

[ORIGINAL ARTICLE]

Lower Rebleeding Rate after Endoscopic Band Ligation than Endoscopic Clipping of the Same Colonic Diverticular Hemorrhagic Lesion: A Historical Multicenter Trial in Saga, Japan

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Abstract:

Objective This historical control study was performed to evaluate i) the rebleeding rate of bleeding colon diverticula treated with endoscopic band ligation (EBL) versus endoscopic clipping (EC) and ii) risk factors for rebleeding of diverticula initially treated by endoscopic hemostasis.

Methods From January 2010 to December 2012, 68 patients were treated with EC, and from January 2013 to August 2016, 67 patients were treated with EBL. All patients in each group were followed up for one year to check for rebleeding.

Results The rebleeding rate was lower in the EBL group (7 of 67, 10%) than in the EC group (21 of 68, 31%; $p < 0.01$). This difference was mainly due to the lower rebleeding rate from the same hemorrhagic diverticulum initially treated by hemostasis (EBL: 4 of 67, 6%; EC: 15 of 68, 22%; $p < 0.01$). The time span until rebleeding in the EBL group was ≤ 1 week. A multivariate analysis indicated that bleeding from the diverticula on the right side of the colon was a high-risk factor for rebleeding from the diverticula (odds ratio, 4.48; 95% confidence interval, 1.22-16.46; $p = 0.02$).

Conclusion The low rebleeding rate in the EBL group was attributed to the low degree of rebleeding from the same diverticulum, indicating that EBL was superior to EC in preventing rebleeding of an initially treated diverticulum.

Key words: endoscopy, hemostasis, right side colon, risk factor, recurrence

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Introduction

The incidence of colonic diverticular hemorrhaging has increased in Japan (1, 2). Aging, the use of oral antithrom-

botic drugs and nonsteroidal anti-inflammatory drugs, and comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease are reported risk factors of diverticular bleeding (3-10). Although spontaneous hemostasis is obtained in 70% to 90% of cases of di-

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verticular hemorrhaging (11-15), colonic diverticular hemorrhaging sometimes results in continuous, severe, and refractory bleeding. Colonoscopy is usually performed for both the diagnosis and treatment of lower gastrointestinal bleeding. When endoscopic hemostasis is not applied to definitive diverticular hemorrhaging with a stigmata of recent hemorrhaging, such as active bleeding, visible vessel, and/or adherent clots, the rate of clinically significant rebleeding within 30 days becomes very high (16, 17).

Endoscopic band ligation (EBL) has been used to achieve hemostasis in patients with colonic diverticular bleeding, and several reports have suggested that EBL might be superior to endoscopic clipping (EC) for hemostasis (18, 19). One of the reasons for the better outcomes obtained with EBL than EC might be a superior effect on late bleeding from a diverticulum initially treated by endoscopic hemostasis; however, this advantage has not been clearly demonstrated.

The aims of the present study were to i) evaluate the rebleeding rate of a bleeding colon diverticulum treated with EBL versus EC and ii) evaluate the risk factors for rebleeding from a diverticulum initially treated by endoscopic hemostasis.

Materials and Methods

Patients

This historical control study included 135 patients with definite colonic diverticular hemorrhaging with stigmata of active bleeding, visible vessel, and/or the adherent clot who received endoscopic hemostasis as the first-line therapy from January 2010 to August 2016 at 7 institutions in Saga Prefecture. No entered patients had a history of diverticular bleeding. The seven institutions were Saga Medical Center Koseikan, Saga Medical School Hospital, National Hospital Organization Ureshino Medical Center, Karatsu Red Cross Hospital, Imari Arita Kyoritsu Hospital, Takagi Hospital, and Yuaikai Oda Hospital. As the first-line treatment, 68 patients were treated with EC from January 2010 to December 2012, and 67 patients were treated with EBL from January 2013 to August 2016.

This study was conducted in accordance with the Helsinki Declaration of the World Medical Association under the approval of the Ethics Committee in Saga Medical School (Number: 20171205).

Endoscopic treatment procedure

After preparation with a glycerin enema, polyethylene glycol, and/or magnesium citrate, the patients underwent colonoscopy within 48 hours after hospitalization. When stigmata of recent hemorrhaging were detected, EC or EBL was performed using the procedures described below.

EC was performed directly on the bleeding vessel or non-bleeding visible vessel. When a bleeding diverticulum was found but not deemed attributable to massive hemorrhaging

and/or strong mass peristalsis, multiple clips were placed indirectly in a zipper fashion to close the bleeding diverticulum.

EBL was performed after identification of a diverticulum with stigmata of recent hemorrhaging. The marking clip was placed near the bleeding diverticulum, and an endoscope with a band ligator device that had an elastic band attached to its tip was reinserted to the target diverticulum. The target diverticulum was suctioned into the cup of the band ligator, and the elastic band was released to stop the bleeding.

Follow-up endoscopy after initial endoscopic treatment

All patients in both groups were followed up for one year after the initial endoscopic hemostasis to check for rebleeding. Patients with continuous massive colorectal hemorrhaging after the initial endoscopic hemostasis underwent additional colonoscopy to identify the source of the colonic diverticular hemorrhaging. Lower gastrointestinal bleeding caused by other diseases, including ischemic colitis, colorectal cancers, vascular ectasia, hemorrhagic colitis, rectal ulcers, small intestinal bleeding, and post-polypectomy bleeding, were ruled out. We checked for endoscopic treatment imprints, such as residual clips, ligated band by EBL, and ulceration by EBL. The rebleeding diverticulum with the imprints was defined as the same diverticulum treated by the initial endoscopic hemostasis. The same diverticulum was defined as i) the residual clips with the recent hemorrhaging stigmata in the EC groups, and ii) ulceration and/or residual bands in the recent hemorrhaging stigmata in the EBL group.

Data analyses

All patients' clinical records, endoscopic images, and endoscopic reports were reviewed. Patients with definite diverticular hemorrhaging were retrospectively evaluated with respect to the following factors: age, sex, bleeding site (the right side of the colon, including the cecum, ascending colon, and transverse colon; and the left side of the colon, including the descending colon and sigmoid colon), hemoglobin value, comorbidities (hypertension, diabetes mellitus, chronic renal failure, cerebrovascular disease, and ischemic heart disease), prescription medications (anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs, steroids, and proton pump inhibitors), and the level of experience of the endoscopist who performed the hemostasis.

After performance of the Shapiro-Wilk test, Student's *t*-test or the Mann-Whitney U test was carried out for continuous variables. Pearson's chi-squared test or Fisher's exact test was used for categorical variables. We also performed a binary logistic regression analysis by including variables with a *p* value of <0.20 in the univariate analysis as well as clinically important variables. Differences were considered statistically significant at *p*<0.05. All analyses were performed with the SPSS software program, version 23 (IBM, Armonk, USA).

Table 1. A Univariate Analysis of the Characteristics of Patients with Definite Diverticular Hemorrhage.

Variable	EC (n=68)	EBL (n=67)	p value
Age, years	73 (64-86)	72 (63-81)	0.14
Male sex	30 (44)	48 (72)	0.11
Bleeding site			
Right colon	35 (51)	45 (67)	0.12
Hemoglobin, mg/dL	10.7±2.5	11.0±2.3	0.45
Comorbidities			
Hypertension	46 (68)	47 (70)	0.93
Diabetes mellitus	15 (22)	12 (18)	0.55
Renal failure	10 (15)	6 (9)	0.23
Cerebrovascular disease	9 (13)	7 (7)	0.23
Ischemic heart disease	17 (25)	13 (19)	0.36
Prescription medication			
Anticoagulants	5 (7)	9 (13)	0.37
Antiplatelet	27 (40)	17 (25)	0.12
NSAIDs	0 (0)	2 (3)	0.33
Steroids	2 (3)	2 (3)	0.57
PPI	17 (25)	15 (22)	0.61
Treated by expert endoscopist*	22 (32)	20 (30)	0.75

Data are presented as median (interquartile range), n (%), or mean±standard deviation. p values were tested by Student's t test or the Mann-Whitney U test for continuous variables and by Pearson's chi-square test or Fisher's exact test for categorical variables. *An expert endoscopist was defined as an endoscopist with >10 years of experience. EC: endoscopic clipping, EBL: endoscopic band ligation, NSAIDs: nonsteroidal anti-inflammatory drugs, PPI: proton pump inhibitor

Table 2. A Univariate Analysis of the Rebleeding Rate and Time to Rebleeding: An Evaluation in i) a Patient after Endoscopic Hemostasis and ii) a Patient with a Diverticulum Initially Treated by Endoscopic Hemostasis.

Variable	EC (n=68)	EBL (n=67)	p value
i) Evaluation of patient after endoscopic hemostasis			
Re-bleeding			<0.01
(+)	21 (31)	7 (10)	
(-)	47 (69)	60 (90)	
Days until rebleeding			0.19
	16 (5-60)	5 (2-71)	
ii) Evaluation of diverticulum initially treated by endoscopic hemostasis			
Re-bleeding			<0.01
(+)	15 (22)	4 (6)	
(-)	53 (78)	63 (94)	
Days until rebleeding			0.06
	24 (6-71)	3 (1-6)	

Data are presented as n (%) or median (interquartile range). p values were tested by Pearson's chi-square test or the Mann-Whitney U test. EC: endoscopic clipping, EBL: endoscopic band ligation

Results

Table 1 compares the characteristics of patients who underwent endoscopic hemostasis for definite diverticular hemorrhaging by EC versus EBL. The background characteris-

tics (age, sex, bleeding site, hemoglobin level, comorbidities, prescription medication, and experience level of the endoscopist) were not markedly different between the two groups. Adverse complications, including perforation, sepsis, and diverticulitis after endoscopic hemostasis, did not occur in the present study.

As shown in Table 2, the rebleeding rate within one year was evaluated both in the patients and in the diverticula treated by endoscopic hemostasis. In the patients, the rebleeding rate in the EBL group (7 of 67, 10%) was significantly lower than that in the EC group (21 of 68, 31%; $p<0.01$). This was due to the lower rebleeding rate of hemorrhagic diverticula treated by endoscopic hemostasis in the EBL group (4 of 67, 6%) than in the EC group (15 of 68, 22%; $p<0.01$). In contrast, the rebleeding rate from the same diverticulum was lower after EBL than EC, and the time span to rebleeding tended to be shorter after EBL (median of 3 days) than after EC (median of 24 days); however, this difference was not statistically significant.

Table 3 shows the risk factors for rebleeding within one year after endoscopic hemostasis. As indicated, only the therapeutic approach (EBL or EC) was a risk factor for rebleeding in all diverticula of a patient as well as in the same diverticulum initially treated by endoscopic hemostasis. Other factors, including the patients' characteristics, comorbidities, and prescription medications, were not risk factors for rebleeding.

Table 4 shows the result of a multivariate analysis with a

Table 3. A Univariate Analysis of the Risk Factors for Rebleeding after Endoscopic Hemostasis.

Variable	All the diverticulum (95% CI), p value	Same diverticulum (95% CI), p value
Treated by EBL	0.26 (0.10-0.67), <0.01	0.22 (0.07-0.72), <0.01
Age of >70 years	1.47 (0.61-3.56), 0.39	0.87 (0.33-2.33), 0.78
Bleeding site		
Right colon	1.96 (0.79-4.84), 0.14	2.94 (0.92-9.41), 0.06
Comorbidities		
Hypertension	0.94 (0.39-2.30), 0.90	1.83 (0.57-5.88), 0.31
Renal failure	1.32 (0.3- 4.46), 0.43	0.86 (0.18-4.11), 0.60
Cerebrovascular disease	1.46 (0.43-4.97), 0.38	0.93 (0.19-4.50), 0.65
Ischemic heart disease	1.55 (0.60-3.97), 0.36	1.30 (0.43-3.96), 0.42
Prescription medication		
Anticoagulants	0.27 (0.03-2.14), 0.17	0.44 (0.06-3.58), 0.38
Antiplatelets	1.19 (0.50-2.86), 0.69	0.51 (0.16-1.63), 0.25

Crude odds ratio of rebleeding from the all the diverticulum of the patient or the same diverticulum initially treated by endoscopic hemostasis. CI: confidence interval, EBL: endoscopic band ligation

Table 4. A Binary Logistic Regression Analysis of the Risk Factors for Rebleeding after Endoscopic Hemostasis.

Variable	All diverticulum (95% CI), p value	Same diverticulum (95% CI), p value
Treated by EBL	0.22 (0.08-0.59), <0.01	0.14 (0.04-0.50), 0.03
Bleeding site		
Right colon	3.00 (1.08-8.35), 0.04	4.48 (1.22-16.46), 0.02

Multiple analyses were performed according to the hemostasis method, age of >70 years, bleeding site, hypertension, renal failure, cerebrovascular disease, ischemic heart disease, anticoagulants, and antiplatelets. Odds ratio of rebleeding from the all the diverticulum of the patient or the same diverticulum initially treated by endoscopic hemostasis. CI: confidence interval, EBL: endoscopic band ligation

binary logistic regression analysis. The analysis was performed with a focus on the endoscopic hemostasis technique (EBL or EC), age, bleeding site, comorbidities (hypertension, renal failure, cerebrovascular disease, and ischemic heart disease), and prescription medications (anticoagulants and antiplatelets). Endoscopic hemostasis performed with EBL decreased the rebleeding risk in all of the diverticula of a patient [odds ratio (OR), 0.22; 95% confidence interval (CI), 0.08-0.59; $p < 0.01$] as well as in the same diverticulum initially treated by endoscopic hemostasis (OR, 0.14; 95% CI, 0.04-0.50; $p = 0.03$). The multivariate analysis indicated

that the risk of rebleeding after endoscopic hemostasis was significantly higher for bleeding diverticula on the right side of the colon as evaluated in all of the diverticula of a patient (OR, 3.00; 95% CI, 1.08-8.35, $p = 0.04$) as well as in the same diverticulum initially treated by endoscopic hemostasis (OR, 4.48; 95% CI, 1.22-16.46, $p = 0.02$).

Discussion

The present historical control trial investigated the rebleeding rate of colonic diverticular hemorrhaging within one year after initial treatment by endoscopic hemostasis. The rebleeding rate was lower in the EBL group than in the EC group, especially for the same diverticulum initially treated by endoscopic hemostasis. In some previous studies, the prognosis for definitive colonic diverticulum hemorrhaging was better in the endoscopic therapy group in that the rate of rebleeding was low (3, 16-27). Among endoscopic therapy techniques, EBL resulted in a lower rebleeding rate than did EC (18, 19). The current study suggested that the lower rebleeding rate in the EBL group might have been attributable to a reduced rate of rebleeding from the same diverticulum.

The possible reasons for the better prognosis of rebleeding in the EBL than EC group are as follows: i) Most definitive diverticular bleeds with stigmata of recent hemorrhaging had a superficial arterial flow under the stig-

mata (16, 28), inducing appropriate hemostasis of EBL and obliterating the blood flow under the diverticulum with consequent reduced rebleeding; ii) the scar formation after EBL might contribute to a lower rebleeding rate, as reported in a previous study (18).

In cases of rebleeding in the EBL group, the median duration until rebleeding from the same diverticulum was 3 days (range, 1-6 days). Possible reasons for rebleeding from the same diverticulum within 7 days include unfastening of the initial band ligation for the bleeding diverticulum, insufficient suction before band ligation, and improper placement of band ligation. In the current study, the risk of rebleeding from the same diverticulum was low in the absence of rebleeding at the 1-week observation after EBL. This is helpful for the clinical observation of colonic diverticular hemorrhaging after EBL.

Bilateral diverticulosis increased the risk of diverticular hemorrhaging (29-31). The risk of recurrence was high in diverticular hemorrhaging on the right side of the colon, especially in the ascending colon after hemostasis with EC (32, 33). These data were consistent with the present finding that bleeding from the diverticulum on the right side of the colon was an independent risk factor for rebleeding. The possible explanations were as follows: i) In Japan, diverticula predominantly develop on the right-sided colon and extend to the left-sided and bilateral colon with aging (34); ii) diverticular bleeding is more easily detected on the right side of the colon than on the left side (22, 32); and iii) the therapeutic approach with colonoscopy was more difficult to perform on the right side of the colon because of poor operability due to hyperactivity of the right colon and massive bleeding. One study, on the other hand, indicated that diverticular hemorrhaging on the left colon was a significant risk factor for early rebleeding (24), which might remain the further explanation for the relationship between the risk of rebleeding and the colon-site.

Our previous study revealed that the cost of hospitalization for colonic diverticular bleeding depended on the rate of repeated bleeding (3). The EBL approach, with its low rebleeding rate, might contribute to the cost-effectiveness of hospitalization for patients with diverticular bleeding. These results suggest that EBL should be the first-choice treatment for a colonic diverticulum, whereas the application of EBL for a bleeding diverticulum might be difficult due to massive bleeding or thick overlying tissue (3, 17-28, 35-40).

This study is associated with several limitations. First, this was a retrospective chart review in a historical control study, which might limit the generalizability of the results across other patient populations. Second, this study was conducted with a limited number of patients. Third, the study was a multicenter trial, and it was difficult to assess the skill level of the endoscopists among the centers. Prospective randomized controlled trials are required to perform accurate comparisons. However, given that the superiority of EBL for definitive diverticular hemorrhaging has already been demonstrated to some extent (18, 19), the clinical significance of

conducting a prospective or randomized controlled trial is unclear.

In conclusion, the lower rebleeding rate in the EBL group than in the EC group may be attributable to the low degree of rebleeding from the same diverticulum, indicating that EBL is superior to EC for preventing rebleeding from an initially successfully treated diverticulum.

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

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