Risk Factors for Postoperative Bleeding in Endoscopic Submucosal Dissection of Colorectal Tumors

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Keywords

Colorectal tumors · Endoscopic submucosal dissection · Postoperative bleeding

Abstract

Background: Colonoscopic removal of adenomatous polyps or early cancer prevents death from colorectal cancer. Endoscopic submucosal dissection (ESD), which enables endoscopists to perform en bloc resection of flat or depressed colorectal tumors >20 mm, has recently been introduced and become a standard procedure in Japan. Although postoperative bleeding (POB) is a major complication associated with ESD, risk factors for POB have not been fully identified. **Methods:** A total of 451 patients (509 lesions) who underwent colorectal ESD were retrospectively analyzed to identify clinical parameters associated with POB. **Results:** POB occurred in 14 patients, and 7 of them had received antithrombotic therapy before ESD. Uni- and multivariate analyses revealed that

antithrombotic therapy and rectal tumor location were strongly associated with POB following colorectal ESD. The incidence of POB was higher in patients on heparin bridge therapy (HBT) for the replacement of antithrombotic therapy than in patients with no HBT. Four of 7 patients (57.1%) on antithrombotic therapy experienced POB from the rectal lesions. **Conclusion:** Antithrombotic therapy and rectal lesions result in a higher POB incidence after colorectal ESD.

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Introduction

It is now generally accepted that the colonoscopic removal of adenomatous polyps or early cancer prevents death from colorectal cancer [1]. Pedunculated colorectal polyps and flat or depressed colorectal tumors are good indications for endoscopic polypectomy (EP) and endoscopic mucosal resection (EMR), respectively [2, 3]. Al-

though EMR is widely used for endoscopic removal of flat or depressed colorectal tumors, en bloc resection of lesions >20 mm is difficult using EMR [4–6]. A fragmented resection technique called endoscopic piecemeal mucosal resection is often employed in such cases [4–6], but a high incidence of local recurrence has been reported in colorectal tumors treated with this resection technique [4–6]. Endoscopic submucosal dissection (ESD), which allows en bloc resection of flat or depressed colorectal tumors >20 mm, has recently been introduced and become a standard procedure in Japan [4–6]. In fact, many studies addressing the efficacy of ESD show that the rates of en bloc and curative resection are higher in patients treated with ESD than in those treated with EMR [7–11]. In contrast, the local recurrence rate was lower in patients treated with ESD than in those treated with EMR [7–11]. Thus, colorectal ESD has enabled the resection of large flat or depressed colorectal tumors as well as a wide variety of adenomas and early colorectal cancers.

As in case of EP and EMR [12, 13], postoperative bleeding (POB) and perforation are both major complications associated with ESD [14]. The percentages of POB following colorectal ESD [7, 11, 14] are highly variable, ranging from 0.5 to 9.6%. Although the POB rate was lower following colorectal ESD than colorectal EMR in a meta-analysis [2], life-threatening bleeding requiring blood transfusion may occur in patients treated with ESD. Therefore, risk factors for POB following colorectal ESD need to be identified.

Antithrombotic therapy with anticoagulants or antiplatelet agents is widely used for the prevention of ischemic cardiovascular events [15–17]. Although antithrombotic therapy is effective for the prevention of ischemic cardiovascular events, the recent use of anticoagulants or antiplatelet agents is considered a major risk factor for POB following EP and EMR [18–20]. According to the recent guidelines of the Japan Gastroenterological Endoscopic Society (JGES), anticoagulants or antiplatelet agents should not be discontinued before endoscopic procedures with low risk of bleeding since the withdrawal of these drugs may cause new-onset cardiovascular events [21]. On the contrary, anticoagulants or antiplatelet agents must be discontinued in patients bearing a low risk of thromboembolism following withdrawal or replaced by heparin bridge therapy (HBT) in patients at high risk of thromboembolism following withdrawal before endoscopic procedures with a high risk of bleeding, such as EMR and ESD [21]. Recent retrospective studies addressing the safety and efficacy of HBT in colorectal EMR and EP revealed that HBT increases rather than de-

creases the risk of POB [22–24]. It should be noted, however, that clinical studies addressing the safety and efficacy of HBT in colorectal ESD are not available. Here, we performed a retrospective analysis to identify the risk factors for POB in patients who underwent colorectal ESD with or without antithrombotic therapy.

Patients and Methods

Patients

This study was a retrospective analysis addressing the safety and efficacy of colorectal ESD. A total of 451 patients (509 lesions) who underwent colorectal ESD at the Kindai University Hospital between April 2010 and February 2017 were enrolled in this study. The Review Board of the Kindai University Faculty of Medicine approved the study design and procedures.

Clinical parameters were obtained from each patient's medical records. They included age, sex, anticoagulant use, antiplatelet agent use, platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), serum creatinine level, colorectal tumor size, endoscopic tumor appearance (0–IIa, 0–IIa + IIc, 0–IIc, 0–IIc + IIa, 0–Is, 0–Is + IIc, laterally spreading tumor granular [LST-G] homogenous type, LST-G nodular mixed type, LST-non-granular [LST-NG] flat elevated type, and LST-NG pseudodepressed type), tumor histology, and tumor location. Tumor location was classified into cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

Management of Anticoagulants and Antiplatelet Agents

Warfarin, dabigatran, rivaroxaban, and edoxaban were used as anticoagulants in this study, while aspirin, ticlopidine, beraprost, cilostazol, eicosapentaenoic acid ethyl ester, and clopidogrel were used as antiplatelet agents. The discontinuation of anticoagulants and/or antiplatelet agents or replacement by HBT was determined by each primary doctor after consultation with cardiologists or neurosurgeons. The discontinuation periods of the above drugs were determined based on the JGES guidelines [21]. HBT was performed using unfractionated heparin sodium, and the dose of heparin was adjusted by monitoring APTT (1.5- to 2.0-fold above the upper limit). HBT was started 3–5 days before ESD and stopped 6 h before ESD. Anticoagulants and antiplatelet agents were resumed 1 or 2 days after ESD.

ESD Procedure

Colorectal ESD was performed under the condition of conscious sedation with midazolam or diazepam. We used a PCF-290Z colonoscope (Olympus) with a transparent hood and irrigation pump. Carbon dioxide insufflation was used during the procedure. Sodium hyaluronate and adrenaline were injected into the submucosal layer to create a submucosal cushion. A flush knife BTS (DK-2620J; Fujifilm) or a DualKnife J (KD-655Q; Olympus) was used to dissect the lesion. The setting of the VIO[®] 300 D (Electrosurgical Generator) were Endocut I (effect 2, time 3, interval 3) for mucosal incisions, swift coagulation (effect 3/40 W) for submucosal dissections, and soft coagulation (effect 6/80 W) for bleeding points; for preventive occlusions of vessels, hemostatic forceps were used. At the end of the procedure, additional coagulation was carefully performed to prevent delayed bleeding.

Fig. 1. Flow diagram of the patients treated with colorectal endoscopic submucosal dissection. HBT, heparin bridge therapy.

Postoperative Bleeding

Emergent colonoscopy was performed in cases of melena. POB was defined as active bleeding or an adherent clot on the resection site that required endoscopic treatment.

Statistical Analysis

The Student *t* test or Fisher exact test was used in univariate analyses. Values of $p < 0.05$ were considered significant. Clinical factors that were significant in univariate analysis were subjected to multivariate analysis.

Results

Flow Diagrams of Patient Selection and Treatment Allocation

Four hundred and fifty-one patients (509 lesions) who underwent colorectal ESD were enrolled in this study. A total of 48 patients (52 lesions) received antithrombotic therapy before ESD. Of them, 17 (18 lesions) were treated with anticoagulants with or without antiplatelet agents, and 31 (34 lesions) were treated with antiplatelet agents alone. Six patients were treated with both anticoagulants and antiplatelet agents. The 48 patients (52 lesions) who received antithrombotic therapy before ESD were categorized into the HBT group (8 patients) and no-HBT group

(40 patients). Patients in the no-HBT group had discontinuation of anticoagulants or antiplatelet agents (17 patients), continuation of anticoagulants or antiplatelet agents before ESD (14 patients), and continuation of 1 anticoagulant or antiplatelet agent in the case of >2 drugs before ESD (9 patients). A flow diagram of the patient selection and treatment allocation is shown in Figure 1.

Risk Factors for POB following Colorectal ESD

Although POB is a common complication of colorectal ESD, its risk factors have not been identified. Previous studies showed that multiple factors such as size, pedunculated form, and proximal location increase the rate of POB following EP [19, 25, 26]. In addition, antithrombotic therapy, hypertension, chronic renal disease, cardiovascular disease, and advanced age were identified as patient-associated risk factors for delayed bleeding [18–20]. Based on these previous reports, we performed a univariate analysis of the clinical parameters in this retrospective study. As shown in Table 1, POB was seen in 14 patients (14 lesions) among the total 451 patients (509 lesions). Endoscopic hemostasis was required for all 14 patients, and 6 needed blood transfusion. One patient required surgery. No significant correlation was seen between bleeding and tumor-related factors such as size and

Table 1. Clinical parameters associated with postoperative bleeding (POB)

Clinical parameters	POB 14 cases (14 lesions)	No POB 437 cases (495 lesions)	<i>p</i> value
Age, years	65.6±12.1	68.3±9.2	0.389 ^b
Males/females	9/5 (64.2/35.8)	236/201 (54.0/46.0)	0.589 ^a
Antithrombotic therapy	7 (50)	45 (8.9)	<0.001 ^a
Anticoagulant agents	3 (21.4)	14 (3.2)	0.009 ^a
Antiplatelet agents	4 (28.6)	39 (7.9)	0.024 ^a
Platelets, μ L	23.6±9.7	22.3±6.1	0.213 ^b
Prothrombin time, INR	1.06±0.13	1.04±0.47	0.923 ^b
APTT, s	32.1±8.8	28.2±6.9	0.189 ^b
Creatinine, mg/dL	0.95±0.57	0.84±0.84	0.637 ^b
Tumor size, mm	32.2±13.6	30.6±14.1	0.784 ^b
Endoscopic appearance			
0-IIa	0 (0)	1 (0)	1.000 ^a
0-IIa + IIc	0 (0)	8 (1.6)	1.000 ^a
0-IIc	0 (0)	1 (0)	1.000 ^a
0-IIc + IIa	0 (0)	2 (0)	1.000 ^a
0-Is	1 (7.1)	41 (8.3)	1.000 ^a
0-Is + IIc	0 (0)	1 (0)	1.000 ^a
LST-G (homogenous)	0 (0)	83 (17.0)	1.000 ^a
LST-G (nodular mixed)	7 (50)	109 (22.0)	0.022 ^a
LST-NG (flat elevated)	5 (35.7)	156 (31.5)	0.774 ^a
LST-NG (pseudodepressed)	1 (7.1)	93 (18.8)	0.484 ^a
Histology (invasive neoplasm)	0 (0)	8 (1.6)	1.000 ^a
Location			
Cecum	0 (0)	88 (17.8)	1.000 ^a
Ascending colon	2 (14.3)	111 (22.4)	0.745 ^a
Transverse colon	3 (21.4)	132 (26.7)	1.000 ^a
Descending colon	0 (0)	13 (2.6)	1.000 ^a
Sigmoid colon	1 (7.1)	61 (12.3)	1.000 ^a
Rectum	8 (57.1)	90 (18.1)	0.002 ^a

Numbers of cases (%) are shown unless indicated otherwise. APTT, activated partial thromboplastin time; LST, laterally spreading tumor; G, granular; NG, nongranular. ^a Fisher exact test. ^b *t* test.

Table 2. Risk factors for postoperative bleeding

	Odds ratio	95% CI	<i>p</i> value
Antithrombotic therapy	4.95	1.48–16.59	0.009
LST-G (mix)	2.12	0.64–7.07	0.22
Rectal tumor	10.81	3.43–34.00	<0.001

LST-G (mix), laterally spreading tumor-granular (nodular mixed).

histology except for the endoscopic appearance of the LST-G mixed nodular type. Interestingly, we found that 8 of 14 patients with POB received ESD for rectal tumors. Thus, the incidence of POB was high in rectal lesions at 8.1% (8/98). Regarding patient-related factors, no signifi-

cant correlation was seen between bleeding and patient-related factors such as age, sex, platelet count, PT, APTT, or serum creatinine level. In contrast, the percentage of POB was much higher in patients with antithrombotic therapy than in those without antithrombotic therapy. Thus, our univariate analysis identified antithrombotic therapy (use of anticoagulants and/or antiplatelet agents) and rectal tumors as risk factors for POB followign colorectal ESD.

We then performed multivariate analysis to confirm the results obtained by the univariate analysis. As shown in Table 2, antithrombotic therapy and rectal tumors were identified as independent risk factors for ESD-related POB, whereas the LST-G mixed nodular type did not show a significant correlation. Collectively, these uni- and multivariate analyses revealed that antithrombotic

Table 3. Characteristics of patients with or without heparin bridge therapy (HBT)

Clinical parameters	HBT 8 cases (9 lesions)	No HBT 40 cases (43 lesions)	<i>p</i> value
Age, years	72.1±6.3	72.1±7.8	0.980 ^b
Males/females	6/2 (75/25)	28/12 (70/30)	1.000 ^a
Anticoagulant agents	8 (100)	9 (22.5)	0.001 ^a
Antiplatelet agents	1 (12.5)	39 (97.5)	<0.001 ^a
Both	1 (12.5)	8 (20)	1.000 ^a
Tumor size, mm	37.1±11.8	29.7±12.1	0.173 ^b
Histology (invasive neoplasm)	0	0	–
Endoscopic appearance			
0-IIa	0 (0)	4 (9.3)	1.000 ^a
0-IIa + IIc	0 (0)	0 (0)	1.000 ^a
0-IIc	0 (0)	0 (0)	1.000 ^a
0-Is	1 (11.1)	4 (9.3)	1.000 ^a
0-Is + IIc	0 (0)	0 (0)	1.000 ^a
LST-G (homogenous)	2 (22.2)	4 (9.3)	0.275 ^a
LST-G (nodular mixed)	2 (22.2)	10 (23.3)	1.000 ^a
LST-NG (flat elevated)	3 (33.3)	11 (25.6)	0.688 ^a
LST-NG (pseudodepressed)	1 (11.1)	10 (23.3)	0.664 ^a
Location			
Cecum	0 (0)	8 (18.6)	1.000 ^a
Ascending colon	2 (22.2)	8 (18.6)	1.000 ^a
Transverse colon	3 (33.3)	13 (30.2)	1.000 ^a
Descending colon	1 (11.1)	3 (7)	1.000 ^a
Sigmoid colon	0 (0)	2 (4.7)	1.000 ^a
Rectum	3 (33.3)	9 (20.9)	0.415 ^a
Postoperative bleeding	2 (22.2)	5 (11.6)	0.59 ^a

Numbers of cases (%) are shown unless indicated otherwise. LST, laterally spreading tumor; G, granular; NG, nongranular. ^a Fisher exact test. ^b *t* test.

therapy and rectal tumor location are strongly associated with POB caused by ESD.

HBT in and POB following Colorectal ESD

Having identified the use of anticoagulants and/or antiplatelet agents as a patient-associated risk factor for POB following colorectal ESD, we tried to evaluate the safety and efficacy of HBT. Eight patients received HBT in this study. Seventeen patients discontinued the antithrombotic therapy, 14 patients continued anticoagulants or antiplatelet agents before ESD, and 9 patients continued only 1 anticoagulant or antiplatelet agent in the case of combined therapy. Characteristics of the patients in the HBT group (8 cases) and no-HBT group (40 cases) are summarized in Table 3. The percentages of POB in the no-HBT and HBT group were 11.6% (5/43) and 22.2% (2/9), respectively. Thus, no significant difference in POB was seen between the HBT and no-HBT groups, although the former exhibited a higher rate of POB than the latter.

As shown above, 7 of 52 cases who received antithrombotic therapy exhibited POB. Detailed clinical information on the 7 cases with POB is summarized in Table 4. Two patients who discontinued warfarin and then received HBT experienced POB (Table 4). One patient who was treated with aspirin in combination with cilostazol and then continued therapy with aspirin alone upon ESD experienced POB. Other cases with POB included 1 patient who discontinued aspirin, 1 who continued aspirin, 1 who continued ticlopidine and aspirin, and 1 who discontinued edoxaban. Thus, a wide variety of anticoagulants and antiplatelet agents caused POB.

Discussion

ESD is widely used to resect flat or depressed colorectal tumors >20 mm [4–6]. The advantages of ESD in colorectal tumor therapy include the higher rate of successful en bloc resection and the lower rate of local recur-

Table 4. Clinical characteristics of 7 cases with antithrombotic therapy and postoperative bleeding

Case No.	Age, years	Sex	Tumor characteristics		Anti-coagulants	Antiplatelet agents	HBT	Blood transfusion
			site	size, mm				
1	67	M	A	30	–	aspirin ticlopidine	–	–
2	71	F	R	43	–	aspirin cilostazol ¹	–	yes
3	72	M	R	25	–	aspirin	–	yes
4	70	M	T	20	–	aspirin ¹	–	–
5	68	M	R	32	warfarin	–	yes	–
6	51	M	R	40	edoxaban ¹	–	–	yes
7	83	M	T	45	warfarin	–	yes	–

A, ascending colon; T, transverse colon; R, rectum; HBT, heparin bridge therapy.

¹ Discontinued before endoscopic submucosal dissection.

rence compared with conventional EMR [7–11]. Thus, colorectal ESD has enabled the resection of large flat or depressed colorectal tumors as well as a wide variety of adenomas and early colorectal cancers. POB is a major complication of ESD. Although the rates of POB are comparable among ESD, EMR, and EP, life-threatening bleeding may occur after colorectal ESD. Therefore, the identification of risk factors for POB is important. In this study, we analyzed 451 patients who underwent colorectal ESD at the Kindai University Hospital and found in uni- and multivariate analyses that rectal tumor location and antithrombotic therapy are independent risk factors for bleeding. Thus, rectal tumor location and antithrombotic therapy are likely to increase the risk of POB following colorectal ESD.

Interestingly, the percentage of POB following colorectal ESD was much higher in patients with rectal tumors than that in patients with tumors in the cecum, ascending colon, transverse colon, descending colon, or sigmoid colon. Among 14 POB cases, 8 had bleeding from rectal lesions. These data are in sharp contrast to those of previous reports showing that location in the right hemicolon is an independent risk factor for delayed postpolypectomy bleeding [25, 27]. Thus, rectal location increases the rate of POB following ESD, while right hemicolon location increases the rate of bleeding following EP. The reason for this difference is unknown. Given the fact there are many veins and arteries in the submucosa of the rectum [28], POB may be caused by injury to the submucosal vessels of the rectum during ESD.

As for patient-related factors, we identified antithrombotic therapy as an independent risk factor for POB fol-

lowing colorectal ESD. Consistent with this finding, the use of anticoagulants or antiplatelet agents is considered to promote POB in patients treated with EP or EMR [18–20]. Thus, the use of anticoagulants or antiplatelet agents increases the risk of POB following EMR, EP, and ESD. We performed a detailed analysis of 7 patients with POB treated with anticoagulants and/or antiplatelet agents before ESD. Unfortunately, we could not identify specific antithrombotic drugs that promote POB following colorectal ESD. Intriguingly, 4 (57.1%) of the 7 patients who received antithrombotic therapy had bleeding from rectal lesions. These data altogether suggest that antithrombotic therapy and rectal location are independent risk factors for POB following colorectal ESD and that colonoscopists must be aware of possible bleeding in patients presenting with these risk factors.

According to the JSGE guidelines, HBT is recommended before endoscopic procedures with a high risk of bleeding, such as EMR and ESD in patients at high risk of thromboembolism upon anticoagulant withdrawal [21]. Based on this guideline, HBT is considered a treatment option for patients who are undergoing colorectal EMR or ESD in the presence of antithrombotic therapy. However, recent retrospective studies addressing the safety and efficacy of HBT in colorectal EMR and EP revealed that HBT increases rather than decreases the risk of POB [22–24]. Consistent with the studies cited above, the rate of POB following colorectal ESD tended to be higher in our HBT group than in our no-HBT group, although the difference was not statistically significant. The reasons for the lack of a significant difference in the rate of POB between the HBT and the no-HBT group are currently un-

known. Strict APTT adjustment, overload effects of discontinued anticoagulants, or time of resuming anticoagulants or antiplatelet agents may affect the rate of POB. It should also be noted that the number of patients in this study, especially in the HBT group, is too small to draw a definite conclusion regarding the relationship between colorectal ESD-related POB and HBT. Therefore, prospective multicenter studies are required to confirm the safety and efficacy of HBT in colorectal ESD.

In conclusion, we identified antithrombotic therapy and rectal location as independent risk factors for POB following colorectal ESD. Future studies are required to confirm our findings and decrease the rate of POB following colorectal ESD.

Disclosure Statement

The authors have no conflicts of interest to declare.

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