (60.8)	<.001
Nonpolypoid	708 (62.1)	109 (39.2)	
Histology, *n* (%)			.41
Adenoma	805 (70.6)	200 (71.9)	
Carcinoma (≥T1)	224 (19.6)	58 (20.9)	
SSL, SSLD	69 (6.0)	9 (3.2)	
Others	43 (3.8)	11 (4.0)	
Lesion size, mm (IQR)	27.0 (20.0-37.0)	31.0 (24.0-50.0)	<.001
Lesion size ≥40 mm, *n* (%)	238 (20.9)	102 (36.7)	<.001
Severe fibrosis, *n* (%)	147 (12.9)	63 (22.7)	<.001
Use of SAP, *n* (%)	586 (51.4)	114 (41.0)	.002
Day to first hematochezia, d (IQR, range)	N/A	1 (1-1, 1-13)	
Procedure			
Procedure time, min (IQR)	74 (47-112)	100 (60-150)	<.001
Procedure time ≥120 min, *n* (%)	251 (22.0)	113 (40.6)	<.001
Endoscopic hemostasis, *n* (%)	N/A	37 (13.3)	

DOAC, Direct oral anticoagulants; *ESD*, endoscopic submucosal dissection; *N/A*, not applicable; *POD*, postoperative day; *SAP*, self-assembling peptide; *SSL*, sessile serrated lesion; *SSLD*, sessile serrated lesion with dysplasia.

Hospitalization

Hospitalization duration was analyzed in 1199 patients after excluding 220 patients whose prolonged hospitalization was due to reasons other than bleeding (eg, perforation, post-endoscopic coagulation syndrome, or patient preference) (Fig. 3). The median length of hospitalization (IQR) was 6 days (5-8 days) in the hematochezia group and 5 days (5-7 days) in the nonhematochezia group, indicating a statistically significant prolongation in the hematochezia group ($P < .001$) (Fig. 3A). In addition,

TABLE 4. Logistic regression analysis of factors related to hematochezia

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	0.998	0.986-1.009	.704			
Sex	0.967	0.742-1.262	.807			
Cardiovascular disease	1.120	0.752-1.669	.577			
Chronic kidney disease	0.976	0.484-1.971	.947			
Use of antithrombotic/antiplatelet agents	1.414	0.993-2.012	.055	1.492	1.016-2.192	.041
Location (sigmoid colon/rectum)	5.464	4.065-7.344	<.001	5.028	3.646-6.933	<.001
Polypoid lesion	2.535	1.938-3.317	<.001	1.321	0.971-1.796	.076
Lesion size ≥40 mm	2.199	1.657-2.917	<.001	1.723	1.208-2.456	.003
Severe fibrosis	1.981	1.425-2.756	<.001	1.255	0.850-1.851	.253
Procedure time	1.005	1.004-1.007	<.001	1.003	1.001-1.005	.006
Use of SAP	0.658	0.505-0.859	.002	0.637	0.478-0.850	.002

OR, Odds ratio; *SAP*, self-assembling peptide.

significant differences in the length of hospitalization were observed among the nonhematochezia, hematochezia (excluding DB), and DB groups ($P < .001$) (Fig. 3B).

DISCUSSION

This study aimed to determine whether the application of SAP after colorectal ESD could reduce hematochezia and prevent its occurrence. Our findings indicate that SAP use significantly reduced the incidence of hematochezia and emerged as an independent factor in the prevention of post-ESD hematochezia. In addition, SAP demonstrated a preventive effect not only against hematochezia but also against DB. This is a large-scale study to demonstrate the efficacy of SAP in reducing post-ESD bleeding in real-world practice.

Tani et al[9] reported that hematochezia occurs in approximately 25% of cases after colorectal ESD, which aligns with the incidence observed in this study. Although hematochezia after ESD is generally not considered a severe adverse event, its occurrence poses a clinical challenge. Notably, endoscopic hemostasis is required in only 2% of patients, even when hematochezia is present.[9] However, hematochezia leads to prolonged hospitalization because of the need for fasting and conservative treatment, resulting in physical and psychological distress for patients. It also increases the burden on medical staff, who must frequently monitor vital signs and respond to bleeding events, whereas physicians must remain prepared for potential emergency endoscopic treatment. Therefore, reducing the incidence of hematochezia is clinically beneficial. In contrast, DB is one of the most serious postprocedural ESD adverse events, often leading to shock and requiring blood transfusion and endoscopic hemostasis. Previous studies have identified several risk factors for DB, including the use of hot biopsy for hemostasis,[22] incomplete suturing of the postresection ulcer,[23] lesion size ≥40 mm,[23,24] presence of rectal lesions,[24] long procedure time,[25] and arterial bleeding during ESD.[7] Given its severity, DB must be prevented, underscoring the importance of developing reliable prophylactic strategies. Because of the low incidence of post-ESD bleeding in clinical practice, the overall clinical impact of our findings could appear limited. Therefore, it is essential to minimize ESD-related bleeding. We believe that the simple and effective prevention of post-ESD bleeding using SAP is clinically meaningful.

Conversely, prophylactic closure using hemostatic clips has been reported as a preventive measure against DB. Several retrospective studies have demonstrated the efficacy of clip closure in preventing DB after colorectal ESD.[26-28] A recent meta-analysis further confirmed that prophylactic closure after colorectal ESD significantly reduced the incidence of DB from 5.2% to 0.9%.[29] However, this approach is associated with additional costs and longer procedure times, raising concerns regarding its indications and cost-effectiveness.[30] Thus, simple and time-saving methods are required.

Recently, a meta-analysis by Gopakumar et al[31] examining the incidence of DB with SAP reported a DB rate of 5.1% after colorectal endoscopic resection. However, the analysis included various procedures, such as EMR and ESD, and involved a relatively small number of cases. More importantly, the report did not directly compare the effects of SAP on bleeding after colorectal endoscopic resection. In the latest RCT by Drews et al,[18] SAP application did not reduce the DB rate after resection of large colorectal lesions (≥20 mm). However, their study used EMR for resection, and the lesion distribution differed from that in our cohort. Moreover, rectal lesions, known to carry a higher risk of postprocedural bleeding, accounted for only 7.2% of cases in the study. In contrast, a cohort trial on ESD reported rectal lesions in 25.5% of patients.[5] Given this

TABLE 5. Characteristics of patients with and without delayed bleeding

Patient	No DB group ($N = 1371$)	DB group ($N = 48$)	*P* value
Age, y (IQR)	71 (62-77)	72 (64-79)	.673
Sex (M/F)	801/570	30/18	.656
Hemoglobin, mg/dL (IQR)			
Pre-ESD	13.4 (12.2-14.5)	13.3 (12.3-14.5)	.899
Post-ESD on POD1	12.9 (11.8-14.1)	12.8 (11.9-14.3)	.972
Comorbidity, *n* (%)			
Cardiovascular disease	155 (11.3)	10 (20.8)	.062
Liver disease	24 (1.8)	0 (0)	1.000
Chronic kidney disease	49 (3.6)	3 (6.3)	.256
Use of antithrombotic/antiplatelet agents, *n* (%)	187 (13.6)	12 (25.0)	.004
Aspirin	81 (5.9)	5 (10.4)	.198
Antiplatelet agents other than aspirin	51 (3.7)	1 (2.1)	.553
Warfarin	12 (0.9)	3 (6.3)	<.001
DOAC	56 (4.1)	4 (8.3)	.151
No. of antithrombotic drugs			
Single/double	176/11	10/2	N/A
Heparin replacement, *n* (%)	11 (0.8)	1 (2.1)	.341
Lesion			
Location			
Right-side colon, *n* (%)	731 (53.3)	19 (39.6)	.061
Left-side colon, *n* (%)	640 (46.7)	29 (60.4)	
Sigmoid colon/rectum, *n* (%)	182/393 (41.9)	4/25 (60.4)	.017
Morphologic type, *n* (%)			
Polypoid	579 (42.2)	23 (47.9)	.460
Nonpolypoid	792 (57.8)	25 (52.1)	
Histology, *n* (%)			.70
Adenoma	972 (70.9)	33 (68.8)	
Carcinoma (≥T1)	270 (19.7)	12 (25.0)	
SSL, SSLD	75 (5.5)	3 (6.2)	
Others	54 (3.9)	0 (0)	
Lesion size, mm (IQR)	28.0 (20.0-38.0)	31.0 (23.8-52.5)	.025
Lesion size ≥40 mm, *n* (%)	323 (23.6)	17 (35.4)	.083
Severe fibrosis, *n* (%)	199 (14.5)	11 (22.9)	.143
Use of SAP, *n* (%)	684 (49.9)	16 (33.3)	.027
Day to first DB, d (IQR, range)	N/A	2 (1-5.5, 1-13)	
Procedure			
Procedure time, min (IQR)	76 (48-119)	117 (68-174)	<.001
Procedure time ≥120 min, *n* (%)	341 (24.9)	23 (47.9)	<.001
Endoscopic hemostasis, *n* (%)	N/A	37 (77.1)	

DB, Delayed bleeding; *DOAC*, direct oral anticoagulants; *ESD*, endoscopic submucosal dissection; *N/A*; not applicable; *POD*, postoperative day; *SAP*, self-assembling peptide; *SSL*, sessile serrated lesion; *SSLD*, sessile serrated lesion with dysplasia.

percentage, our study reflects real-world clinical practice for colorectal ESD.

This study investigated the effectiveness of SAP in preventing hematochezia after colorectal ESD. The incidence rates of hematochezia and DB in our study were consistent with those reported in previous studies, supporting the relevance of our cohort for further investigation. Both hematochezia and DB occurred significantly less frequently in the SAP group than in the non-SAP group. However, the non-SAP group presented characteristics that were more

TABLE 6. Logistic regression analysis of factors related to delayed bleeding

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.001	0.976-1.027	.944			
Sex	1.186	0.655-2.148	.574			
Cardiovascular disease	2.065	1.009-4.226	.047	1.516	0.604-3.803	.375
Chronic kidney disease	1.779	0.540-5.990	.339			
Use of antithrombotic/antiplatelet agents	2.111	1.079-4.130	.029	1.730	0.773-4.086	.221
Location (sigmoid colon/rectum)	2.113	1.173-3.805	.013	1.939	1.063-3.537	.031
Polypoid lesion	1.258	0.707-2.239	.434			
Lesion size ≥40 mm	1.779	0.972-3.257	.062	0.958	0.462-1.988	.908
Severe fibrosis	1.751	0.879-3.490	.111	0.988	0.451-2.167	.977
Procedure time	1.006	1.003-1.008	<.001	1.005	1.002-1.009	.001
Use of SAP	0.502	0.273-0.924	.027	0.516	0.278-0.957	.036

OR, Odds ratio; *SAP*, self-assembling peptide.

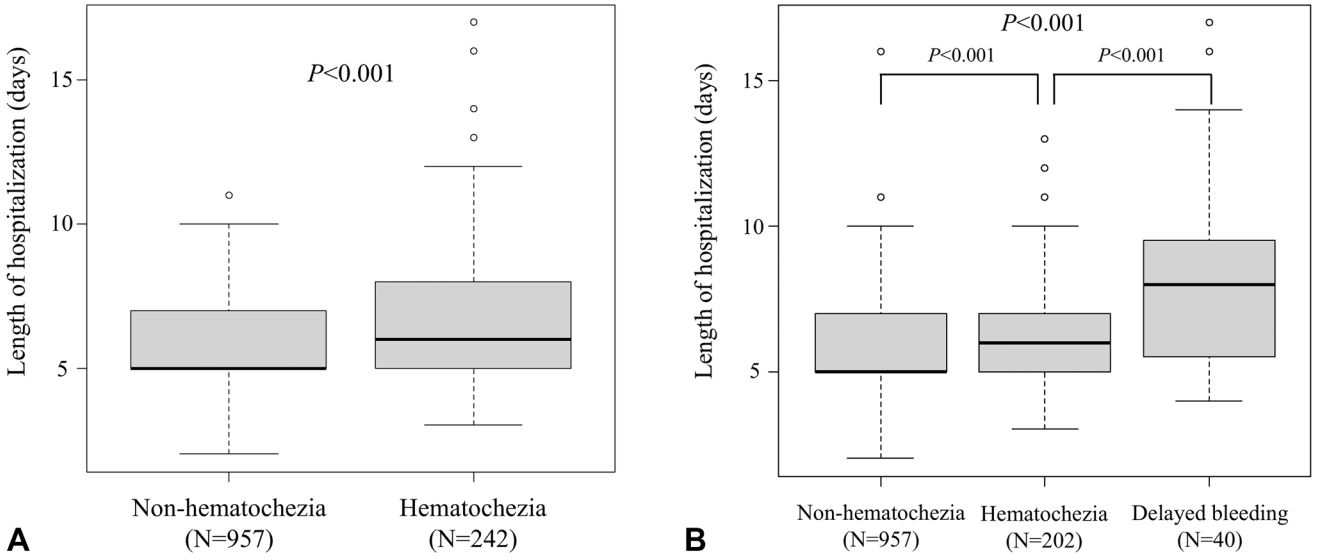


Figure 3. Comparison of hospitalizations. **A,** Comparison of hospitalization duration between patients without and with hematochezia. **B,** Comparison of hospitalization duration among 3 groups: nonhematochezia, hematochezia (excluding delayed bleeding), and delayed bleeding.

likely to predispose to hematochezia, including a higher prevalence of cardiovascular disease history, heparin replacement, and a lesion size of ≥40 mm. To address these imbalances, propensity score matching was applied to adjust for key background characteristics related to post-ESD bleeding, namely, location, use of antithrombotic/antiplatelet agents, heparin replacement, and a lesion size of ≥40 mm. After matching, the SAP group showed significantly lower incidence rates of hematochezia and DB. Multivariate analysis further confirmed that SAP was the sole factor independently associated with hematochezia reduction. Notably, in patients receiving anticoagulant or antiplatelet agents, both hematochezia and DB decreased without significant differences (Supplementary Table 1, available online at www.giejournal.org). SAP may be effective in preventing hematochezia after ESD in patients receiving anticoagulant/antiplatelet therapy. Furthermore, we visualized the number of days from ESD to the onset of bleeding (Supplementary Fig. 1, available online at www.giejournal.org). In the cases of hematochezia and DB, there was no significant difference between the non-SAP and SAP groups (Tables 1 and 2).

SAP appears to be effective in preventing post-ESD hemorrhage by forming an extracellular scaffold matrix triggered by the pH change upon contact with blood. When evaluating the effectiveness of SAP, it is important to determine whether the SAP remains attached to the ulcer bed for a certain period of time. Regarding the point, animal studies have shown that SAP adheres to the ulcer bed for several days.[32]

This study had some limitations. First, the retrospective design and endoscopist-directed allocation of SAP use

introduced a potential selection bias. Second, SAP was used for intraoperative bleeding, with the remaining amount sprayed on the ulcer bed after ESD, as insurance in Japan covers its use only during active endoscopic procedures. To address this, the application was limited to cases in which at least 80% of the ulcer base could be covered. However, quantification of SAP coverage and objective evaluations were not performed. The criterion for 80% ulcer coverage after ESD was determined based on the endoscopist's subjective assessment. Third, variations in endoscopist skill levels may have influenced vessel handling and hemostasis during ESD. Fourth, additional thermal coagulation using hemostatic forceps was permitted after ESD, which could have affected the outcomes. However, postprocedural coagulation is commonly performed in clinical practice, which presents a challenge for isolating the efficacy of SAP alone. Fifth, the enrollment period differed between the SAP and non-SAP groups. However, most patients in this study were treated after 2022, and the timing of ESD likely had a minimal influence on postprocedural bleeding risk, reducing concerns about major bias. Sixth, the efficacy of SAP in this report cannot be generalized to quite large lesions where sufficient coverage is difficult to achieve.

In conclusion, this study demonstrated that SAP significantly reduced hematochezia and DB after colorectal ESD. These findings highlight the novel hemostatic effect of SAP on post-ESD bleeding. However, a prospective multicenter RCT is warranted for a more accurate evaluation.

PATIENT CONSENT

Informed consent was obtained through an opt-out process, with study details disclosed on the website of the Department of Gastroenterology and Hepatology, Nagoya University (https://www.med.nagoya-u.ac.jp/gastroenterology/research/).

DISCLOSURE

All authors declare that they have no conflicts of interest. No funding was received for this study.

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DIVERSITY, EQUITY, AND INCLUSION

We worked to ensure gender balance in the recruitment of human subjects. We worked to ensure ethnic or other types of diversity in the recruitment of human subjects.

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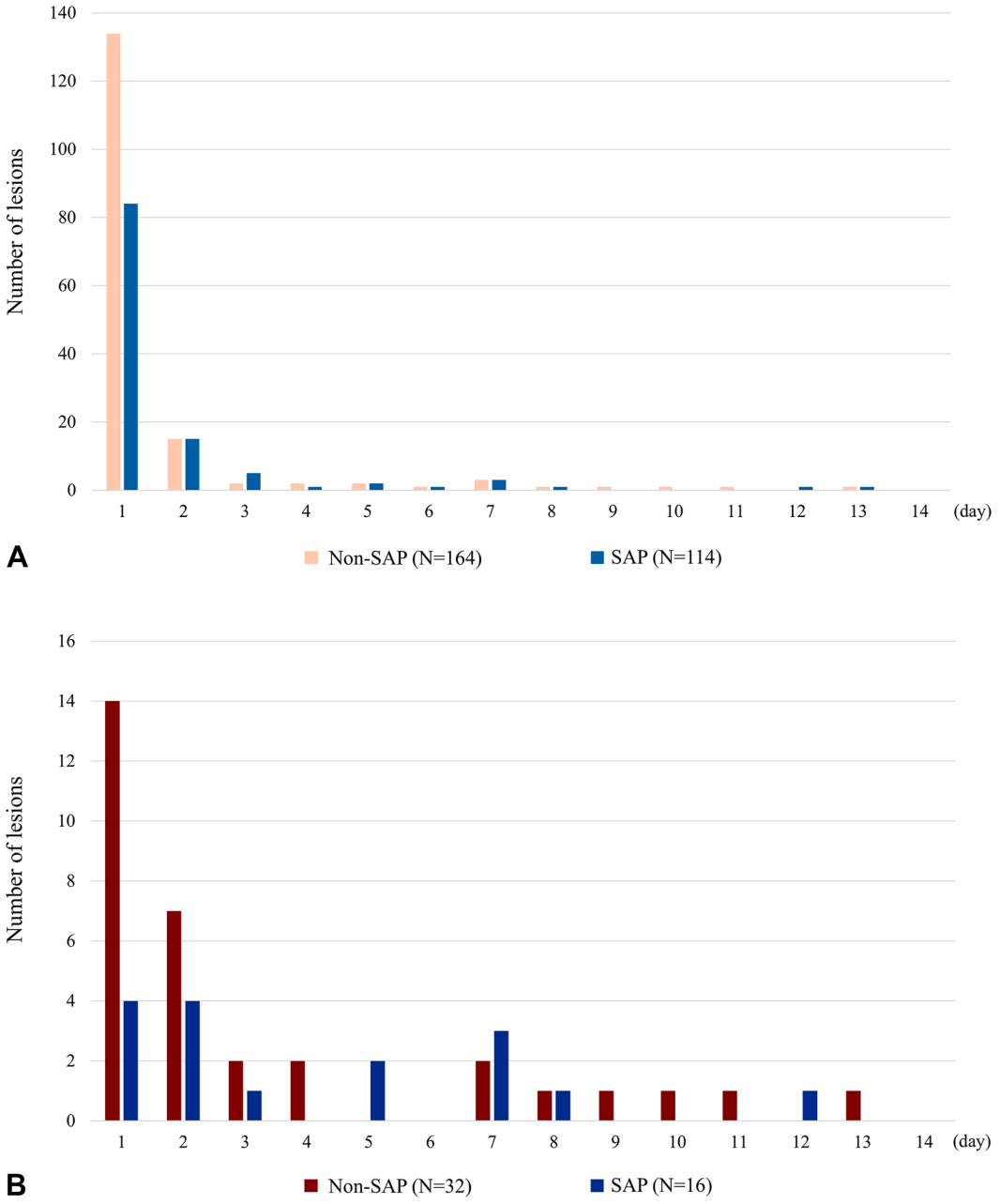
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Abbreviations: DB, delayed bleeding; DOACs, direct oral anticoagulants; ESD, endoscopic submucosal dissection; JGES, Japan Gastroenterological Endoscopy Society; OR, odds ratio; PT-INR, prothrombin time/international normalized ratio; RCT, randomized controlled trial; SAP, self-assembling peptide.

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Supplementary Figure 1. The number of days from endoscopic submucosal dissection to the onset of first bleeding **A,** Hematochezia. **B,** Delayed bleeding. *SAP*, Self-assembling peptide.

SUPPLEMENTARY TABLE 1. Characteristics of patients on antithrombotic/antiplatelet therapy

	Non-SAP group (*N* = 108)	SAP group (*N* = 91)	*P* value
Lesion			
Location			.153
Cecum-descending colon	66 (61.1)	46 (50.5)	
Sigmoid colon/rectum	42 (38.9)	45 (49.5)	
Lesion size ≥40 mm, *n* (%)	27 (25.0)	21 (23.1)	.868
Result			
Hematochezia, *n* (%)	31 (28.7)	18 (19.8)	.186
Mild	22 (20.4)	15 (16.5)	.332
Moderate/severe	8 (7.4)/1 (0.9)	3 (3.3)/0 (0)	
Time to first hematochezia, *n* (%)			
<24 h	22 (20.4)	12 (13.2)	.759
≥24 h	9 (8.3)	6 (6.6)	
Delayed bleeding, *n* (%)	9 (8.3)	3 (3.3)	.231

SAP, Self-assembling peptide.