Recent Trends in Treatment for Colonic Diverticular Bleeding in Japan

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Keywords

Colonic diverticular bleeding · Endoscopic treatment · Nonsteroidal anti-inflammatory drugs

Abstract

Background: In both Western countries and in Japan, the incidence of colonic diverticular bleeding has increased with increased use of antithrombotic and nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, the Japan Gastroenterological Association issued guidelines for colonic diverticular bleeding and colonic diverticulitis in Japanese in 2017 and in English in 2019. However, the guidelines contain unresolved problems. Herein, we review the recent treatment trends for colonic diverticular bleeding in Japan. **Summary:** Colonic diverticular bleeding necessitates frequent blood transfusions due to rebleeding, and patients require prolonged hospitalization. Endoscopic treatment plays an important role in treating diverticular bleeding. Currently, endoscopic band ligation (EBL) and endoscopic clipping are used in Japan for diverticular hemorrhage when the source of the hemorrhage is identified. EBL results in significantly lower early (<30 days) and 1-year rebleeding rates and long-term recurrence rates compared with endoscopic clipping. Furthermore, the proportion of patients requiring transcatheter arterial embolization or surgery after EBL is significantly lower than that following endoscopic clipping. Several reports state that EBL is superior to endoscopic clipping; however, EBL has associated complications, and it is necessary to carefully consider the individual patient. **Key Messages:** EBL

is superior to endoscopic clipping regarding short- and long-term rebleeding rates and the rate of transition to surgery and embolization. Methods for preventing diverticular hemorrhage have not been established, but NSAIDs should be discontinued if possible. Prevention strategies for diverticular bleeding need to be evaluated in studies with large sample sizes.

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Introduction

In both Western countries and in Japan, the number of patients with colonic diverticula has increased due to changing dietary habits and aging [1, 2]. The incidence of colonic diverticular bleeding has also increased with increased antithrombotic and nonsteroidal anti-inflammatory drug (NSAID) use for age-related arteriosclerosis and musculoskeletal diseases [3–7].

Colonic diverticula occur mainly in the sigmoid colon in Western countries, whereas the right colon is more commonly involved in Asian countries [2, 8]; however, the proportion of diverticula in the left colon increases with age. As the location of the diverticulum differs with race, diverticular bleeding sites differ between Japan and Western countries [2]. In addition, contrast-enhanced computed tomography (CE-CT) is more widely available in Japan compared with other countries [9]. Thus, there are several differences in the treatment and diagnosis of diverticular bleeding between Japan and other countries,

and management adapted to Japanese circumstances is needed. Guidelines for colonic diverticular bleeding and colonic diverticulitis were issued by the Japan Gastroenterological Association in Japanese in 2017 and in English by 2019 [10]. However, there are unresolved problems in the guidelines, and several endoscopic treatments have become more widely used since the publication of these guidelines. A workshop on diverticular hemorrhage was held at the 15th annual meeting of the Japanese Gastroenterological Association in February 2019. Based on the contents of this workshop, we herein review the recent epidemiology, diagnosis, endoscopic treatments, and outcomes of diverticular bleeding in Japan.

Epidemiology

A cohort study from Japan showed that the cumulative incidence of diverticular bleeding is 0.21% at 1 year, 2.2% at 5 years, and 10% at 10 years, and that the overall incidence is 0.46 per 1,000 patient-years [8]. Additionally, the 1- and 2-year recurrence rates of colonic diverticular bleeding in Japan are 20–35% and 33–42%, respectively [7, 11, 12]. The incidence of colonic diverticular bleeding in Japan increased significantly from 1.02% in 2003 to 1.67% in 2011 due to an increased number of patients aged 40–59 years [2]. The incidence of diverticular bleeding increased during the 9-year study period, even when the data were adjusted in accordance with age and sex [2]. Another report stated that the incidence of diverticular bleeding in the lower gastrointestinal tract increased from 5.9% from 1995 to 2006 to 23.0% from 2007 to 2013 [1]. The incidence of diverticular bleeding tended to increase each year, with a marked increase after 2003 [1].

Diverticular hemorrhage is clearly increasing in Japan, and it is important to know the risks of bleeding and rebleeding. Several reports discuss the risk of colonic diverticular bleeding and recurrence. Conditions that increase the risk of diverticular bleeding are hypertension, diabetes mellitus, cardiovascular disease, and high body mass index [7, 13]. Smoking and drinking may also increase the risk of diverticular bleeding [4]. In addition, NSAIDs (including aspirin) increase the risk of bleeding via diverticular mucosal injury [3–7, 13] and are significant risk factors for colonic diverticular bleeding in patients older than 65 years [6]. The risk of diverticular bleeding secondary to NSAIDs has an OR of 2.8–7.5 [3–7]. Furthermore, dual NSAID or antiplatelet therapy carries a higher risk of diverticular bleeding than monotherapy (single NSAID, adjusted OR [aOR] 3.6, $p < 0.01$; dual NSAID

therapy, aOR 23, $p < 0.01$; single antiplatelet drug, aOR 2.0, $p < 0.01$; dual antiplatelet therapy, aOR 4.1, $p < 0.01$) [5]. The risk of recurrent bleeding is increased in patients receiving NSAIDs or steroids and in patients <50 years of age or with a history of diverticular bleeding [6, 7, 11, 12, 14]. One report stated that the long-term recurrence of diverticular bleeding decreases when NSAIDs are discontinued; the probability of recurrence at 12 months is 9.4% in patients who discontinue NSAIDs compared with 77% in continued users [15]. Thus, NSAIDs should be discontinued if possible, but cessation of antiplatelet drugs may lead to cardiovascular events.

Diagnosis

Colonoscopy can be used for both diagnosis and treatment of diverticular bleeding. Rebleeding rates are high (65.8%) without endoscopic treatment for stigma of recent hemorrhage (SRH)-positive diverticula [16]; therefore, SRH-positive diverticula are an indication for endoscopic hemostasis. Urgent colonoscopy within 12–24 h of admission has a higher rate of SRH identification [17], and the rapid identification of SRH contributes to the success rate of endoscopic treatment. Therefore, the Japanese guidelines recommend colonoscopy as an initial diagnostic modality in patients with diverticular bleeding [10].

Nagata et al. [9] reported that the detection rate is significantly higher with colonoscopy following CE-CT for vascular lesions (35.7%) versus colonoscopy alone (20.6%; $p = 0.01$), leading to an increase in the incidence of cases treated endoscopically (34.9% for colonoscopy after CE-CT versus 13.4% for colonoscopy alone; $p < 0.01$). Sugiyama et al. [18] also reported that colonoscopy after CE-CT with bleeding has a significantly higher detection rate (60%) compared with colonoscopy alone (31%; $p < 0.05$). However, because of the limited evidence supporting CE-CT before colonoscopy, CE-CT is recommended only in a select group of patients [2, 10].

In addition to the order of examinations, the timing of CE-CT or colonoscopy following bleeding is also important [9, 17–19]. One study reported that the rate of extravasation tends to be high when CE-CT is performed within 2 h of the last episode of hematochezia [10]. Additionally, the interval between the first hematochezia and colonoscopy in cases where the bleeding point was detected by colonoscopy (median 23.5 h) is shorter than that in cases where the bleeding point is not detected (median 43.6 h). The bleeding diverticulum is more often

Fig. 1. Images of EBL for colonic diverticular hemorrhage. **a** The diverticulum is marked with endoclips before the colonoscope is removed. **b** The target diverticulum is suctioned in the band ligation cup. **c** Endoscopic view of a lesion treated with EBL.

Fig. 2. Images of endoscopic clipping for colonic diverticular hemorrhage. **a** Colonic diverticulum with active bleeding. **b** Indirect placement of hemoclips to achieve complete closure of the diverticular orifice.

identified when colonoscopy is performed early versus late ($p < 0.01$) [18]. However, large prospective studies are needed to determine the optimal time to perform CE-CT and/or colonoscopy after diverticular bleeding.

Endoscopic Treatments

Diverticular hemorrhage has a high hemostatic rate of 70–80%, even with conservative treatment alone. However, without endoscopic treatment, the incidence of rebleeding is very high [10]. Frequent blood transfusions associated with rebleeding and prolonged hospitalization are clinical problems, and endoscopic treatment is important in preventing rebleeding. Currently, endoscopic

band ligation (EBL) and endoscopic clipping are used in Japan for diverticular hemorrhage when the source of the hemorrhage is identified [20–24].

In EBL, an SRH-positive diverticulum is identified and marked with endoclips before the colonoscope is removed. The colonoscope is then reinserted to the target diverticulum with an elastic-band-ligator device. The target diverticulum is suctioned into the band ligator cup, and the elastic band is released to stop the bleeding (Fig. 1).

Endoscopic clipping is performed directly on the vessels whenever possible. When direct placement cannot be performed because of a deep diverticulum or massive hemorrhage, multiple clips are placed indirectly in a zipper fashion to close the bleeding diverticulum (Fig. 2).

Table 1. Outcomes of diverticular bleeding treated with EBL or EC

Study [Ref. No.]	Number of patients	Bleeding rate, %		<i>p</i> value	Follow-up period
		EBL	EC		
Setoyama et al. [22], 2011	66	5.6	33.3	0.018*	30 days
Nakano et al. [20], 2015	100	14, 23, 26, 41	38, 49, 59, 68	0.0036**	1, 12, 24, 36 months
Nagata et al. [23], 2018	108	11.5	37.0	0.018*	1 year
Okamoto et al. [24], 2018	135	10.0	31.0	<0.01*	1 year
Ikeya et al. [14], 2015	101	15.0			30 days

* Chi-square test.

** Kaplan-Meier method.

EBL, endoscopic band ligation; EC, endoscopic clipping.

The primary hemostasis rate is approximately 90% for both endoscopic clipping and EBL, with no significant difference between the 2 techniques [21]. In addition, the selection of endoscopic treatment method does not significantly differ between high-volume centers (≥ 700 beds) and low-volume centers [19].

Recently, reports have described hemostasis for colonic diverticular bleeding using an over-the-scope clip (OTSC) system [25]. The OTSC system was developed to close perforations, leaks, and fistulas; however, this system is not used commonly in Japan and has only been reported in limited cases such as older patients with high surgical risks and several comorbidities. Another method called endoscopic detachable snare ligation (EDSL) has been used instead of EBL to treat colonic diverticular bleeding because it does not require reinsertion of the colonoscope; the early rebleeding rate is reportedly significantly lower for EDSL (6.8%) than for endoscopic clipping (23%) [26]. However, EDSL has only been evaluated in a few reports, and more research is needed to compare EDSL with endoscopic clipping and EBL.

Table 1 shows the main studies in Japan that have evaluated the outcomes of endoscopic clipping and EBL [14, 20, 22–24]. The early (<30 days) and 1-year rebleeding rates are significantly lower after EBL compared with endoscopic clipping. This difference is mainly secondary to the significantly lower rebleeding rate from the same hemorrhagic diverticulum initially treated by endoscopic hemostasis via EBL (6%) versus endoscopic clipping (22%; $p < 0.01$) [24]. Patients with early rebleeding (≤ 7 days) have bleeding from the same diverticulum, while patients with late rebleeding (after 2 months) have bleeding from a different diverticulum [24]. In other words, early rebleeding is mainly secondary to inadequate hemostasis [23, 24].

Nakano et al. [20] reported cumulative incidences of rebleeding at 1, 12, 24, and 36 months after first treatment of 14, 23, 26, and 41% after EBL and 38, 49, 59, and 68% after endoscopic clipping, respectively (log-rank test, $p = 0.0036$). Long-term outcomes following EBL for colonic diverticular bleeding are significantly superior to those after endoscopic clipping. There are 2 reasons that EBL has a lower rebleeding rate than endoscopic clipping. First, diverticular bleeding with SRH has superficial arterial flow under the stigma [16], and so ligating the superficial blood vessels with EBL will also block the blood flow under the diverticulum and stop the bleeding more reliably compared with endoscopic clipping. Second, EBL causes the diverticulum to become scarred and disappear [20]. The risk factors for rebleeding after EBL are diverticula in the left colon, age <50 years, active bleeding, high body mass index, and the use of NSAIDs or antiplatelet drugs [11–14].

EBL results in a significantly smaller proportion of patients requiring transcatheter arterial embolization or surgery than endoscopic clipping ($p = 0.003$) [21]. However, although several reports state that EBL produces better results than endoscopic clipping, EBL cannot be selected in all patients. If the diverticulum is firm or large, sufficient suction may not be obtained, and EBL treatment may fail. Although EBL is considered a safe method, it does carry the risk of perforation due to aspiration of the thin diverticular walls. Some reports have also described complications such as delayed perforation and diverticulitis after EBL, with a high risk in patients using steroids and those receiving hemodialysis [27, 28]. The appropriate endoscopic treatment should be selected in consideration of the location and size of the diverticulum and the use of steroids and hemodialysis. In particular, EBL might be difficult when the bleeding point is in the proximal colon.

Increased medical costs secondary to an aging population is an important issue in Japan, and it is important to obtain information about expensive treatments and the risks of expensive medical care. Endoscopic colonic hemostasis costs 103,900 yen, and blood transfusions cost 3,500–4,500 yen (2019 medical care fees in Japan). The prices of the endoscopic treatment tools for EBL (MD-48710 EVL Devices; Sumitomo Bakelite Company, Tokyo, Japan), endoscopic clipping (EZ clip™; Olympus, Tokyo, Japan), and an OTSC system are 14,500 yen/kit, 975 yen/clip, and 79,800 yen/set, respectively. Thus, the OTSC method is very expensive compared with endoscopic clipping and EBL.

Regardless of the type of endoscopic treatment and antithrombotic drugs, blood transfusion (OR 3.8, $p = 0.048$) and rebleeding (OR 5.3, $p = 0.017$) result in high hospitalization costs [29]. The independent risk factors for blood transfusion requirement are female sex (OR 2.5, $p = 0.02$), warfarin use (OR 9.3, $p < 0.01$), and chronic kidney disease (OR 5.9, $p < 0.01$) [30]. Furthermore, age >70 years (OR 2.1, $p = 0.04$) and NSAID use (OR 11, $p < 0.01$) are independent risk factors for prolonged hospitalization (>8 days) [30]. Patients at high risk for blood transfusion must be treated carefully and completely, and each physician should be aware of the risks and be mindful of preventing excessive treatment.

Conclusion

We described the recent trends in treating diverticular hemorrhage in Japan. Although EBL has many advantages over endoscopic clipping, the indications for each treatment must be considered for each patient. Furthermore, validation of EDSL and EBL is still limited, and further research is needed. Regarding EBL, long-term studies are required, and verification is required to determine the ideal timing of CE-CT and colonoscopy. The indications for diverticular hemorrhage prevention methods are unclear; however, discontinuation of NSAIDs is recommended when possible. The prevention of diverticular bleeding needs to be investigated in studies with large sample sizes.

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Disclosure Statement

The authors declare no conflicts of interest regarding this review article.

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