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BRIEF ARTICLE

Outcome of patients who have undergone total enteroscopy for obscure gastrointestinal bleeding

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Abstract

AIM: To assess the diagnostic success and outcome among patients with obscure gastrointestinal bleeding who underwent total enteroscopy with double-balloon endoscopy.

METHODS: Total enteroscopy was attempted in 156 patients between August 2003 and June 2008 at Hiroshima University Hospital and achieved in 75 (48.1%). It is assessed whether sources of bleeding were identified, treatment methods, complications, and 1-year outcomes (including re-bleeding) after treatment, and we compared re-bleeding rates among patients.

RESULTS: The source of small bowel bleeding was identified in 36 (48.0%) of the 75 total enteroscopy patients; the source was outside the small bowel in 11 patients (14.7%) and not identified in 28 patients (37.3%). Sixty-one of the 75 patients were followed up for more than 1 year (27.2 ± 13.3 mo). Four (6.6%) of these patients showed signs of re-bleeding during the first year, but bleeding did not recur after treatment. Although statistical significance was not reached, a marked difference was found in the re-bleeding rate between patients in whom total enteroscopy findings were positive (8.6%, 3/35) and negative (3.8%, 1/26) (3/35 *vs* 1/26, $P = 0.63$).

CONCLUSION: A good outcome can be expected for patients who undergo total enteroscopy and receive proper treatment for the source of bleeding in the small bowel.

Key words: Double-balloon endoscopy; Small bowel; Obscure gastrointestinal bleeding; Total enteroscopy; Outcome

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INTRODUCTION

Approximately 1%-5% of cases of gastrointestinal (GI) bleeding cannot be diagnosed by upper-GI and lower-GI endoscopic examination[1,2]. In such cases, the small bowel is the suspected source of obscure GI bleeding (OGIB)[3]. Until recently, push enteroscopy[4,5] and intraoperative enteroscopy[6,7] have been the standard modalities for diagnosing OGIB. However, push enteroscopy does not reach deep into the small bowel because of the short length of the scope, and intraoperative enteroscopy

is an invasive procedure that requires general anesthesia. Double-balloon endoscopy (DBE) was developed by Yamamoto *et al*[8-10] in 2001, and it has been clinically available since 2003. DBE allows examination of the entire small bowel (total enteroscopy) through a combined oral and anal approach, providing also for diagnosis and therapeutic interventions in cases of small bowel lesions. There are many reports regarding diagnoses, therapeutic interventions, and outcomes in patients with OGIB who have undergone DBE[11-22]. However, there are no reports regarding the diagnosis of small bowel lesions in patients with OGIB based on total enteroscopy. We undertook a retrospective study to assess diagnoses and long-term outcomes in patients who have undergone total enteroscopy for OGIB.

MATERIALS AND METHODS

Patients

The study involved 156 patients in whom DBE was performed for OGIB at Hiroshima University Hospital during the period August 2003 through June 2008. Total enteroscopy was achieved in 75 (48.1%). All patients had already undergone standard upper-GI and lower-GI endoscopy at our hospital or elsewhere. OGIB was defined by the following American Gastroenterological Association criteria[3]: overt (*vs* occult) GI bleeding and recurrent fecal occult bleeding with iron-deficiency anemia that was not identifiable by upper-GI and lower-GI endoscopy, for example, hematemesis, hematochezia, or melena.

Methods

We evaluated whether sources of bleeding in the small bowel were diagnosed by DBE, whether treatment was performed during DBE, and whether complications ensued. Preliminary diagnosis was made on the basis of endoscopic findings and clinical history. Final diagnosis was made on the basis of histologic examination of biopsy specimens and/or surgically resected specimens. If a detected lesion did not explain a patient's complaints, (for example, a single small lymphangioma), the lesion was not identified as the source of the OGIB.

We also evaluated clinical outcomes. Clinical outcome was described as either continued bleeding or complete resolution of the bleeding, regardless of whether treatment was performed. Re-bleeding was defined as hematochezia, melena, or the need for blood transfusion during follow-up. In the patients who underwent total enteroscopy, clinical variables were assessed over a 1-year follow-up period. These included general condition, bleeding episodes, hemoglobin level, treatment, and blood transfusion. For patients in whom re-bleeding occurred, the source of re-bleeding, final diagnosis, treatment method, and clinical outcome after the second treatment were evaluated.

DBE procedure

The DBE system (Fujifilm, Kanagawa, Japan) consisted of a videoendoscope with a working length of 200 cm, a flexible overtube with a total length of 145 cm, and a pressure-controlled pump system. The EN-450P5 endoscope with the TS-12140 overtube, or the EN-450T5 endoscope with the TS-13140 overtube, was used; both systems have a balloon attached to the tip of the endoscope and another attached to the tip of the overtube. The balloons can be inflated and deflated with a single touch by using a specially designed pump, while the balloon pressure is accurately monitored.

Total enteroscopy was first performed by anal approach, and tattoo injection was performed at the most proximal site reached by the endoscope. DBE was then carried out by oral approach to examine the remaining area. DBE by oral approach was performed within 2 d after DBE by anal approach. For both approaches, intestinal looping was checked fluoroscopically. DBE by anal approach was performed after bowel preparation with an oral electrolyte lavage as for regular lower-GI endoscopy. DBE by oral approach was performed after overnight fasting. Patients were sedated with midazolam and pethidine or pentazocine, if necessary. Blood pressure, heart rate, and oxygen saturation were monitored during the DBE procedures.

Total enteroscopy was considered successful when the enteroscope reached the tattoo mark made during the prior approach.

Follow-up

Cases were excluded from the study if the source of bleeding was determined to be outside the small bowel. All patients underwent follow-up examinations at our hospital or an affiliated hospital, and data were obtained from the patients' medical records or by correspondence with the affiliated hospital.

Statistical analysis

Continuous data are shown as mean ± SD and range. Differences in re-bleeding rates were analyzed by Fisher's exact probability test or χ^2 test. $P < 0.05$ was considered statistically significant. JMP software, version 5.01J (SAS Institute Inc., Cary, NC, United States), was used for all statistical analyses.

RESULTS

DBE-based diagnosis and treatment of OGIB

Clinical characteristics of the 75 patients who underwent total enteroscopy are summarized in Table 1. The source of bleeding was identified in the small bowel in 36 of these patients (48.0%) and outside the small bowel in 11 of these patients (14.7%). The source of bleeding was not traced to the digestive tract in 28 patients (37.3%). The sources of bleeding identified in the small bowel were as follows: tumor (n = 7), vascular lesion (n = 5), ulcerative lesion (n = 23), and Meckel's diverticulum (n = 1) (Table 2). Specific treatments were performed in 27 patients (75.0%) in whom the source of bleeding was identified in the small bowel by total enteroscopy. Specific treatments were as follows: medical treatment (n = 9); en-

Table 1 Clinical characteristics of patients (n = 75) who underwent total enteroscopy for obscure gastrointestinal bleeding at our hospital, August 2003 to June 2008 (mean ± SD) n (%)

Sex ratio (M/F)	44/31
Age (yr)	62.8 ± 16.9
Comorbid illness	
Cardiovascular disease	16 (21.3)
Chronic renal disease	9 (12.0)
Chronic liver disease	6 (8.0)
Cerebrovascular disease	4 (5.3)
Chronic respiratory disease	4 (5.3)
Use of anticoagulants	14 (18.7)
Use of non-steroidal anti-inflammatory drugs	11 (14.7)
Bleeding type	
Overt	56 (74.7)
Occult	19 (25.3)
Time from last bleeding episode to DBE (d)	33.2 ± 18.0
Blood transfusion	18 (24.0)
Hb before DBE (g/dL)	10.9 ± 2.5

Number of patients is shown unless otherwise indicated. Hb: Hemoglobin; DBE: Double-balloon endoscopy.

Table 2 Identification and treatment of bleeding source in the small bowel by total enteroscopy

Source of bleeding	n	Bleeding type overt/occult	Specific therapy
Tumor			
Hamartoma	2	1/1	Endoscopic resection (2)
Lipoma	1	1/0	Endoscopic resection (1)
Gastrointestinal stromal tumor	3	3/0	Surgery (3)
Leiomyosarcoma	1	1/0	Surgery (1)
Vascular lesion			
Angioectasia	4	3/1	Endoscopic hemostasis (4)
Arteriovenous malformation	1	1/0	Endoscopic hemostasis (1)
Ulcerative lesion			
Drug-induced ulcer	9	5/4	Medication (4), clinical observation (5)
Anastomotic ulcer	5	3/2	Endoscopic hemostasis (5)
Nonspecific erosion	4	4/0	Clinical observation (4)
Enteric tuberculosis	3	2/1	Medication (3)
Crohn's disease	1	1/0	Medication (1)
Radiation enteritis	1	1/0	Endoscopic hemostasis (1)
Other			
Meckel's diverticulum	1	1/0	Medication (1)

Number of patients is shown unless otherwise indicated.

doscopic hemostasis (clip placement, n = 7; argon plasma coagulation and/or injection therapy, n = 4); endoscopic resection (endoscopic mucosal resection, n = 1; polypectomy, n = 2); and surgery (n = 4). Non-specific treatment was performed for the other 9 patients.

Table 3 Outcome of patients who underwent total enteroscopy for obscure gastrointestinal bleeding (mean ± SD) n (%)

Number of follow-up cases	61
Observation period after DBE (mo)	27.2 ± 13.3
Re-bleeding rate	4 (6.6)
Time period from DBE to re-bleeding episode (mo)	7.0 ± 4.2
Number of patients who underwent transfusion	3 (4.9)
Outcome	
Survival	60
Death	1

Number of patients is shown unless otherwise indicated. DBE: Double-balloon endoscopy.

Complications of DBE

Two patients experienced complications from the diagnostic DBE. One suffered aspiration pneumonia and the other suffered acute pancreatitis. These 2 patients received medical treatment and recovered within a few days. One patient experienced a complication after therapeutic DBE: bleeding occurred after polypectomy for lipoma in the jejunum, and endoscopic hemostasis with clip placement and blood transfusion was required.

Clinical outcomes and re-bleeding rates

Data were obtained for 61 of the patients with OGIB who were followed up for more than 1 year after total enteroscopy. Excluded were the 11 patients in whom the source of bleeding was outside the small bowel and 1 patient who was lost to follow-up. The outcome and clinical course of these cases are shown in Table 3 and Figure 1, respectively. Four patients (6.6%) (4 women; mean age, 67.8 ± 7.0 years) showed signs of re-bleeding, such as hematochezia, melena, or a need for blood transfusion during this follow-up period (Table 4). The average observation period until the re-bleeding episode after total enteroscopy was 7.0 ± 4.2 mo. In 3 of the 4 patients, the re-bleeding derived from the same lesion identified upon initial total enteroscopy: 2 enteric tuberculosis lesions and 1 angioectasia. Medical treatment without endoscopic hemostasis and clinical observation was continued for the 2 patients with enteric tuberculosis. The patient in whom angioectasia was found underwent endoscopic hemostasis after epinephrine injection and argon plasma coagulation during DBE. In 1 patient in whom re-bleeding occurred, the source of the bleeding had not been identified during initial total enteroscopy. This patient was discharged from our hospital after the initial DBE examination, but severe hematochezia developed 1 mo later. Blood transfusion was performed, and DBE performed immediately thereafter revealed an arteriovenous malformation as the bleeding source. Endoscopic hemostasis with argon plasma coagulation and clip placement was performed. However, the hemorrhage did not stop, so angiography and surgical intervention were undertaken. Bleeding did

Table 4 Patients with obscure gastrointestinal bleeding in whom re-bleeding occurred after total enteroscopy

Patient	Bleeding type	Hb (g/dL)	Initial diagnosis	Initial treatment	Time after DBE (mo)	Hb (g/dL) after treatment	Final diagnosis	Second treatment	Transfusion	Re-bleeding after second treatment
78-yr-old woman	Overt	12.3	Enteric tuberculosis	Medication	10	6.6	Enteric tuberculosis	Medication	No	No
66-yr-old woman	Occult	10.1	Enteric tuberculosis	Medication	7	7.5	Enteric tuberculosis	Medication	Yes	No
62-yr-old woman	Overt	10.6	Angioectasia	EH	10	8.3	Angioectasia	EH	Yes	No
65-yr-old woman	Overt	6.5	No source of bleeding	No treatment	1	6.0	Arteriovenous malformation	EH→ angiography	Yes	No

Hb: Hemoglobin; EH: Endoscopic hemostasis; DBE: Double-balloon endoscopy.

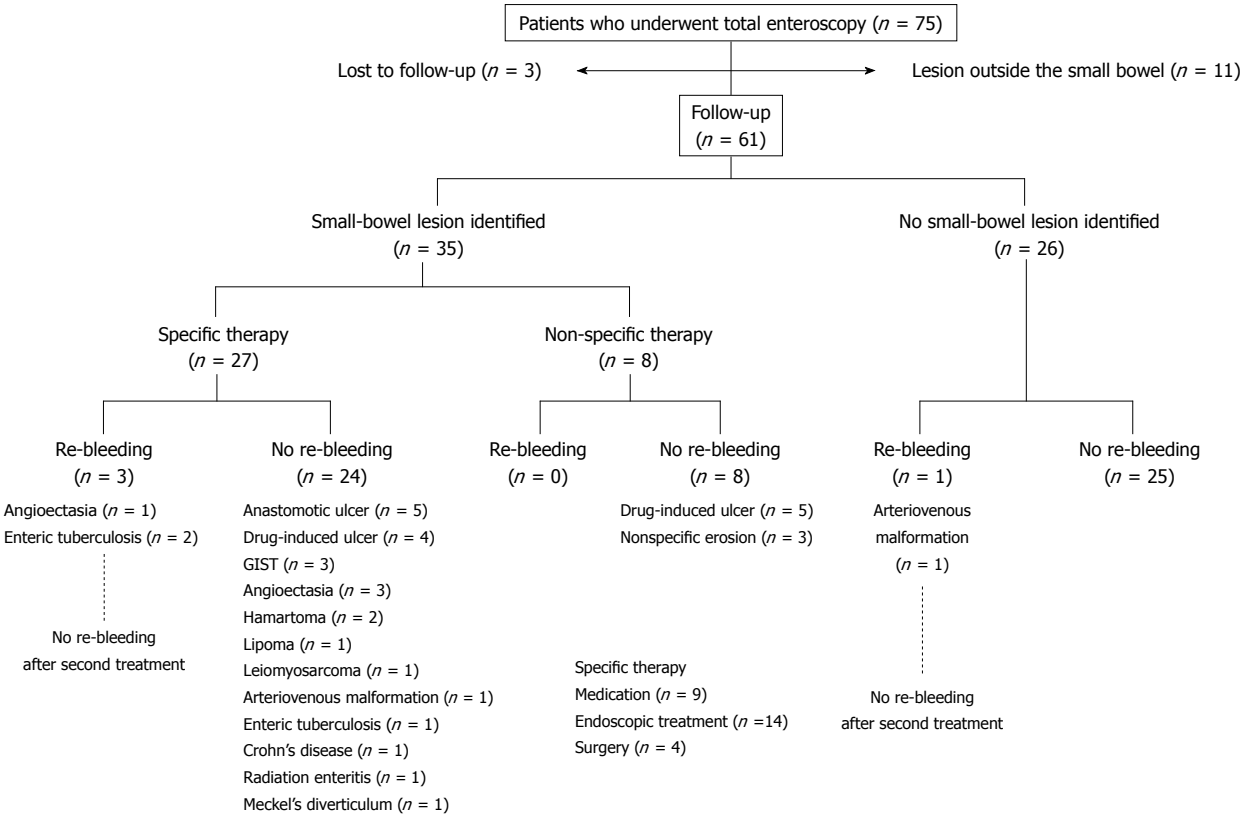

Figure 1 Clinical course after total enteroscopy for obscure gastrointestinal bleeding. GIST: Gastrointestinal stromal tumor.

not recur after the second treatment in any of the 4 patients, and they remain healthy. The re-bleeding rate for patients with positive total enteroscopy findings was 8.6% (3/35), and that for patients with negative total enteroscopy findings was 3.8% (1/26). The difference between these 2 groups was not significant ($P = 0.63$). One patient died from leiomyosarcoma with multiple metastatic liver tumors 26 mo after the initial DBE examination.

DISCUSSION

There have been several reports concerning diagnoses and outcomes in patients with OGIB in which the small bowel was the source of bleeding[23-29]; however, the entire small bowel was not examined by DBE in these patients. Ours is the first report on the prognosis of OGIB originating from a small bowel lesion that was identified through total enteroscopy performed by means of DBE. Overall, the source of bleeding, whether within or outside the small bowel, was identified in 62.7% of cases in which total enteroscopy was performed by DBE. The source of bleeding was found to be outside the small bowel in 14.7% of patients. Arakawa *et al*[29] reported lesions outside the small bowel in 9.3% of patients. It has been reported that identification of lesions responsible for OGIB by means of DBE is successful in only 50%-76% of cases[24,30-32]; however, the reports include cases of small lesions that were unlikely to be the source

of bleeding and cases in which the interior of the entire small bowel could not be observed. Therefore, the reports do not describe the true diagnostic performance of total enteroscopy by means of DBE in patients with OGIB.

Re-bleeding occurred in 8.6% of our patients in whom the source of bleeding was identified by initial total enteroscopy and proper treatment was performed. This rate is lower than the rates reported by Hadithi *et al*[23] (14.3%), by Hsu *et al*[25] and Madisch *et al*[28] (20.0%), and by Kameda *et al*[26] (19.0%). These reports do not clarify whether the sources of bleeding were identified by initial DBE or whether total enteroscopy was achieved. Re-bleeding from a small bowel lesion occurred in 3.8% (n = 1) of our patients in whom the source of bleeding was not identified by initial total enteroscopy. This rate is lower than rates reported previously (8.7%-80.0%)[23-25,28]. Possible reasons are as follows: patients in whom the entire small bowel was not observed were included in our study; lesions outside the small bowel were included; and only lesions that were believed to be the clear source of bleeding were included.

Our data show that identifying a lesion in the small bowel and administering proper treatment results in a decrease in the re-bleeding rate, as well as a good clinical outcome. According to Arakawa *et al*[29], vascular lesions account for approximately 80% of cases of re-bleeding. Vascular lesions were the cause in 2 of our 4 patients with re-bleeding. In 1 of our patients, there was a problematic arteriovenous malformation that was not discovered during initial total enteroscopy. It is possible that the hemorrhage had stopped spontaneously by the time DBE was performed. In general, however, there is little possibility of re-bleeding from the small bowel because, if no lesions are identified in the small bowel by total enteroscopy, only exceptional minute vascular lesions would cause re-bleeding.

Among our patients, the average follow-up period was 27.2 mo after total enteroscopy, but the average period until re-bleeding was 7.0 mo, and all re-bleedings occurred within 1 year. In the Fujimori *et al*[24] and Kameda *et al*[26] series, 75.0% and 83.3% of patients, respectively, experienced re-bleeding within 1 year. Thus, we believe it is necessary to monitor patients for at least 1 year after the source of bleeding has been identified and treatment has been performed. Moreover, performing total enteroscopy in patients with OGIB is helpful in administering proper treatment for the source of bleeding and for diagnosing previously unidentified GI lesions.

One of the issues of DBE is insertability. The reported rate at which total enteroscopy is achieved by means of DBE falls between 40% and 86%[12,33-36]; however, from multicenter studies in Western countries, a much lower rate of 15%-16% was reported[37-39]. Insertion of the endoscope into a deeply situated small bowel is difficult, particularly in postoperative cases and cases of adhesion. The usefulness of capsule endoscopy (CE)[40] has been reported for such cases. Total enteroscopy has been achieved by CE in 74%-83% of cases[36,41-44]. Moreover, CE is a safe modality for diagnosing OGIB[41-44]. Although CE is suitable as an initial screening for OGIB, one disadvantage of CE is that submucosal tumors are overlooked[45-48], and CE does not provide for histopathologic biopsy or endoscopic treatment when a lesion is detected. Also, there are no reports concerning diagnostic agreement between DBE and CE in patients who have undergone total enteroscopy for OGIB. Thus, DBE is an essential modality for both diagnosing and treating small bowel lesions. Efforts are needed to improve instruments to increase insertability.

We assessed the prognosis of OGIB in patients for whom a small bowel lesion was identified as the source of bleeding by total enteroscopy. Total enteroscopy was performed by DBE, and when no source of bleeding was identified or proper treatment was administered for an identified source of bleeding, the outcome was satisfactory. However, considering the possibility of re-bleeding, a follow-up period of 1 year seems necessary for patients who have undergone treatment.

Our data lead us to conclude that total enteroscopy by DBE is advantageous over general DBE for patients with OGIB. A good outcome can be expected for such patients when the entire small bowel is examined by DBE and proper treatment is given for the source of bleeding in the small bowel.

COMMENTS

Background

There are many reports regarding diagnoses, therapeutic interventions, and outcomes in patients with obscure gastrointestinal bleeding (OGIB) who have undergone double-balloon endoscopy (DBE). However, there are no reports regarding the diagnosis of small bowel lesions in patients with OGIB based on total enteroscopy.

Research frontiers

The authors undertook a retrospective study to assess diagnoses and long-term outcomes in patients who had undergone total enteroscopy for OGIB.

Innovations and breakthroughs

The study found that total enteroscopy by DBE is advantageous over general DBE for patients with OGIB.

Peer review

The authors have presented a well written documentation of total enteroscopy for obscure gastrointestinal bleeding.

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