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False-negative double-balloon enteroscopy in overt small bowel bleeding: long-term follow-up after negative results

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Abstract

Background and aim Double-balloon enteroscopy (DBE) performed to investigate overt small bowel bleeding can miss the source of bleeding. We investigated the clinical outcomes of patients with negative DBE results for suspected overt small bowel bleeding, which is defined in the current guidelines as obscure gastrointestinal bleeding.

Methods We reviewed the prospectively collected medical records of patients who underwent DBE at our hospital between May 1, 2004 and April 30, 2016. During this period, 297 patients underwent DBE for suspected overt small bowel bleeding. The first DBE yielded negative results for 83 patients (27.9%). Written interviews, telephone interviews, and medical records of these patients were reviewed in April 2017. Follow-up data were collected for 63 patients (75.9%).

Results During a mean follow-up period of 83.5 months, re-bleeding occurred in 21 of 63 patients (33.3%) after a mean of 23.0 months after the first DBE yielded negative results. The bleeding source was identified in 19 of 21 patients (90.5%). In 15 of these 19 patients (78.9%), the source was the small intestine. Among these 15 patients, 14 (93.3%) had bleeding sites within reach of the first DBE and 3 (20%) experienced their first incidence of re-bleeding more than 3 years after the first DBE. The need for transfusion for the first bleeding episode was a predictor of re-bleeding (odds ratio 7.5; 95% confidence interval 1.7–33.0).

Conclusions False-negative DBE results for overt small bowel bleeding are not rare, and the first re-bleeding episode can occur 3 years later. Repeat DBE when re-bleeding occurs should be considered, even if the first DBE results were negative.

Keywords Small intestine · Gastrointestinal hemorrhage · Double-balloon enteroscopy · Outcome research

Small bowel bleeding, a relatively uncommon condition, accounts for approximately 1.2–5% of all gastrointestinal (GI) bleeding cases [1, 2]. Current clinical guidelines for small bowel bleeding propose that the term "small bowel bleeding" should be replaced with the previous classification of obscure GI bleeding (OGIB) [3, 4]. OGIB was previously defined as either hematochezia or melena with negative bidirectional endoscopic evaluation results, including ileocolonoscopy and esophagogastroduodenoscopy (EGD) results. However, the most recent guidelines recommend that OGIB should be used to describe patients without any bleeding source identified even after standard upper and lower endoscopy, small bowel evaluation with small bowel capsule endoscopy (SBCE) and/or enteroscopy, and radiographic testing.

Double-balloon enteroscopy (DBE), which was developed in 2001 [5], has resulted in marked changes in the treatment of small bowel disease [6, 7] because it enables deeper intubation and treatment of the small bowel compared with traditional endoscopy. The diagnostic yield (DY) of DBE for patients suspected of having small bowel bleeding (previous overt OGIB) has been reported to be approximately 60% [8, 9]. However, the evaluation of DY is sometimes difficult because some patients have bleeding sources that can be missed by conventional endoscopy, such as EGD and colonoscopy (CS) [10, 11]. A recent meta-analysis showed that the rate of complete small bowel enteroscopy

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is higher for DBE (40%) than for single-balloon enteroscopy (13.8%) [12]. SBCE is non-invasive and has the same DY for small bowel bleeding as DBE [8], although it does not have the capability to treat the bleeding site directly and can miss small bowel tumors. These results suggest that DBE could be the best modality for suspected overt small bowel bleeding. However, the bleeding source is sometimes not found with DBE. According to the current guidelines, those patients are defined as having OGIB; however, the current definition of OGIB differs from the previous definition of OGIB [2, 3]. Some studies have evaluated the long-term outcomes of positive DBE results for small bowel bleeding [13–18]. However, only a few small studies have investigated the re-bleeding rate after negative DBE results [6, 19–21]. In addition, the observation period was not long in those previous studies. The present study aimed to evaluate the long-term outcomes of patients with negative DBE results for suspected small bowel bleeding (current OGIB) on a larger scale with longer observation times and to assess the risk factors for and characteristics of re-bleeding in those patients.

Materials and methods

Patient selection

We reviewed the prospectively collected data of patients who underwent DBE at Sendai Kousei Hospital, a tertiary referral hospital, between May 1, 2004 and April 30, 2016. The data included medical history, indication of DBE, and clinical and endoscopic findings. All patients had undergone EGD and CS before DBE. Written informed consent was obtained from all patients for every DBE procedure. During the study, 297 patients underwent DBE for suspected overt small bowel bleeding (previous overt OGIB). Among the 297 patients, 83 (27.9%) had negative results according to the first DBE. Furthermore, we reviewed the medical records of those patients to assess the long-term outcomes. For patients not followed-up at our hospital, we conducted written and telephone interviews with the patients or their immediate relatives in April 2017 to determine whether the patients had re-bleeding episodes after the first procedure that yielded negative results. During the interviews, we asked patients if they had bleeding episodes after discharge. If they had re-bleeding episodes, then we asked if they presented to another hospital for further examinations or interventions. Most patients with re-bleeding came to our hospital at the time of re-bleeding. Of 21 patients with re-bleeding, three patients went to another hospital on occurrence of re-bleeding. Sixty-three patients (75.9%) were eligible for follow-up in this study.

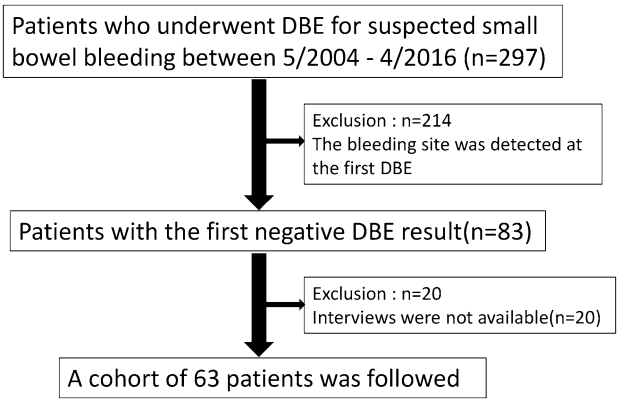

Fig. 1 Flowchart of the study design

The study enrollment flowchart is shown in Fig. 1. The study protocol was approved by the ethics committees of our hospital (Institutional ID: 28-38).

Data collection and definition

During the DBE procedures, data including age, sex, clinical features, initial vital signs, laboratory findings, timing of endoscopy, diagnosis using endoscopy, need for transfusion, units required for blood transfusion, concomitant use of SBCE, bleeding characteristics, adverse events, medications such as anti-thrombotic agents, proton pump inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs), and comorbidities such as cardiovascular disease, chronic kidney disease, and cirrhosis were recorded in our DBE database. We extracted the data of patients who underwent DBE for suspected overt small bowel bleeding. We categorized the bleeding source as ulcer (more than 10 mm in diameter), vascular lesion (according to the Yano classification) [22], tumor lesion with ulcer or erosion, and diverticular disease with ulcers or vessels. We excluded the following as bleeding sources: angioectasia less than 1 mm (Yano classification type 1a) without oozing, non-bleeding polyp, lipoma, lymphangioma, and diverticula without any sign of bleeding. We defined DBE results as negative when there was no sign of those bleeding sources. All patients underwent blood tests before and after DBE. Blood transfusions were performed with a target hemoglobin of 7–8 g/dL, but patient factors such as cardiovascular diseases, hemodynamic status, and ongoing bleeding were also considered. We defined the follow-up period as the time between the first negative DBE results and the day of interview or death. SBCE was not always performed in a setting wherein enteroscopy could be performed within 24 h. We performed SBCE when we failed to complete total enteroscopy. Re-bleeding was defined as overt bleeding identified by patients.

Procedures

At our hospital, endoscopy and computed tomography (CT) can be performed 24 h per day, 7 days per week. For patients with suspected small bowel bleeding, we typically performed EGD, CS, and contrast-enhanced CT (CECT) before DBE. The application of SBCE before DBE depended on the decision of the physician treating the patient. All DBE procedures were performed under the supervision of two experts (T.M. and M.N.) who had performed more than 500 DBE procedures. If it was impossible to perform total enteroscopy, then a submucosal tattoo was placed to mark the deepest insertion site and another enteroscopic route was adopted. For patients with re-bleeding after the first negative DBE results, we typically performed CECT again to predict the bleeding source and then proceeded to performed DBE. The DBE direction was decided on the basis of the nature of the bleeding or the anticipated location of the bleeding according to the results for other modalities. We performed emergency DBE within 24 h of admission when re-bleeding occurred.

Statistical analysis

Continuous variables are expressed as mean (standard deviation), and categorical data are presented as absolute numbers and percentages. Statistically significant differences in the clinical parameters were evaluated using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Follow-up data for intervals without re-bleeding were analyzed using the Kaplan–Meier method. Furthermore, univariate and multivariate analyses were performed using logistic regression models to identify the predictors of re-bleeding. For the multivariate analysis, only variables with $P < 0.1$ in the univariate analyses were included as covariates. $P < 0.05$ was considered statistically significant. All analyses were performed using EZR software (version 1.36; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [23].

Results

Patients and clinical presentation

Characteristics of the patients enrolled in this study and their clinical presentations are shown in Table 1. The backgrounds of the enrolled patients and non-enrolled patients were not significant (Supplemental Table 1). SBCE was performed in 31 (49.2%) of the 63 patients enrolled in this study. The mean follow-up period was 83.6 months (range 6–146 months). Blood transfusions were required for 34 patients (54.0%). The mean interval time from the last bleeding episode to the first negative DBE results was 19.2 days (0–62 days); the first DBE was performed within 24 h after the last bleeding episode for ten patients (16.1%). For 40 patients (63.5%), total enteroscopy was performed during the first DBE. No adverse events were related to DBE.

Table 1 Background of the 63 patients with the first negative DBE for suspected small bowel bleeding

Mean age, years (range)	62.7 ± 15.8 (18–84)
Sex (male/female)	43/20
Observation period, months (range)	83.5 ± 42.0 (6–146)
Bleeding presentation (melena/hematochezia)	42/21
Multiple bleeding episodes	44 (69.8%)
Total enteroscopy	40 (63.5%)
SBCE use before DBE	31 (49.2%)
Interval from last bleeding episode to DBE, days	19.2 (0–62)
– DBE within 24 h from the last bleeding	10 (16.1%)
Patients receiving blood transfusions before DBE	34 (54.0%)

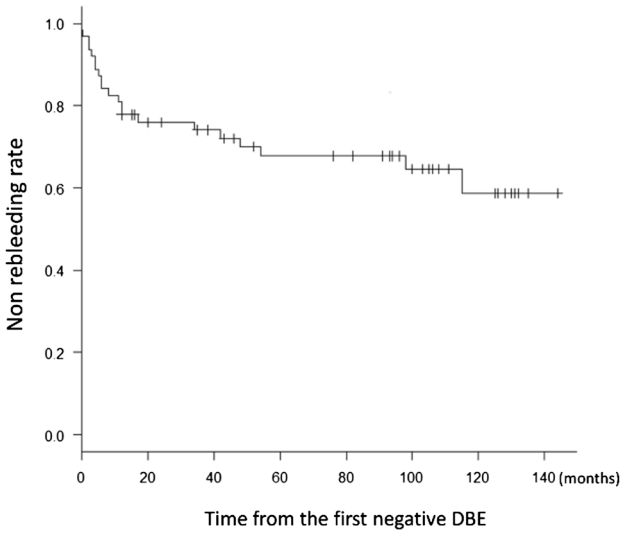

Fig. 2 Rate of no re-bleeding after the first negative DBE results

Cause and rate of re-bleeding

Re-bleeding occurred in 21 patients (33.3%), with a mean interval between the first negative DBE results and re-bleeding of 23.5 months (range 0–115 months) (Fig. 2). All patients underwent dynamic CECT for re-bleeding. The bleeding source was identified in 19 patients (90.5%) (Fig. 3). Among them, 15 (78.9%) had a lesion in the small bowel (Table 2). The colon (angioectasia) was the bleeding source for two

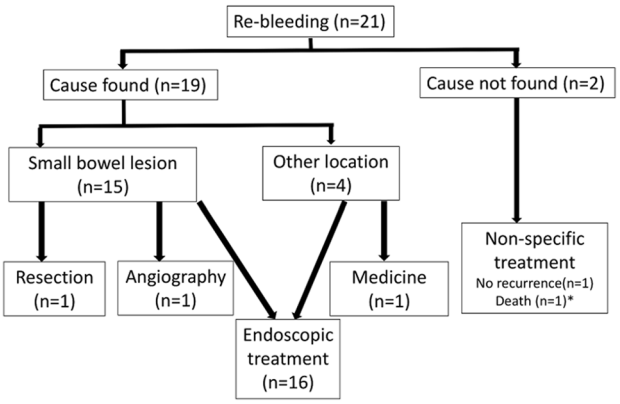

Fig. 3 Clinical course after re-bleeding. *The patient died of cirrhosis of the liver

Table 2 Rebleeding from the small bowel after the first negative DBE

Location	
Duodenum	8 (53.3%)
Ileum/jejunum	7 (46.7%)
Characteristics	
Vascular	9 (60%)
Yano classification type 1b	2
Yano classification type 2a	6
Yano classification type 2b	1
Ulcerative	5 (33.3%)
Diverticulum (duplication)	1 (6.7%)
Time to first rebleeding	
Mean, month (range)	15.3 (0–54)
< 1 month	2 (13.3%)
1–12 month	8 (53.3%)
12–24 month	1 (6.7%)
24–36 month	1 (6.7%)
> 36 month	3 (20%)
Treatment	
Endoscopy	13 (86.7%)
Angiography	2 (13.3%)
Resection	1 (6.7%)
Recurrent bleeding after treatment	
Yes	4 (26.7%)
No	11 (73.3%)

patients; the second portion of the duodenum (ulcer) was the bleeding source for one patient, and the stomach (angioectasia) was the bleeding source for one patient.

Clinical course and long-term outcomes of patients with re-bleeding from small bowel lesions

Among the 15 patients with re-bleeding from small bowel lesions (Table 2), 14 (93.3%) had a lesion within the reach of the first DBE that yielded negative results and 9 (60%) had a vascular lesion. Of those nine vascular lesions, seven (77.8%) were determined to be Yano classification type 2a. The interval between the first negative DBE results and the first re-bleeding episode was more than 3 years for three patients (20%).

Emergency DBE within 24 h after the first re-bleeding episode successfully identified small bowel lesions in 13 cases. In another case, dynamic CECT revealed bleeding from duodenal diverticulum, and push enteroscopy was used for hemostasis [24]. In yet another case, dynamic CECT showed bleeding from the jejunum, but emergency total enteroscopy and SBCE failed to find the lesion. Angiography was used to identify the arterial vascular malformation in the small bowel, and coil embolization was performed.

Four patients (26.7%) experienced repeated bleeding episodes even after identification and treatment of the lesion; all of these patients had lesions located in the duodenum distal to the ampulla of Vater. One patient who had vasculitis died of massive gastrointestinal bleeding that was uncontrollable after DBE and angiography at 6 months after the first negative DBE results.

Predictors of re-bleeding

We compared the patient backgrounds of those with and without re-bleeding (Table 3). Both the univariate analysis and multivariate analysis indicated that the need for a blood transfusion was the only factor associated with re-bleeding after the first DBE that yielded negative results. There was no association between the timing of DBE, concomitant use of SBCE, bleeding characteristics, multiple bleeding episodes, use of medication such as anti-thrombotic agents, proton pump inhibitors, and NSAIDs, and presence of comorbidities.

Discussion

In this retrospective study, the rate of re-bleeding after the first negative DBE results was 33.3%, and the follow-up period was approximately 7 years. Most re-bleeding lesions (19/21) were identified during the second work-up. Moreover, most identified lesions (15/19) were located in the small bowel. The rate of re-bleeding (33.3%) was similar to that observed in previous studies (16.7–42.9%) [6, 19–21]. However, the number of the patients enrolled in the current analysis (63 patients) was higher and the follow-up duration

Table 3 Predictive factors for rebleeding

Variables	Rebleeding ($n=21$)	Non-rebleeding ($n=42$)	Univariate analysis (p value)	Multivariate analysis (p value)	Odds ratio (95% CI)
Age, years (mean ± SD)	67.7 ± 12.4	61.1 ± 16.8	0.169		
Sex, male/female	13/8	30/12	0.567		
Melena/hematochezia	13/8	29/13	0.584		
Multiple bleeding episode	18 (85.7%)	26 (61.9%)	0.080	0.29	2.3 (0.49–10.7)
Total enteroscopy	13 (61.9%)	27 (64.3%)	1.00		
SBCE use before DBE	9 (42.9%)	22 (52.4%)	0.595		
Interval from bleeding episode to DBE, days	17.6 ± 19.2	20.9 ± 15.4	0.320		
– DBE within 24 hours from the last bleeding	5 (23.8%)	5 (11.9%)	0.195		
The need for blood transfusion before DBE	18 (85.7%)	16 (38.1%)	0.0004	0.007	7.5 (1.7–33.0)
– Transfused RCC, unit	7.0 ± 5.9	3.2 ± 5.7	0.018		
Medical comorbidities					
Chronic kidney disease (on dialysis)	2 (9.5%)	0	0.108		
Liver cirrhosis	1 (4.8%)	0	0.333		
Cardiovascular disease	9 (42.9%)	10(23.8%)	0.151		
Diabetes mellitus	5 (23.8%)	6 (14.3%)	0.483		
Medications					
Anti-platelet agents	5 (23.8%)	12 (28.6%)	0.771		
Anti-coagulation agents	3 (14.3%)	3 (7.1%)	0.391		
NSAIDs/aspirin	4 (19.1%)	3 (7.1%)	0.209		
PPI	9 (42.9%)	8 (19.1%)	0.070	0.173	2.7 (0.65–10.9)

(mean follow-up, 83.5 months) was longer than those of previous studies (24–42 patients with a mean follow-up of 15–65 months) [6, 19–21]. Long-term follow-up is important for evaluating re-bleeding. In our study, three patients experienced their first re-bleeding episode more than 3 years after the first negative DBE results; the longest time interval was 54 months. This indicates that small bowel bleeding can recur several years after it has stopped spontaneously. Therefore, DBE should be performed for patients with a history of OGIB.

Notably, most small bowel bleeding lesions were located within the reach of the first DBE that yielded negative results, suggesting that missing the bleeding source with DBE is not associated with the insertion depth. How can the detection of small bowel lesions at the time of the first bleeding episode be improved? The timing of DBE could contribute to this improvement. A few studies have suggested that emergency DBE is better than non-emergency DBE and is associated with a lower recurrent bleeding rate [25, 26]. Another study showed that emergency DBE is technically feasible and may facilitate the diagnosis and management of patients with massive overt small bowel bleeding [27]. In our study, we successfully identified the lesion with emergency DBE in most cases of re-bleeding. The concomitant use of dynamic CECT or CT enterography could also contribute to the improvement in detection. Generally, CT has a lower DY for small bowel bleeding than does SBCE and DBE [28]. However, Agrawal et al. found that CT enterography identified the lesion in approximately one-half of OGIB cases with negative SBCE results [29]. In addition, a meta-analysis demonstrated that urgent CT angiography for patients with massive bleeding was excellent in terms of lesion localization, with a pooled sensitivity of 89% and specificity of 89% for a total of 198 patients [30]. Although we performed CECT for all cases before the first DBE that yielded negative results, repeated CECT at the time of re-bleeding also helped identify the bleeding site in one of our cases [24].

In this study, we attempted to identify the predictive factors for re-bleeding after the first negative DBE. We found a correlation with the need for blood transfusion at the time of the first bleeding episode. A previous study [21] revealed similar results; the authors found correlations with the need for blood transfusion and multiple bleeding episodes. In contrast, previous studies of small bowel bleeding with positive DBE results demonstrated an association between re-bleeding and cirrhosis [17, 18], aortic valve stenosis [15, 18], chronic renal disease [14, 18], Osler-Weber-Rendu syndrome [16, 18], cardiac disease [14, 15], a high number of lesions (> 10) [15], and anti-thrombotic agents [15]. We assumed that this difference was not surprising because totally different patient groups and small numbers of the patients were

involved. Larger studies are needed to determine whether those comorbidities and medications are truly associated with re-bleeding.

This study had some limitations. This was a retrospective analysis, and we could not follow-up all patients, which means that selection bias was possible. The study was conducted at a single tertiary hospital. In addition, the sample size was not large, although it was larger than that of previous studies. Finally, SBCE was not performed for all cases; therefore, this may have resulted in missed lesions. A meta-analysis showed that the use of SBCE before DBE improves the DY for small bowel bleeding [8]. However, we emphasized on the performance of DBE over SBCE because the timing of DBE could be the most important factor in overt bleeding [25–27]. Notably, we successfully identified most bleeding sources at the time of re-bleeding with the use of emergency DBE.

In conclusion, false-negative DBE results for overt small bowel bleeding is not rare. Re-bleeding episodes can occur more than 3 years after the first negative DBE results. DBE is a safe and effective procedure for patients with a history of OGIB at the time of re-bleeding. The timing of DBE and concurrent CT use are important because most missed and recurrent small bowel bleeding lesions were within the reach of the first DBE that yielded negative results in this study. Long-term observation and repeated DBE at the time of re-bleeding should be considered even if the first DBE results are negative.

Author contributions Study conception and design: RH, TM, MN; Data analysis and interpretation: RH, TM; Drafting of the article: RH; Critical revision: TM, MN; Final approval of the article: TM.

Compliance with ethical standards

Disclosures Drs. Rintaro Hashimoto, Tomoki Matsuda, and Masato Nakahori have no conflicts of interest or financial ties to disclose.

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