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【 ORIGINAL ARTICLE 】

Effectiveness of Clipping for Definitive Colonic Diverticular Bleeding in Preventing Early Recurrent Bleeding

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Abstract:

Objective Clipping is a common technique for managing colonic diverticular bleeding (CDB), despite the lack of published evidence regarding its effectiveness. We aimed to evaluate the effectiveness of clipping for CDB in preventing early recurrent bleeding.

Methods This dual-center retrospective study included 93 patients who underwent emergency hospitalization for bloody stool, diagnosed with definitive CDB, and treated with clipping or conservative treatment. The primary outcome was early recurrent bleeding. A logistic regression analysis was performed to assess the association between the occurrence of early recurrent bleeding and clipping with adjustment for propensity scores. Secondary outcomes included death, transfusion, length of hospitalization, need for transcatheter arterial embolization or surgery, and adverse events.

Results The patient characteristics were similar between the clipping (n=85) and conservative treatment (n=8) groups. The rate of early recurrent bleeding was significantly lower in the clipping group than in the conservative treatment group [23.5% (20 cases) vs. 75% (6 cases), p=0.005]. In the propensity score-adjusted logistic regression analysis, the odds ratio for early recurrent bleeding in the clipping group was 0.094 (95% confidence interval, 0.008-0.633, p=0.026). Secondary outcomes were not significantly different between the two groups. Stigmata of recent hemorrhage (SRH) at the time of recurrent bleeding was identified in 79.2% of patients (19/24). In the clipping group, recurrent bleeding was observed in 62.5% of cases (10/16) from the same diverticulum. However, early recurrent bleeding tended to be less likely with direct clipping (p=0.072).

Conclusion Clipping for definite CDB was more effective in preventing early recurrent bleeding than conservative treatment.

Key words: clipping, colonic diverticular bleeding, colonoscopy, early recurrent bleeding

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Introduction

Colonic diverticular bleeding (CDB) accounts for 26.4-33% cases of acute lower gastrointestinal bleeding (1-3). Furthermore, its incidence increases with age (4). Despite the spontaneous cessation of bleeding in 70-90% cases of CDB (5, 6), 20-30% of CDB cases can still result in recurrent bleeding in the first year (5, 7, 8). Early recurrent bleeding (within 30 days after initial colonoscopy) is particularly more likely to occur from the same diverticulum (9, 10). As a result, patients might require blood transfusions, additional treatment, or long-term hospitalization (11). Therefore, early recurrent bleeding is a significant consequence of CDB and needs to be addressed.

CDB is diagnosed by colonoscopy, and the rate of recurrent bleeding is high when stigmata of recent hemorrhage (SRH) is observed, thus necessitating endoscopic treat-

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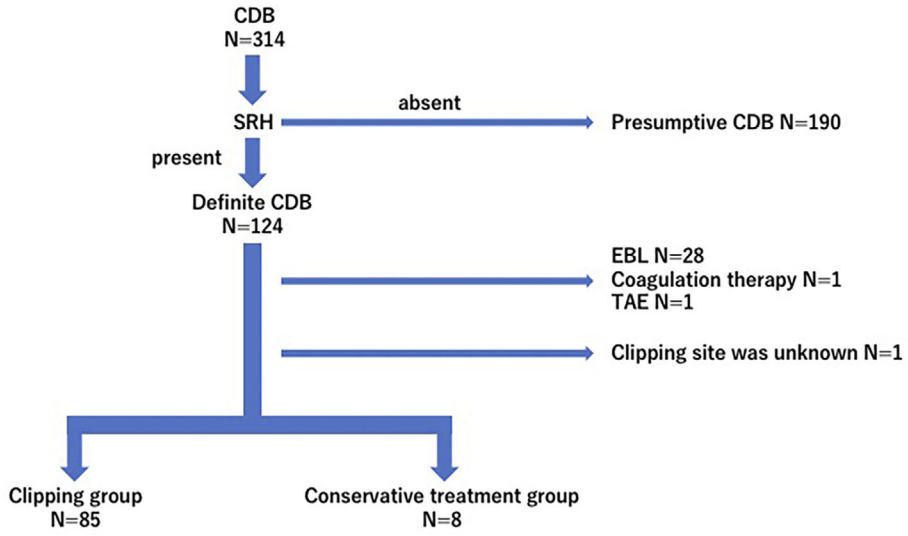

Figure 1. **Flowchart showing the enrollment of study participants. CDB: colonic diverticular bleeding, SRH: stigmata of recent hemorrhage, EBL: endoscopic band ligation, TAE: transcatheter arterial embolization**

ment (12-15). Endoscopic treatment of CDB includes clipping, bipolar coagulation, epinephrine injection, and endoscopic band ligation (EBL). Clipping is a minimally invasive, simple, widely used, and effective mode of treatment as per the guidelines in Japan, the United Kingdom, and the United States (14, 16-20). However, evidence supporting the effectiveness of clipping for CDB, such as initial hemostasis and prevention of recurrent bleeding, is based on only a few case reports and case series (18-23). Furthermore, there is little to no evidence comparing its effectiveness to that of conservative treatment. In contrast, clipping has reportedly been associated with a higher rate of early recurrent bleeding than EBL in recent years (9-11, 24, 25). Therefore, the efficacy of clipping in preventing early recurrent bleeding in definite CDB is unclear.

In this study, we retrospectively compared clipping and conservative treatment to determine the effectiveness of clipping in preventing early recurrent bleeding in definite CDB.

Materials and Methods

Study design and population

A total of 314 patients with CDB with bloody stool underwent emergency hospitalization at Toranomon Hospital and Toranomon Hospital Kajigaya between January 2011 and August 2020. Of the 314 patients admitted with bloody stool, 124 were found have definite CDB, for which initial colonoscopy revealed SRH.

We included patients who had received clipping or conservative treatment in the study. Conservative treatment included bowel rest, fluid resuscitation, and blood transfusions without any endoscopic treatment for SRH. We excluded those who had undergone coagulation therapy, EBL, and transcatheter arterial embolization (TAE) for definite CDB. In addition, we excluded another patient in whom we were unable to determine if the clipping site was a diverticulum with a bleeding source. Ultimately, 93 patients with definite CDB who had undergone either clipping or conservative treatment were selected (Fig. 1). All of the patients underwent a minimum observation period of 30 days after the initial colonoscopy.

This study was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in Brazil 2013). Furthermore, it was approved by the Ethics Committees of Toranomon Hospital and Toranomon Hospital Kajigaya. The need for informed consent was waived due to the retrospective nature of the study.

The diagnosis of CDB

CDB was classified as definite or presumptive based on the criteria reported by Jensen et al. (13) and Zuckerman et al. (26). Definite CDB was defined as CDB with SRH (12, 13), such as active bleeding (Fig. 2a), a visible vessel (Fig. 2b), or an adherent clot (Fig. 2c). However, in cases of presumptive CDB, bleeding sources apart from CDB were unable to be recognized, even with modalities other than colonoscopy.

Procedure

Considering the general condition of the patients, the operators decided to perform bowel preparation using either polyethylene glycol or an enema, and in some cases, no specific bowel preparation was performed. In most cases colonoscopy was performed using a PCF-Q260JI or PCF-H 290I scope (Olympus Medical Systems, Tokyo, Japan). Other scopes (CF-Q260AI, PCF-H290Z, PCF-H290TI, or PCF-PQ260L, Olympus Medical Systems; EC-590MP, FUJIFILM, Saitama, Japan) were also used for colonoscopy. The scope was used with a soft cap (D201-10704, D201-11804,

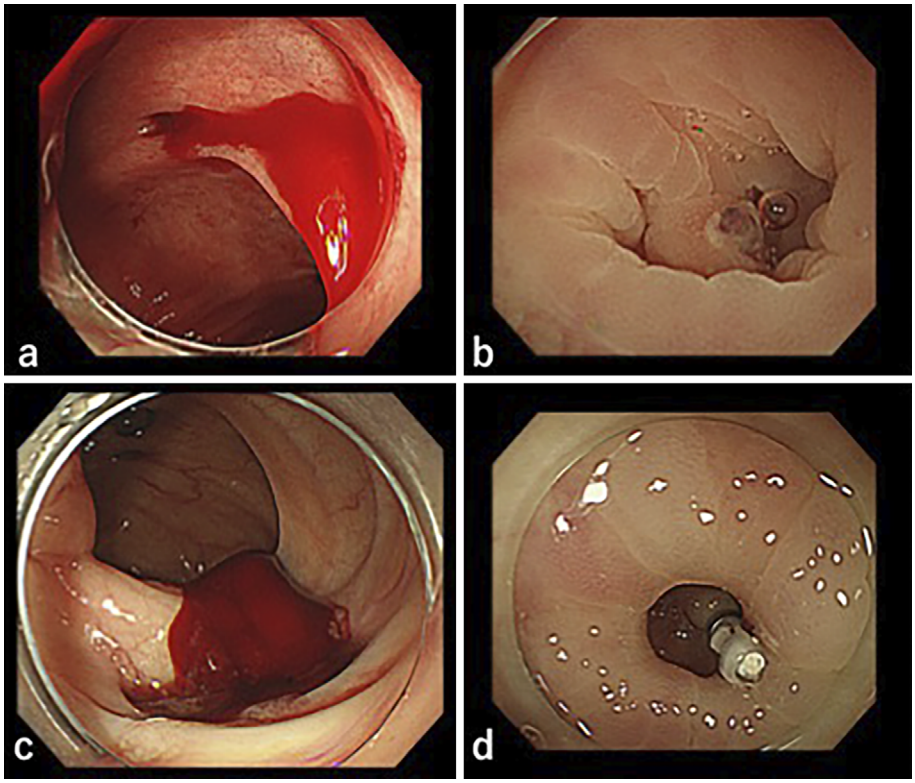

Figure 2. **Stigmata of recent hemorrhaging and the clipping method. a: Active bleeding, b: Visible vessel, c: Adherent clot, d: Direct method for visible vessel.**

D201-12704, or D201-13404; Olympus Medical Systems) and water jet device in all colonoscopies. Endoscopic treatment for CDB with SRH was performed at the discretion of the individual operators. Clipping was predominantly conducted using hemoclips (HX-610-135S or HX-610-135, Olympus Medical Systems; ROCC-D-26-195-C, Micro-Tech, Nanjing, China). These hemoclips were used for the so-called direct method (Fig. 2d), where they were placed on the vessel as close to the bleeding as possible (23). In contrast, indirect clipping was performed in the Zipper fashion when either the source of the bleeding could not be confirmed due to massive bleeding or it was difficult to insert the clip into the diverticulum (23).

Measurements

We evaluated the following using existing electronic medical records: age, sex, body mass index (BMI), drinking status, smoking status, comorbidities (Charlson Comorbidity Index) (27), medical history (CDB, diabetes mellitus, chronic kidney diseases, hypertension, and dyslipidemia), severity of bleeding (systolic blood pressure, pulse, and shock), laboratory investigations, antithrombotic drug use, computed tomography (CT) before colonoscopy, endoscopic factors, CT during early recurrent bleeding, and colonoscopy during early recurrent bleeding. Shock was defined as systolic blood pressure <90 mmHg and/or pulse >100 bpm. Early colonoscopy was defined as a colonoscopy performed within 24 hours of admission to the hospital. The decision to continue or discontinue antithrombotic drugs was made by the attending physician in consultation with a cardiovascular and cerebrovascular disease specialist, based on the patient's condition. Blood transfusions were considered upon observing a decrease in the hemoglobin levels to <8 g/dL with active bleeding or unstable vital signs. Drug use was defined as the oral administration of a drug within 1 month of admission. The expert endoscopists were staff members of Toranomon Hospital or Toranomon Hospital Kajigaya who were also specialist members of the Japan Gastroenterological Endoscopy Society.

Outcome measures

Early recurrent bleeding (within 30 days of initial colonoscopy) was the primary outcome measure. Recurrent bleeding was defined as significant amounts of fresh bloody or wine-colored stool with no lower abdominal pain. When possible, patients underwent endoscopy and CT at the time of recurrent bleeding. Furthermore, the absence of other sources of bleeding was confirmed by colonoscopy and CT (10). Secondary outcomes included mortality within 30 days after colonoscopy, blood transfusion after initial colonoscopy, need for operation, need for TAE, length of hospitalization, and adverse events (thromboembolism embolism, perforation, and diverticulitis). Furthermore, the following were also evaluated: 1) the rate at which diverticula with SRH were identified during early recurrent bleeding, 2) the rate of recurrent bleeding from the same diverticulum, and 3) the rate at which endoscopic clips were dislodged in the clipping group. A subgroup analysis was likewise per-

formed where the characteristics of the clipping group were compared based on the presence or absence of early recurrent bleeding.

Statistical analyses

The continuous and non-normally distributed variables are expressed as medians and interquartile ranges. We compared the median quantitative values using Wilcoxon's rank-sum test. In contrast. Fisher's exact test was used to compare the categorical variables. We evaluated the odds ratio for the primary outcome. To adjust for patient characteristics, we calculated propensity scores using a logistic regression analysis. Propensity scores were estimated using the following variables: age, sex, BMI, smoking status, Charlson Comorbidity Index, CDB, diabetes mellitus, chronic kidney diseases, hypertension, dyslipidemia, systolic blood pressure, pulse, shock, hemoglobin, platelets, albumin, non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, antiplatelet, time to colonoscopy, bowel preparation (polyethylene glycol-electrolyte), SRH type (active bleeding), SRH location, and bilateral colonic diverticulosis. C-statistics were calculated, and a logistic regression analysis was performed to assess the association between the occurrence of early recurrent bleeding and clipping with adjustment for propensity scores. The statistical significance and tendency were set at $p<0.05$ and $p<0.1$, respectively.

All analyses were performed using the R software program, version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 85 and 8 patients in the clipping and conservative treatment groups, respectively. Seven patients in the conservative group did not undergo any endoscopic treatment because the operators could not locate the diverticulum with SRH, even though it was found during colonoscopy. In addition, in one case, endoscopic treatment was not selected by the operator, at his discretion.

Table 1 summarizes the characteristics of the patients. There were no significant differences between the clipping and conservative treatment groups. The clipping group tended to use less NSAIDs than the conservative treatment group (p=0.097). The clipping method used was the direct method in 49.4% (42 patients) and the indirect method in 50.6% (43 patients). The primary and secondary outcomes are shown in Table 2 and 3. We observed early recurrent bleeding in 20 (23.5%) and 6 (75%) patients in the clipping and conservative treatment groups, respectively. The rate of early recurrent bleeding was significantly lower in the clipping group than in the conservative treatment group (p= 0.005). The C statistic of the propensity score in this study was 0.574. In the propensity score-adjusted logistic regression analysis, the odds ratio for early recurrent bleeding in the clipping group was 0.094 (95% confidence interval, 0.008-0.633, p=0.026). Thus, clipping was deemed effective in preventing early recurrent bleeding.

A high rate of early recurrent bleeding was seen in the conservative treatment group, except in two cases. In the first case, an 84-year-old woman with a high CCI who was taking NSAIDs and low-dose aspirin (LDA). Her hemodynamic status was stable, but contrast-enhanced CT showed extravasation in the sigmoid colon; an expert endoscopist thus performed early colonoscopy. Active bleeding from the diverticulum was identified; however, there was a large amount of residue, and the diverticulum was lost after spontaneous hemostasis. The duration of colonoscopy was 88 minutes. Oral administration of NSAIDs and LDA was continued, and meals were started the day after colonoscopy.

In the second case, a 70-year-old man had a CCI of 0 and a history of taking NSAIDs. He had tachycardia. A non-expert colonoscopist performed early colonoscopy and found active bleeding in the transverse colon; however, the bleeding had stopped spontaneously before the diverticulum was identified. The duration of colonoscopy was 89 minutes. Oral administration of NSAIDs was continued, and meals were started three days after colonoscopy.

Table 2 summarizes the secondary outcomes; no significant differences between the groups were noted.

Table 4 shows the colonoscopy and CT findings during early recurrent bleeding. The rate at which diverticula with SRH were identified was 79.2%, where they were detected in 84.2% of the patients in the clipping group and 60.0% of those in the conservative treatment group. In the clipping group, 62.5% had recurrent bleeding from the same diverticulum, but clips had remained intact in 80% of them. In two cases, the clips became dislodged and were lost after indirect clipping.

In the subgroup analysis of the clipping group, there was no significant difference in the characteristics based on the presence or absence of early recurrent bleeding (Table 5). However, early recurrent bleeding tended to be reduced with direct clipping (p=0.072).

Discussion

Conducting prospective controlled interventional studies is difficult due to ethical considerations, as it is mandatory to follow the recommended endoscopic treatment for CDB with SRH. Therefore, we compared clipping with conservative treatment by collecting the data of patients who had been conservatively treated for other reasons, such as being unable to locate the diverticulum with SRH despite it being found during colonoscopy. This is the first study to report the effectiveness of clipping in preventing early recurrent bleeding in definite CDB compared to conservative treatment.

Colonic diverticula tend to occur at the site of penetration of the vasa recta on both sides of the tenia of the colon and escape to the serosal side. CDB results from the destruction of a visible vessel in the inflamed tissue or at the base of the ulcer (28). Clipping is expected to stop bleeding tempo-

Table 1. Characteristics of Patients Who Underwent Either Clipping or Conservative Treatment.

	Clipping group n=85	Conservative group n=8	p value
Age (median [IQR])	72.00 [62.00, 80.00]	68.00 [60.25, 75.25]	0.419
Male	66 (77.6)	5 (62.5)	0.388
BMI (median [IQR])	23.10 [20.80, 25.50]	22.60 [20.53, 24.52]	0.696
Current drinker	32 (37.6)	5 (62.5)	0.258
Current smoker	8 (9.4)	0 (0.0)	1.000
Charlson comorbidity index ≥2	31 (36.5)	4 (50.0)	0.469
Medical history			
Colonic diverticular bleeding	28 (32.9)	3 (37.5)	1.000
Diabetes mellitus	25 (29.4)	3 (37.5)	0.693
Chronic kidney diseases	19 (22.4)	3 (37.5)	0.388
Hypertension	50 (58.8)	5 (62.5)	1.000
Dyslipidemia	29 (34.1)	3 (37.5)	1.000
Bleeding severity			
Systolic blood pressure (mmHg) (median [IQR])	135.00 [115.00, 149.00]	126.50 [113.75, 141.50]	0.443
Pulse bpm (median [IQR])	88.00 [80.00, 101.00]	102.00 [85.25, 106.25]	0.344
Shock	10 (11.8)	1 (12.5)	1.000
Transfusion before colonoscopy	19 (22.4)	2 (25.0)	1.000
Laboratory data			
Hemoglobin g/dL (median [IQR])	11.90 [9.80, 13.10]	11.95 [11.07, 13.10]	0.737
Platelets 10^4/μL (median [IQR])	20.50 [17.90, 25.20]	22.65 [19.62, 28.62]	0.173
Albumin mg/dL (median [IQR])	3.80 [3.50, 4.00]	3.90 [3.77, 4.05]	0.259
Creatinine mg/dL (median [IQR])	0.90 [0.73, 1.10]	0.79 [0.63, 1.04]	0.472
Medication			
NSAIDs	11 (12.9)	3 (37.5)	0.097
LDA	19 (22.4)	2 (25.0)	1.000
Antiplatelet	13 (15.3)	2 (25.0)	0.611
Anticoagulant	7 (8.2)	0 (0.0)	1.000
CT examination before colonoscopy			
Contrast-enhanced CT	40 (47.1)	2 (25.0)	0.287
Extravasation, out of contrast-enhanced CT	10 (25.0)	1 (50.0)	0.460
Endoscopic factors			
Time to colonoscopy (hour) (median [IQR])	7.00 [5.00, 23.00]	4.00 [4.00, 4.75]	0.115
Early colonoscopy	68 (80.0)	7 (87.5)	1.000
Bowel preparation			0.324
Polyethylene glycol-electrolyte	68 (80.0)	5 (62.5)	
Enema	15 (17.6)	3 (37.5)	
None	2 (2.4)	0 (0.0)	
SRH type			0.075
Active bleeding	59 (69.4)	5 (62.5)	
Visible vessel	17 (20.0)	0 (0.0)	
Adherent clot	9 (10.6)	3 (37.5)	
SRH location in the right side of colon	59 (69.4)	7 (87.5)	0.430
Bilateral colonic diverticulosis	61 (71.8)	6 (75.0)	1.000
Caps on colonoscope	85 (100)	8 (100)	1.000
Expert endoscopist	41 (48.2)	4 (50.0)	1.000
Time during colonoscopy	48.00 [36.00, 68.00]	51.00 [43.75, 88.25]	0.423
Clipping methods			
Direct clipping	42 (49.4)	-	
Indirect clipping	43 (50.6)	-	

Values are n (%) or median [IQR]. Early colonoscopy was defined as colonoscopy performed within 24 hours of the hospital visit. IQR: interquartile range, BMI: body mass index, NSAIDs: nonsteroidal anti-inflammatory drugs, LDA: low dose aspirin, CT: computed tomography, SRH: stigmata of recent hemorrhage, EBL: endoscopic band ligation

Table 2. Clinical Outcomes of Patients Who Underwent Clipping and Conservative Treatment.

	Clipping group (n=85)	Conservative group (n=8)	p value
Early recurrent bleeding	20 (23.5)	6 (75.0)	0.005
Death	0 (0.0)	0 (0.0)	NA
Units of transfusion after colonoscopy (median [IQR])	0.00 [0.00, 2.00]	0.00 [0.00, 4.50]	0.568
Length of stay days (median [IQR])	8.00 [6.00, 11.00]	8.00 [7.00, 13.00]	0.531
Surgery	1 (1.2)	0 (0.0)	1.000
TAE	1 (1.2)	0 (0.0)	1.000
Thrombosis	0 (0.0)	0 (0.0)	NA
Diverticulitis	0 (0.0)	0 (0.0)	NA
Colon perforation	0 (0.0)	0 (0.0)	NA

Values are n (%) or median [IQR]. IQR: interquartile range, TAE: transcatheter arterial embolization

Table 3. Odds Ratio for Early Recurrent Bleeding between the Conservative Treatment Group and the Clipping Group, Using Propensity Score-adjusted Logistic Regression Analysis.

	Odds ratio	95% confidence interval	p value
Clipping group	0.094	0.008-0.633	0.026

Table 4. Colonoscopy and Computed Tomography Findings during Early Recurrent Bleeding in the Clipping and Conservative Treatment Groups.

	Clipping group (n=20)	Conservative group (n=6)
Repeat colonoscopy	19 (95.0)	5 (83.3)
SRH	16 (84.2)	3 (60.0)
Same diverticulum	10 (62.5)	1 (20.0)
Clip remaining intact	8 (80.0)	-
Direct clipping	2 (25.0)	-
Indirect clipping	6 (75.0)	-
Clip dislodge	2 (20.0)	-
Direct clipping	0 (0.0)	-
Indirect clipping	2 (100.0)	-
Different diverticulum	4 (25.0)	2 (40.0)
Unevaluable	2 (12.5)	2 (40.0)
Treatment for SRH		
Clipping	14 (87.5)	1 (33.3)
EBL	2 (12.5)	2 (66.7)
Conservative treatment	0 (0.0)	0 (0.0)
CT	2 (10.0)	1 (16.7)

Values are n (%). SRH: stigmata of recent hemorrhage, EBL: endoscopic band ligation, CT: computed tomography

rarily and prevent recurrent bleeding by clipping the bleeding source directly or indirectly. The rate of early recurrent bleeding for clipping is reportedly 0-50% (9, 10, 19, 21-24, 29-34). A review of 10 reports that included 383 patients mentioned an average rate of 24% (35). In our study, the rate of early recurrent bleeding was similar to that reported in previous studies. In addition, the odds ratio for early recurrent bleeding in the clipping group indicated a preventive effect. Although clipping prevented early recurrent bleeding, there was no difference in secondary outcomes when compared to that in conservative treatment. While such results suggest that clipping may not affect secondary outcomes, this finding may be a type II error owing to the small sample size. Consequently, it is necessary to verify the secondary outcomes in a study with a larger sample of cases.

No significant difference was found in the univariate analysis of early recurrent bleeding within the clipping group. However, direct clipping did tend to reduce early recurrent bleeding. In fact, the rates of early recurrent bleeding were 14.3% (6/42) and 32.6% (14/43) for the direct and indirect methods, respectively (Supplementary Material 1). A number of studies have reported rates of 0-14.3% and 21.2-35.7% for early recurrent bleeding with the direct and indirect methods, respectively (10, 23, 34). Furthermore, the usefulness of the direct clipping method for preventing early recurrent bleeding has been reported and compared with that of the indirect method (24, 34). The direct method can prevent premature recurrent bleeding by directly clamping the blood vessels. In cases from the clipping group wherein bleeding from the same diverticulum was endoscopically confirmed, the clips remained intact in many cases, so it was considered that the clipping had not been effective. However, most of the clipping methods were indirect, suggesting the importance of direct clipping of blood vessels. Even among cases managed with the direct method, there were two cases of recurrent bleeding wherein the clip remained intact. It is possible that the blood vessel could not be directly clipped in these two cases. CDB may be difficult to clip directly if the source of bleeding is at the base of the diverticulum or if there is severe bleeding. However, CDB should be clipped by the direct method whenever possible.

Furthermore, no patients required surgery or TAE when they were treated by the direct clipping method, but some patients did require either surgery or TAE when treated by the indirect clipping method. (Supplementary Material 1). This result may also support the usefulness of the direct method. However, because indirect clipping resulted in a significantly lower rate of early recurrent bleeding than conservative treatment, as assessed using an univariate analysis (Supplementary Material 2), the effect of indirect clipping

Table 5. Characteristics of the Clipping Group Based on the Presence or Absence of Early Recurrent Bleeding.

Early recurrent bleeding	Presence n=20	Absence n=67	p value
Age (median [IQR])	71.50 [62.75, 77.50]	72.00 [62.00, 80.00]	0.808
Male	18 (90.0)	48 (73.8)	0.218
BMI (median [IQR])	22.85 [20.58, 24.90]	23.20 [21.30, 25.50]	0.527
Current drinker	8 (40.0)	24 (36.9)	0.798
Current smoker	5 (25.0)	13 (20.0)	0.755
Charlson comorbidity index ≥2	7 (35.0)	24 (36.9)	1.000
Medical history			
Colonic diverticular bleeding	5 (25.0)	23 (35.4)	0.430
Diabetes mellitus	5 (25.0)	20 (30.8)	0.781
Chronic kidney diseases	4 (20.0)	15 (23.1)	1.000
Hypertension	13 (65.0)	37 (56.9)	0.609
Dyslipidemia	10 (50.0)	19 (29.2)	0.109
Bleeding severity			
Systolic blood pressure (mmHg) (median [IQR])	136.00 [106.50, 153.00]	135.00 [116.00, 149.00]	0.872
Pulse bpm (median [IQR])	89.00 [81.75, 98.50]	87.00 [78.00, 103.00]	0.690
Shock	3 (15.0)	7 (10.8)	0.694
Transfusion before colonoscopy	3 (15.0)	16 (24.6)	0.542
Laboratory data			
Hemoglobin g/dL (median [IQR])	12.25 [10.65, 13.50]	11.80 [9.60, 13.00]	0.422
Platelets 10^4/μL (median [IQR])	19.85 [17.30, 25.32]	20.50 [17.90, 25.20]	0.784
Albumin mg/dL (median [IQR])	3.75 [3.55, 4.00]	3.80 [3.50, 4.00]	0.724
Creatinine mg/dL (median [IQR])	0.90 [0.74, 1.09]	0.84 [0.71, 1.12]	0.860
Medication			
NSAIDs	2 (10.0)	9 (13.8)	1.000
LDA	5 (25.0)	14 (21.5)	0.764
Antiplatelet	4 (20.0)	9 (13.8)	0.494
Anticoagulant	1 (5.0)	6 (9.2)	1.000
CT examination			
Contrast-enhanced CT before colonoscopy	9 (45.0)	31 (46.3)	1.000
Extravasation, out of contrast-enhanced CT	4 (44.4)	6 (19.4)	0.190
Endoscopic factors			
Time to colonoscopy (h) (median [IQR])	6.00 [4.00, 18.75]	7.00 [5.00, 24.00]	0.423
Early colonoscopy	17 (85.0)	51 (78.5)	0.751
Bowel preparation			
Polyethylene glycol-electrolyte	18 (90.0)	50 (76.9)	0.338
Enema	2 (10.0)	13 (20.0)	0.504
None	0 (0.0)	2 (3.1)	
SRH type			0.560
Active bleeding	16 (80.0)	43 (66.2)	
Visible vessel	3 (15.0)	14 (21.5)	
Adherent clot	1 (5.0)	8 (12.3)	
SRH location in the right side of colon	14 (70.0)	45 (69.2)	1.000
Bilateral colonic diverticulosis	14 (70.0)	47 (72.3)	1.000
Caps on colonoscope	20 (100)	67 (100)	1.000
Expert endoscopist	13 (65.0)	28 (43.1)	0.125
Time during colonoscopy	40.00 [27.25, 70.00]	50.00 [38.00, 68.00]	0.223
Clipping methods			
Direct clipping	6 (30.0)	36 (55.4)	0.072

Values are n (%) or median [IQR]. Early colonoscopy was defined as colonoscopy performed within 24 hours of the hospital visit. IQR: interquartile range, BMI: body mass index, NSAIDs: nonsteroidal anti-inflammatory drugs, LDA: low dose aspirin, CT: computed tomography, SRH: stigmata of recent hemorrhage

on preventing recurrent bleeding cannot be completely denied.

There has only been one report of early recurrent bleeding after conservative treatment for definite CDB, where the recurrence rate was 65.8% (12). The rate was as high as 84.2% during active bleeding (12). In our study, the recurrent bleeding rate was 75.0%. We considered that there were two possible reasons for the high recurrent bleeding rate in the conservative group. First, the conservative treatment group tended to take NSAIDs more often than the clipping group. NSAIDs and aspirin are factors for recurrent bleeding in CDB, so the oral administration of NSAIDs may have influenced recurrent bleeding (36, 37). Second, in the conservative treatment group, SRH was found in the right colon in 87.5% of cases. In one case without SRH in the right colon, there was no recurrent bleeding. All cases of recurrent bleeding in the conservative treatment group demonstrated SRH in the right colon. Because the diverticulum of the right colon is anatomically large (28), it may be susceptible to mechanical stimulation and recurrent bleeding. The recurrence of bleeding may also be affected by whether the bleeding vessel is venous or arterial. Because diverticular bleeding in the right colon is often severe (38-41), arterial bleeding may occur more commonly in the right colon than in the left colon. Consequently, the right colon may also be prone to recurrent bleeding. As such, this may have influenced the high recurrent bleeding rates in the conservative treatment group.

However, there were two cases in which bleeding did not recur even with conservative treatment. These cases were characterized by a pulse rate of <100 beats per minute, no shock, and no history of CDB (Supplementary Material 3). According to previous reports (42-44), shock symptoms, such as tachycardia and hypotension and a history of colonic diverticulum bleeding, are predictors of continuous and recurrent bleeding. Their absence may have prevented recurrent bleeding. However, the frequent use of NSAIDs and aspirin was a feature of the conservative treatment group. This result made it difficult to explain the absence of recurrent bleeding. It is possible that some factor other than NSAIDs and aspirin prevented recurrent bleeding in this group. The small number of cases may have had an effect. Considering this, verification through larger studies will be necessary in the future.

Clipping is widely used because it is less damaging to the tissue than thermal coagulation. Since the colonic diverticulum has no muscular layer, it is thought to be easy to perforate depending on the treatment, and it can be said that minimally invasive treatment such as clipping is therefore appropriate for the treatment of CDB. There have been no reports of colon perforation associated with clipping, and indeed, in this study as well, no diverticulitis or colon perforation was observed in any patients for whom clipping was performed, and it was considered extremely safe. However, it should be noted that Kume et al. (45) reported sepsis after clipping using the indirect method.

Recently a number of studies have reported the effectiveness of EBL compared to that of clipping in preventing recurrent bleeding (10, 24, 32). In EBL, the diverticulum with SRH is aspirated and ligated. Thus, the diverticulum is expected to be scarred and eventually disappear (10). Hence, the preventive effect on recurrent bleeding is likely to be greater than that of clipping. However, there is no marked difference in the preventive effect of clipping on recurrent bleeding using either the direct method or EBL (34). In addition, the simple and low-invasive characteristics of clipping may lead to its widespread use in the future (14).

Several limitations associated with the present study warrant mention. First, this dual-center retrospective study was based on medical records, and ethical considerations prevented the prospective collection of cases of conservative treatment of CDB with SRH who were indicated for endoscopic treatment. Second, the conservative treatment group consisted of a small sample size because of the difficulty associated with sample collection. The inclusion of more centers should thus be considered in future studies to overcome these limitations. Third, the inclusion of only Japanese patients and a difference in the location of the diverticula makes it difficult to generalize our results to Western patients (4, 46). Fourth, the measured confounder was adjusted with propensity scores, but the unmeasured confounder was not.

Notwithstanding the limitations acknowledged, this study is the first to report the effectiveness of clipping for preventing early recurrent bleeding in definite CDB compared to that of conservative treatment.

In conclusion, clipping is an effective treatment option for preventing early recurrent bleeding in definite CDB. It is also safe and will continue to be a treatment option.

The authors state that they have no Conflict of Interest (COI).

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