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Long-Term Outcome after Double-Balloon Endoscopy in Patients with Obscure Gastrointestinal Bleeding

Minoru Fujita[a] Noriaki Manabe[b] Keisuke Honda[c] Ken-ichi Tarumi[a]
Takahisa Murao[a] Shinji Katada[a] Yoshiki Kimura[a] Hiroshi Matsumoto[a]
Tomoari Kamada[a] Akiko Shiotani[a] Jiro Hata[b] Ken Haruma[a]

[a]Division of Gastroenterology, Department of Internal Medicine, [b]Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, and [c]Department of General Medicine, Kawasaki Medical School, Kurashiki, Japan

Key Words
Obscure gastrointestinal bleeding · Double-balloon endoscopy · Long-term outcome

Abstract
Background and Aims: There are limited data concerning the clinical outcome of patients with obscure gastrointestinal bleeding (OGIB) after double-balloon endoscopy (DBE). The aim of the present study was to evaluate the long-term outcome of patients with OGIB after DBE. ***Patients and Methods:*** Eighty-seven consecutive patients with OGIB (47 men and 40 women; mean age 65.3 years) underwent DBE between July 2006 and December 2009. The criteria for assessment included documented iron deficiency anemia/occult or obscure small intestinal bleeding, and overt small intestinal bleeding. They were followed for a mean period of 41.4 months after DBE, and were divided into two groups according to their outcome, that is a good clinical course group (GC group) and a poor clinical course group (PC group). The clinical characteristics associated with rebleeding after DBE were analyzed by comparison of these two groups. ***Results:*** The source of bleeding was identified in 40 patients (46.0%) and endoscopic treatment was required in 21 of them (52.5%). The most frequent source of bleeding was ulcers/erosions (18.4%). During the follow-up period, 39 patients (44.8%) experienced bleeding and/or persistent iron deficiency anemia after DBE, while 48 patients did not. There were no significant differences of clinical characteristics between the two groups. However, there were more patients with diverticular bleeding in the GC group than the PC group, and there were significantly more patients with treatable small intestinal tumors/polyps in the GC group. There were also more patients with normal DBE findings in the GC group. ***Conclusion:*** This study demonstrated that the rebleeding rate after DBE varies depending on the source of bleeding.

Introduction

Gastrointestinal (GI) bleeding is frequently encountered in daily practice. Among patients with GI bleeding, up to 5% with recurrent bleeding cannot be diagnosed by upper GI endoscopy and colonoscopy, with the source of bleeding presumably being located in the small intestine

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Noriaki Manabe, MD, PhD
Division of Endoscopy and Ultrasonography
Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School
577 Matsushima, Kurashiki, Okayama 701-0192 (Japan)
Tel. +81 86 462 1111, Fax +81 86 462 1199, E-Mail n_manabe@hkg.odn.ne.jp

[1]. This is known as obscure GI bleeding (OGIB). It is difficult to locate the source of bleeding in patients with OGIB and frequent blood transfusions are often required. Therefore, it is considered that OGIB represents a distinct clinical entity with a significantly worse outcome than upper GI bleeding or colonic bleeding [2].

Capsule endoscopy is a non-invasive examination that has led to significant advances in the diagnosis of OGIB [3], but it does not allow the operator to carry out tissue sampling or treatment. On the other hand, the double-balloon endoscopy (DBE) method of Yamamoto et al. [4] allows to-and-fro observation and even therapeutic intervention can be performed. The usefulness of DBE for the diagnosis and treatment of small bowel lesions has been documented [5–7]. However, the long-term outcome after DBE in patients with OGIB is not completely known. The aim of this study was to evaluate the long-term outcome in patients with OGIB who underwent DBE at our hospital.

Patients and Methods

Inclusion/Exclusion Criteria

Between July 2006 and December 2009, 87 consecutive patients with OGIB underwent DBE at Kawasaki Medical School Hospital. All of the patients had previously undergone more than one upper and lower endoscopic examination without the source of bleeding being identified. Exclusion criteria were cardiopulmonary disease or severe liver dysfunction that prohibited conscious sedation and coexistence of non-bleeding disorders that could cause anemia (e.g., hematogenous malignancy or renal failure). Informed consent was obtained from each patient before the procedure.

Double-Balloon Endoscopy

The DBE system (Fujinon Toshiba ES System Co. Ltd, Tokyo, Japan) consisted of a video endoscope with a biopsy channel that had an internal diameter of 2.2 mm (EN-450P5) or 2.8 mm (EN-450T5), a flexible overtube, and a balloon controller.

The endoscope was advanced into the distal small intestine via either an oral or anal approach. In preparation for this procedure, we instructed patients to fast overnight for the oral approach, while preparation for the anal approach was the same as that for colonoscopy. In the 59 emergency patients with active bleeding, we performed DBE without any bowel preparation. All patients were premedicated with 0.1 mg/kg of midazolam by intravenous injection. In addition, they were given 10 mg of scopolamine butylbromide intravenously if they complained of abdominal pain due to spasm of the small bowel.

Before endoscope insertion, the overtube was advanced over the endoscope from the tip with both balloons deflated. When both balloons reached the duodenum via the oral approach or the cecum via the anal approach, the balloon attached to the overtube was inflated to fix the tube at that site in intestine. Then the endoscope was inserted further after the overtube had been immobilized. When the tip of the endoscope had been advanced as far as possible, the overtube balloon was deflated and the overtube was advanced along the endoscope towards its tip. When the end of the overtube again reached the tip of the endoscope, the overtube balloon was reinflated to maintain the tube in position. Subsequently, the overtube was gently withdrawn with its balloon inflated so that the intestine became bunched on the overtube, which prevented looping of the endoscope. This sequence was repeated until the entire small bowel had been examined. The route of insertion was chosen according to the suspected location of the lesion as estimated from clinical findings. Oral insertion was chosen when a jejunal lesion was suspected (usually in patients with melena), and anal insertion was chosen when an ileal lesion was suspected (usually in patients with hematochezia). If it was difficult to determine the possible location of the lesion, we tried the oral route first.

For all lesions observed by DBE, biopsy specimens were obtained and treatment was provided as necessary. We closely monitored changes of the pulse rate and oxygen saturation during the procedure.

Assessment of Endoscopic Findings

We categorized the sources of small bowel bleeding as ulcers/erosions, vascular lesions, tumors/polyps, and diverticula. When two or more possible sources of bleeding were observed, we documented the lesion most likely to be responsible for bleeding. In this study, no patient was determined to have two or more definite bleeding sources. We did not evaluate small intestinal lesions that could not be considered as bleeding sources, such as small lipomas, tiny non-bleeding polyps, small diverticula without vessels (<1.0 cm), lymphangiectasia, and other non-significant findings.

Endoscopic Treatment

We did not perform endoscopic treatment of ulcers unless the ulcer was accompanied by visible bleeding vessels. For vascular lesions, we generally performed endoscopic hemostasis by argon plasma coagulation, electrocoagulation, or clipping (fig. 1a, b) according to the type of lesion on the basis of the Yano-Yamamoto classification [8]. For tumors, we generally performed endoscopic mucosal resection as long as the tumor diameter was <1.5 cm.

Data Collection

This study was approved by our institutional review board. The medical charts of all patients with OGIB who underwent DBE were reviewed. From these charts, we retrospectively obtained information on patient characteristics, symptoms related to GI bleeding at the first visit to our hospital, and medications that could influence GI bleeding. In 2009, symptoms related to GI bleeding and medications were evaluated at long-term follow-up by mail contact with 59 patients and telephone contact with 28 patients who did not respond to mail contact.

Categorization of the Outcome

Based on the long-term outcome, the patients were divided into two groups, which were a good clinical course group (GC group) and a poor clinical course group (PC group). The GC group included patients whose GI bleeding stopped and whose iron deficiency anemia improved after DBE, while the PC group was formed by patients who had relapse of bleeding and/or persistent iron deficiency anemia during the follow-up period.

Statistical Analysis

Data are expressed as the mean ± SD. Results were analyzed by the Mann-Whitney U test for comparison of two independent groups. The χ^2 test (with Yates' correction, if required) was used to compare proportional data. The criterion for statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

Demographic data on the patients with OGIB who underwent DBE are shown in table 1. The mean duration of follow-up was 40.4 ± 16.2 months (range 2–66). A total of 72 patients (82.8%) had coexisting diseases, including chronic renal failure in 13, hypertension in 9, cardiovascular disease in 8, malignancy in 8, chronic hepatitis and/or liver cirrhosis in 7, cerebrovascular disease in 6, arteriosclerosis obliterans and/or abdominal aortic aneurysm in 5, and diabetes in 5 patients. The duration of OGIB was 38.4 ± 15.8 months. The mean hemoglobin (Hb) was 9.2 ± 2.5 g/dl. A total of 32 patients (36.8%) required red blood cell transfusion and the mean transfusion volume was 4.4 ± 4.9 units. Fourteen patients were taking low-dose aspirin, 14 patients were using warfarin sodium, and 6 patients were on non-steroidal anti-inflammatory drugs (NSAIDs).

Diagnosis of OGIB by DBE

DBE was performed successfully in all 87 patients without any complications. We examined the small intestine via the oral approach in 31 patients, via the anal approach in 30 patients, and via both the oral and anal approaches in 30 patients (total endoscopy). Among the 87 patients, 40 were identified as having potential sources of small intestinal bleeding, for an overall diagnostic yield of 46.0%. The diagnostic yield was 55.0% (22/40) for the oral approach, 27.5% (11/40) for the anal approach, and 17.5% (7/40) for the combined approaches. The potential bleeding sources could be divided into four main groups, as summarized in table 2. There were 16 ulcers/erosions, including 6 NSAID ulcers, 3 ulcers due to Crohn's disease, 2 tuberculous ulcers, 1 anastomotic ulcer, 1 ulcer due to cytomegalovirus infection, and 3 other small intestinal ulcers. There were 9 vascular lesions, including 7 telangiectasias, 1 arteriovenous malformation, and 1 case of Rendou-Osler-Weber disease. In addition, there were 10 tumors/polyps (3 cancers, 2 stromal tumors, 2 malignant lymphomas, 1 carcinoid, 1 metastatic tumor, and 1 hamartoma) and 5 diverticula (4 small intestinal diverticula and 1 Meckel's diverticulum).

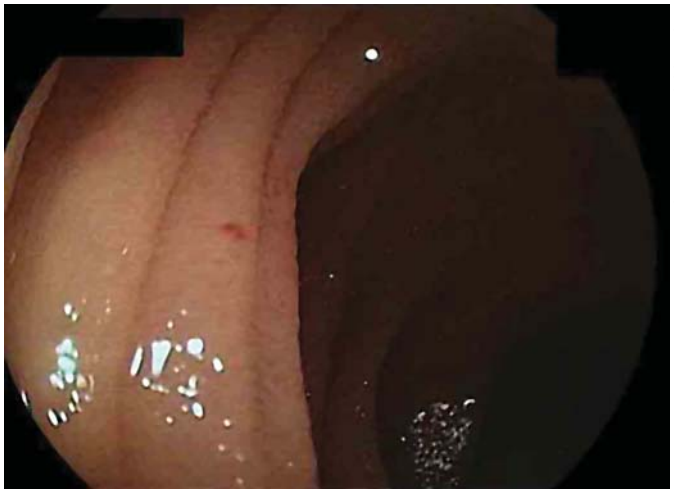

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Fig. 1. An 81-year-old woman was admitted for investigation of OGIB. She was taking warfarin sodium for the treatment of aortic stenosis. Recurrent melena and iron deficiency anemia had continued for 3 years without any site of bleeding having been identified by either upper GI endoscopy or colonoscopy. A DBE image (oral approach) shows an area of punctate erythema with oozing in the proximal jejunum.

Table 1. Characteristics of the 87 patients

Male/female	47/40
Mean age ± SD, years	65.3 ± 15.3
Mean duration of follow-up ± SD, months	40.4 ± 16.2
Mean duration of OGIB ± SD, months	38.4 ± 15.8
Medications	
Low-dose aspirin	14
Warfarin sodium	14
NSAIDs	6

OGIB = Obscure gastrointestinal bleeding; NSAIDs = non-steroidal anti-inflammatory drugs.

Treatment

Among the 40 patients with an endoscopic diagnosis of small intestinal bleeding, 21 (52.5%) received treatment. Among the 7 patients with angiodysplasia, 3 received endoscopic clipping and 1 underwent transcatheter arterial embolization. The patient with arteriovenous malformation also received transcatheter arterial embolization. Among the 16 patients with ulcers/erosions, 2 with NSAID ulcers received argon plasma coagulation and endoscopic clipping, 1 with Crohn's disease received surgical resection, 2 with Crohn's disease were treated with anti-tumor

Table 2. Endoscopic diagnosis and treatment in the two groups

	GC group (n = 48)		PC group (n = 39)	
Ulcerative lesions	6		10	
	NSAID-induced	3	NSAID-induced	3
	Crohn's disease	1	Crohn's disease	2
	tuberculous	1	tuberculous	1
	cytomegalovirus infection	1	anastomotic	1
Treatment	clipping	1	clipping	0
	argon plasma coagulation	0	argon plasma coagulation	1
	surgical resection	0	surgical resection	1
	discontinuation of NSAIDs	1		
	anti-TNF-α antibody	1	discontinuation of NSAIDs	1
	ganciclovir	1	anti-TNF-α antibody	1
	no treatment	2	no treatment	2
Vascular lesions	4		5	
	telangiectasia	4	telangiectasia	3
			arteriovenous malformation	1
			Rendou-Osler-Weber disease	1
Treatment	clipping	2	clipping	2
	transcatheter arterial embolization	1	transcatheter arterial embolization	1
	argon plasma coagulation	1	argon plasma coagulation	1
Tumorous lesions	6		4	
	cancer	2	malignant lymphoma	2
	stromal tumor	2	cancer	1
	carcinoid	1	metastatic tumor	1
	hamartoma	1		
Treatment	endoscopic or surgical resection	6*	endoscopic or surgical resection	0
	chemotherapy	0	chemotherapy	2
			no treatment	2
Diverticula	5*		0	
	small intestinal diverticula	4		
	Meckel's diverticulum	1		
Treatment	1		0	
	surgical resection	1		
No lesion		20		12

GC group = Good clinical course group; PC group = poor clinical course group. * $p < 0.05$ vs. PC group.

necrosis factor-α antibody, 1 with cytomegalovirus infection was treated by ganciclovir, and 2 patients with NSAID ulcers were managed by stopping administration of the culprit drugs. Eight patients with ulcers/erosions were observed conservatively. Among the 10 patients with tumors/polyps, 1 with cancer, 2 with stromal tumors, and 1 with carcinoid received surgical treatment. One patient with malignant lymphoma received chemotheraphy and the patient with a hamartoma underwent endoscopic polypectomy. Among 5 patients with diverticula, the patient with a Meckel's diverticulum underwent surgical resection.

Long-Term Outcome

There were 48 patients (55.2%) in the GC group and 39 patients (44.8%) in the PC group (table 2). There were no significant differences between these two groups with regard to age, gender, observation period, and use of anticoagulants such as low-dose aspirin and/or warfarin. Among the patients with normal findings at the first DBE procedure, 62.5% had no recurrent bleeding during the follow-up period. There were more patients with normal DBE findings in the GC group. Regarding the source of bleeding, diverticulum was more frequent in the GC

group than in the PC group ($p < 0.05$), while there were no significant between-group differences in the number of patients with ulcers/erosions, vascular diseases, or tumors/polyps.

The treatment of both groups is shown in table 2. There were no significant between-group differences of the treatment provided for ulcers/erosions, vascular diseases, and diverticula. However, significantly more patients with small intestinal tumors/polyps received treatment in the GC group ($p < 0.05$) (table 2).

Discussion

This study showed that 48% of patients with OGIB had no further small intestinal bleeding at a mean follow-up period of 41.4 ± 16.5 months after DBE. The most common source of bleeding was ulcerative lesions. The rate of recurrent bleeding and/or need for iron therapy or transfusions was high with ulcerative and vascular lesions, unlike tumors and diverticula. In addition, 62.5% of OGIB patients with normal findings at the first DBE procedure had no further episodes of bleeding during the follow-up period.

DBE was first described by Yamamoto et al. [9] in 2001, and it allows complete endoscopic visualization and treatment of the small intestine. According to previous reports, OGIB was the indication for DBE in 36–100% of examinations and the overall diagnostic yield of DBE ranged from 43 to 80% [10–12]. Diagnostic or therapeutic success was reported in 55–75% of examinations, but the long-term outcome of patients with OGIB after DBE has not been studied in detail. In fact, there have been only two reports on the outcome of DBE with a follow-up period of more than 2 years [13, 14]. A study by Gerson et al. [13] examined the long-term outcome in 135 patients with OGIB who underwent DBE. According to their study, approximately 60% of patients had no bleeding after an average follow-up period of 30 months. In addition, a study by Shinozaki et al. [14] examined the outcome after 2.4 years in 151 patients undergoing DBE for OGIB, and they reported that small intestinal bleeding was controlled in 64% of the patients. In the present study, 55.1% of patients had no bleeding after a mean follow-up period of 3.4 years. The rate of freedom from small intestinal bleeding was lower in our study than in the two previous reports. There are at least two possible reasons for the lower rate of bleeding control in the present series. First, we had 71 patients (81.6%) with concomitant diseases such as cardiovascular disease, cerebrovascular disease, and arteriosclerosis obliterans and/or abdominal aortic aneurysm, among whom 19 patients (21.8%) could not stop anticoagulant therapy and this may have increased the risk of recurrent bleeding. Second, the lower rate of control may have been related to the difference in the follow-up period, since our follow-up period was longer than those of the two previous studies. It has been reported that there has been a significant increase in the incidence of coronary heart disease and that use of anticoagulants is increasing [15]. In Japan, the elderly population with artrial fibrillation is increasing, and the need for anticoagulant therapy is also increasing as a result [16]. Therefore, we did not consider the profile of our study subjects to be unusual, even though their mean age was slightly older than that of the subjects in the previous two studies.

In the current study, we demonstrated that both small intestinal vascular lesions and ulcerative lesions were associated with lower rates of control of OGIB after DBE than other small intestinal lesions. With regard to vascular lesions, our results are consistent with some previous reports that small bowel bleeding arising from vascular lesions is difficult to control [14, 17]. There are at least two possible reasons for the lower rate of control of bleeding from small intestinal vascular lesions. First, the patients with vascular lesion often tended to have multiple lesions. When we encounter small intestinal bleeding from multiple vascular lesions, it may be impossible to treat all of the lesions. In the present study, 7 patients (77.8%) had multiple vascular lesions and 6 of them (85.7%) had recurrent bleeding during the follow-up period. Second, it is sometimes difficult to identify small vascular lesions as the bleeding source, especially when small intestinal bleeding ceases spontaneously. In this study, 6 patients (66.7%) with a final diagnosis of small intestinal bleeding from vascular lesions did not have a detectable bleeding site at the first DBE examination. This study also showed that patients with bleeding from small intestinal ulcers achieve a low rate of control (12.5%). Previous studies have indicated that the rebleeding rate of small intestinal ulcers ranges from 35 to 40% [13, 14], which is lower than in our study. We considered the following possible reasons for the difference between our results and those of other studies. First, 81.6% of our patients had concomitant diseases such as cardiovascular or cerebrovascular disease and some of them could not stop anticoagulant therapy, which may have led to a tendency for rebleeding. Second, 10 patients (62.5%) with small intestinal ulcers were in a poor general condition (total serum protein level <6.5 mg/dl), resulting in a reduced capacity for healing

of the ulcerative lesions. On the other hand, all of the patients with tumors/polyps who underwent endoscopic or surgical resection achieved control of OGIB. In contrast, the patients with tumors/polyps from the PC group did not undergo endoscopic or surgical resection of these lesions because of problems such as severe cardiovascular disease or multiple metastatic tumors.

In the present study, there was no further bleeding in 62.5% of the patients with normal DBE findings, which is a higher rate than in previous studies [13, 18]. This high rate of freedom from further bleeding was possibly related to a difference in the extent of small bowel examination, which reduced the possibility of false-negative endoscopic studies. The number of subjects enrolled in the current study was relatively small, so further investigation of a larger number of OGIB patients with a longer follow-up period is required to confirm our results.

In conclusion, the rebleeding rate was 33.3% in our patients with OGIB, most of whom were elderly and had coexisting diseases. It should be remembered that the rebleeding rate after DBE varies with the source of bleeding, being higher for ulcers/erosions and vascular lesions than for tumors/polyps or diverticula.

Disclosure Statement

All authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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