J Chin Med Assoc

ORIGINAL ARTICLE

Early double-balloon enteroscopy was not related to better clinical outcomes in patients with suspected overt small bowel bleeding

Yong-Cheng Ye[a,b,c], Kuan-Yi Sung[a,b,c], Tien-En Chang[a,b,c], Pei-Shan Wu[a,b,c], Yen-Po Wang[a,b,c,d,*], Jiing-Chyuan Luo[b,c], Ming-Chih Hou[a,b,c], Ching-Liang Lu[a,b,c,d]

[a]Endoscopy Center For Diagnosis and Treatment, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [c]Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [d]Institute of Brain Science, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

Abstract

Background: Device-assisted enteroscopy has been used for over 20 years for the management of patients with suspected small bowel bleeding. Unlike esophagogastroduodenoscopy and colonoscopy, the appropriate timing of enteroscopy is still unknown. In recent guidelines, early enteroscopy is suggested to maximize diagnostic yield and therapeutic yield in patients with suspected small bowel bleeding. However, few studies have identified its influence on clinical outcomes, including mortality or rebleeding rate. We conducted this study to evaluate the influence of the timing of double-balloon enteroscopy on clinical outcomes in patients with suspected small bowel bleeding.

Methods: Patients with overt small bowel bleeding who underwent double-balloon enteroscopy from January 2013 to February 2021 were retrospectively reviewed. Patients were categorized into an early enteroscopy group (≤14 days) and a nonearly enteroscopy group (>14 days). Clinical outcomes, including short-term mortality and rebleeding rate, long-term mortality and rebleeding rate, diagnostic yield, and therapeutic yield, were analyzed.

Results: A total of 100 patients (mean age, 66.2 years; 53% male) were included, and 44 patients were stratified into the early enteroscopy group. The diagnostic yield, therapeutic yield, mortality, and rebleeding rate were similar between two groups. In multivariate conditional logistic regression analysis, there were no significant differences between two groups regarding the 30-day rebleeding rate (adjusted odds ratio [aOR], 1.43; 95% CI, 0.47-4.33), 90-day rebleeding rate (aOR, 1.18; 95% CI, 0.47-2.94), 30-day mortality rate (aOR, 1.29; 95% CI, 0.21-8.13), 90-day mortality rate (aOR, 1.94; 95% CI, 0.48-7.87), and 90-day bleeding-related mortality (aOR, 2.18; 95% CI, 0.24-19.52). The Kaplan-Meier survival curve analysis showed that the timing of DBE was not associated with the long-term rebleeding rate or mortality rate ($p = 0.57$ and 0.83, respectively).

Conclusion: The timing of enteroscopy did not influence the clinical outcomes, including the short-term mortality rate, short-term rebleeding rate, long-term mortality rate, and rebleeding rate, in patients with suspected overt small bowel bleeding.

Keywords: Double-balloon enteroscopy; Gastrointestinal hemorrhage; Treatment outcome

1. INTRODUCTION

Small bowel bleeding accounts for approximately 5% to 10% of all gastrointestinal tract bleeding cases.[1,2] Capsule endoscopy can be used in evaluation, while device-assisted enteroscopy, including single-balloon enteroscopy, double-balloon enteroscopy (DBE), and spiral enteroscopy, is a well-established procedure for the evaluation and treatment of patients with suspected small bowel bleeding.[3–5] Capsule endoscopy is suggested as the first-line examination in patients with suspected small bowel bleeding[2,6,7] and is favorable within 48 hours to maximize the diagnostic yield.[8] Device-assisted enteroscopy after a previous positive capsule endoscopy for histopathological diagnosis and hemostasis is the current standard management of patients with suspected small bowel bleeding, and the diagnostic yield of DBE after a positive capsule endoscopy was significantly higher than that after a negative capsule endoscopy.[9]

The appropriate timing of endoscopy is an important issue in the management of gastrointestinal bleeding. Patients with acute nonvariceal upper gastrointestinal bleeding should undergo endoscopy within 24 hours,[10] which is associated with better outcomes, including lower 30-day mortality, in-hospital mortality, and 30-day transfusion rates.[11,12] In contrast, early colonoscopy within 24 hours does not reduce mortality, diagnostic yield, or endoscopic intervention in patients with acute lower gastrointestinal bleeding.[13–15] Early colonoscopy was even related to an increased risk of rebleeding and hospital readmissions in patients with acute lower intestinal bleeding.[16]

** Address correspondence. Dr. Yen-Po Wang, Endoscopy Center For Diagnosis and Treatment, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: ulnafu@gmail.com; ypwang@vghtpe.gov.tw (Y.-P. Wang).*

Conflicts of interest: Dr. Ming-Chih Hou, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2024) 87: 377-383.

Received June 28, 2023; accepted January 9, 2024.

doi: 10.1097/JCMA.0000000000001067

The small bowel is located between the upper gastrointestinal tract and colon, and the optimal timing of enteroscopy in patients with acute suspected small bowel bleeding is a conflicting issue. The Japanese Society of Gastroenterology recommends device-assisted enteroscopy to be performed within 2 weeks after bleeding episodes in patients with overt small bowel bleeding.[17] The European Society of Gastrointestinal Endoscopy (ESGE) also recommends device-assisted enteroscopy to be performed within 48 to 72 hours after bleeding episodes in patients with overt small bowel bleeding to maximize the diagnostic yield.[8] However, these consensuses are mostly based on results from capsule endoscopy.[8] In some studies, the definition of early enteroscopy was calculated from the last date of gastrointestinal bleeding, rather than the start date of gastrointestinal bleeding.[17] In a recent meta-analysis, early evaluation of overt small bowel bleeding was found with better diagnostic yield and therapeutic yield. However, significant heterogeneity existed.[18] Moreover, most previous studies only focused on the performance of diagnostic yield and therapeutic yield rather than clinical outcome.[19–23] Only a few studies identified clinical outcomes such as mortality or rebleeding rate. The severity of bleeding, including hemoglobin level and the need for transfusion, was lacking in most studies.[19,24] This study aims to compare an early DBE (≤14 days) with a nonearly DBE (>14 days) regarding rebleeding rate, mortality rate, diagnostic yield, and therapeutic yield.

2. METHODS

2.1. Study population

We retrospectively reviewed all consecutive patients who underwent DBE for suspected overt small bowel bleeding between January 2013 and February 2021 at tertiary medical center. Suspected overt gastrointestinal tract bleeding was defined as gastrointestinal bleeding that was visible to the patient or physician, including hematemesis, melena, or hematochezia.[2] Suspected overt small bowel bleeding was defined as suspected overt gastrointestinal tract bleeding with at least one set of negative findings on esophagogastroduodenoscopy and colonoscopy. Patients who received DBE due to occult gastrointestinal tract bleeding, which was defined as iron deficiency anemia or a positive fecal occult blood test, or other indications, such as Crohn disease follow-up, polypectomy, and anastomotic dilation, were excluded. For those patients, a sequential approach with a diagnostic examination (eg, capsule endoscopy, computed tomography (CT) angiography) followed by enteroscopy was clinically preferred.[8] For hemodynamically unstable patients, CT angiography and conventional angiography were arranged for overt massive GI bleeding, whereas multiphasic CT (CTA) was performed to identify the site of bleeding for those patients with hemodynamically stable and active overt bleeding.[2] We also offered supportive management, including adequate intravenous fluid supplementation and frequent complete blood count monitoring for maintaining an adequate level of hemoglobin.[2] The patients' medical records and demographic data were reviewed, including clinical manifestation, comorbidity, medication history, transfusion requirement, hemoglobin level, onset time of bleeding episode, execution time of DBE, therapeutic procedure, mortality, and rebleeding episode. The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the institutional review board, and informed consent was waived by the institutional review board due to the retrospective design.

2.2. DBE procedure and timing

DBE procedures were performed using the Fujifilm Double-Balloon Enteroscopy System (EN-450T5/W or EN-530T; Fujifilm Inc, Saitama, Japan). Patients fasted over 8 hours before enteroscopy. The insertion route of DBE was performed with the antegrade and/or retrograde approach, depending on the location of the abnormal finding on capsule endoscopy or the appearance of the abnormal stool. When a retrograde approach was anticipated, bowel preparation consisting of a 2-L polyethylene glycol solution divided into two doses was executed. All DBE was performed under intravenous heavy sedation with propofol, midazolam, and alfentanil administered by staff anesthesiologists. The timing of DBE was defined as the interval between the onset (first day) of the bleeding episode and the start of the procedure, and the patients were divided into two groups: within 14 days (early group) and after 14 days (nonearly group). We used the cutoff of 14 days based on the Japanese Society of Gastroenterology recommendation about the timing of device-assisted enteroscopy.[17] We also performed further sensitivity analysis by dividing patients into two groups: those within 7 days (urgent group) and those after 7 days (nonurgent group).

2.3. DBE findings and therapeutic procedure

A positive diagnostic finding was defined as either visible bleeding or an inactive lesion that was likely to be the source of bleeding relevant to bleeding manifestation. Endoscopic lesions include angioectasia, ulcers, tumors, diverticulum, Dieulafoy lesions, Meckel diverticulum, arteriovenous malformations, pseudoaneurysms, and bleeding polyps.

Endoscopic therapeutic procedure was defined as endoscopic hemostasis, resection or polypectomy, and the therapy mentioned above was considered for therapy yield analysis. Endoscopic hemostasis included argon plasma coagulation (APC) (ERBE, Tübingen, Germany) for electrocoagulation and EZ Clip (Olympus, Tokyo, Japan) or SureClip (Micro-Tech Endoscopy, Nanjing, China) for clipping. Endoscopic polypectomy was performed for polyps with active bleeding. Endoscopic mucosal resection was performed for submucosal lesions or large polypoid lesions with active bleeding. Biopsy or surgery was not considered to be an endoscopic therapeutic procedure.

2.4. Clinical outcome

The primary outcomes were the rebleeding rate and mortality rate. The 30-day rebleeding rate, 90-day rebleeding rate, 30-day mortality rate, 90-day mortality rate, long-term rebleeding rate, and long-term bleeding-related mortality rate were assessed. Rebleeding was defined as evidence of overt gastrointestinal tract bleeding (including melena, hematemesis, or hematochezia) or a decreased level of hemoglobin greater than 2 g/dL after exclusion of any other causes of anemia. Mortality data were reviewed, and the cause of mortality was categorized into bleeding-related mortality, infection, cardiovascular, respiratory or cancer. Bleeding-related mortality was defined as the cause of death directly associated with uncontrolled small bowel bleeding, which might present as hemorrhagic shock or multiple organ failure due to uncontrolled bleeding.

2.5. Statistical analysis

Data are presented as the mean ± SD or counts with percentages, as appropriate. The demographic data, mortality, rebleeding episode, diagnostic yield, and therapeutic yield were compared between patients who received early DBE or nonearly DBE using the chi-square test and Student's *t* tests for categorical and continuous variables, respectively. Logistic regression analysis was conducted to evaluate the impact of DBE timing on clinical outcomes, including 30- and 90-day mortality, 30- and 90-day rebleeding episodes, and 30- and 90-day bleeding-related mortality. The Kaplan-Meier method with the log-rank test was used to evaluate the association between the timing of

enteroscopy and the long-term rebleeding or bleeding-related mortality rate. p values <0.05 were considered statistically significant. All data were analyzed with SPSS Statistics version 25 (IBM, NY, USA).

3. RESULTS

A total of 100 patients with suspected overt small bowel bleeding who underwent DBE at tertiary medical center were enrolled in this study. Of the 100 patients, 44 patients (44%) underwent early DBE, and the other 56 patients (56%) underwent nonearly DBE. The median duration between the bleeding event to the enteroscopy was 10 and 28 days in early DBE and nonearly DBE groups, respectively. The patients' mean age was 66.24 ± 15.17 years old, and 53% of this cohort was male. Twenty-three patients (41.1%) received capsule endoscopy in nonearly DBE group and 15 patients (34.1%) underwent capsule endoscopy in early group. Most patients (75%) received enteroscopy via an antegrade approach, 12% received enteroscopy via a retrograde approach, and 13 patients (13%) received enteroscopy bidirectionally. The packed red blood cell transfusion received by patients did not differ statistically between the early DBE group and nonearly DBE group (14.64 units vs 11.84 units, p = 0.48). The baseline characteristics between the two groups were not significantly different (Table 1).

3.1. Clinical outcome

The overall diagnostic yield of DBE for bleeding source was comparable between the early DBE group and the nonearly DBE group (88.6% vs 89.3%, p = 0.92). The presence of active visible bleeding was slightly greater in the early DBE group than in the nonearly DBE group, although not achieving statistical significance (53.6% vs 46.4%, p = 0.23). The endoscopic therapeutic yield of DBE was also similar in both groups (63.6% in the early DBE group vs 62.5% in the nonearly group, p = 0.91). In terms of rebleeding events, the rebleeding rate was similar between the early DBE group and the nonearly DBE group at 30 (15.9% vs 19.6%, p = 0.63) and 90 days (29.5% vs 30.4%, p = 0.93) after DBE (Table 2). Comparing 30- and 90-day overall mortality, no significant difference was noted between the groups (6.8% in the early DBE group vs 5.4% in the nonearly group, p = 0.76; 9.1% vs 12.5%, p = 0.59, respectively). Bleeding-related mortality was similar in

Table 1

Demographic data of patients with overt small bowel bleeding receiving double-balloon enteroscopy

	Total n = 100	Early DBE n = 44	Nonearly DBE n = 56	
	n (%)	n (%)	n (%)	*p*
Age	66.2 ± 15.2	68.8 ± 13.3	64.2 ± 16.3	0.13
Sex (male)	53 (53%)	23 (52.3%)	30 (53.6%)	0.89
Hypertension	50 (50%)	22 (50%)	28 (50%)	1
Type II diabetes mellitus	37 (37%)	15 (34.1%)	22 (39.3%)	0.59
End-stage renal disease	25 (25%)	10 (22.7%)	15 (26.8%)	0.64
Coronary artery disease	15 (15%)	8 (18.2%)	7 (12.5%)	0.43
Atrial fibrillation	7 (7%)	2 (4.5%)	5 (8.9%)	0.39
Antiplatelet	19 (19%)	11 (25%)	8 (14.3%)	0.18
Anticoagulant	7 (7%)	2 (4.5%)	5 (8.9%)	0.39
Previous gastrointestinal bleeding history	36 (36%)	17 (38.6%)	19 (33.9%)	0.63
Capsule endoscopy	38 (38%)	15 (34.1%)	23 (41.1%)	0.48
Insertion route				0.59
Antegrade	75 (75%)	33 (75%)	42 (75%)	
Antegrade and retrograde	13 (13%)	7 (15.9%)	6 (10.7%)	
Retrograde	12 (12%)	4 (9.1%)	8 (14.3%)	
Lowest hemoglobin level, g/dL	7.04 ± 1.69	7.11 ± 1.82	6.99 ± 1.6	0.74
Packed red blood cell transfusion, U	13.07 ± 19.7	14.64 ± 18.99	11.84 ± 20.32	0.48

DBE = double-balloon enteroscopy.

Table 2

Clinical outcomes of patients with overt small bowel bleeding receiving double-balloon enteroscopy

	Total n = 100	Early DBE n = 44	Nonearly DBE n = 56	
	n (%)	n (%)	n (%)	*p*
Rebleeding in 30 d	18 (18%)	7 (15.9%)	11 (19.6%)	0.63
Rebleeding in 90 d	30 (30.0%)	13 (29.5%)	17 (30.4%)	0.93
Death in 30 d	6 (6.0%)	3 (6.8%)	3 (5.4%)	0.76
Death in 90 d	11 (11.0%)	4 (9.1%)	7 (12.5%)	0.59
Long-term bleeding-related mortality	4 (4%)	2 (4.5%)	2 (3.6%)	0.81
Long-term all-cause mortality	34 (34%)	13 (29.5%)	21 (37.5%)	0.41

DBE = double-balloon enteroscopy.

both groups (4.5% in the early DBE group vs 3.6% in the nonearly group, $p = 0.81$).

In multivariate logistic regression analysis, early DBE was not related to a better 30-day rebleeding rate, 90-day rebleeding rate, 30-day mortality rate, 90-day mortality rate, or bleeding-related mortality (Table 3). Using Kaplan-Meier survival curve analysis, the long-term rebleeding rate also did not differ between the early DBE and nonearly DBE groups ($p = 0.57$), with a mean follow-up duration of 669.1 days (Fig. 1). Long-term bleeding-related mortality also did not differ between the early DBE and nonearly DBE groups ($p = 0.83$), with a mean follow-up duration of 889.36 days (Fig. 2). Moreover, the 90-day rebleeding rate and mortality did not differ between the early DBE and nonearly DBE groups according to Kaplan-Meier survival curve analysis (Supplemental Figure 1, http://links.lww.com/JCMA/A236, and Supplemental Figure 2, http://links.lww.com/JCMA/A237).

Patients were also divided into two groups according to the timing of the enteroscopy: within 7 days (urgent group) and after 7 days (nonurgent group). The baseline characteristics between two groups were shown in Supplemental Table 1, http://links.lww.com/JCMA/A235. The urgent group (within 7 days) had significantly greater 30-day rebleeding and mortality (Supplemental Table 2, http://links.lww.com/JCMA/A235). According to the multivariate logistic regression analysis, the urgent group (within 7 days) had a worsened 30-day mortality rate compared with the nonurgent group (adjusted odds ratio [OR], 0.13; $p = 0.045$ [Supplemental Table 3, http://links.lww.com/JCMA/A235]).

3.2. DBE findings and therapeutic procedure

In DBE findings, the most prevalent positive diagnosis was angioectasia (45%), followed by ulcers (20%), tumors (14%), diverticulum (7%), and polyps (3%) (Table 4). The DBE finding was similar in the early DBE group and nonearly DBE group ($p = 0.94$).

In patients receiving therapeutic interventions, APC (27%) was the most common endoscopic procedure for hemostasis, followed

Table 3

Multivariate conditional logistic regression models in patients with overt small bowel bleeding receiving double-balloon enteroscopy

	Nonearly vs early DBE		Nonearly vs early DBE	
	Crude OR (95% CI)	*p*	Adjust OR[a] (95% CI)	*p*
30-d rebleeding	1.2 (0.46-3.67)	0.63	1.43 (0.47-4.33)	0.53
90-d rebleeding	1.04 (0.44-2.46)	0.93	1.18 (0.47-2.94)	0.72
30-d mortality	0.77 (0.15-4.03)	0.76	1.29 (0.21-8.13)	0.79
90-d mortality	1.43 (0.39-5.23)	0.59	1.94 (0.48-7.87)	0.36
30-d bleeding-related mortality	2.43 (0.24-24.24)	0.45	5.86 (0.17-200.99)	0.33
90-d bleeding-related mortality	1.19 (0.19-7.44)	0.85	2.18 (0.24-19.52)	0.49

DBE = double-balloon enteroscopy; OR = odds ratio.

[a]Adjusted for age, sex, packed red blood cell transfusion unit, antiplatelet, anticoagulant, and previous gastrointestinal bleeding history.

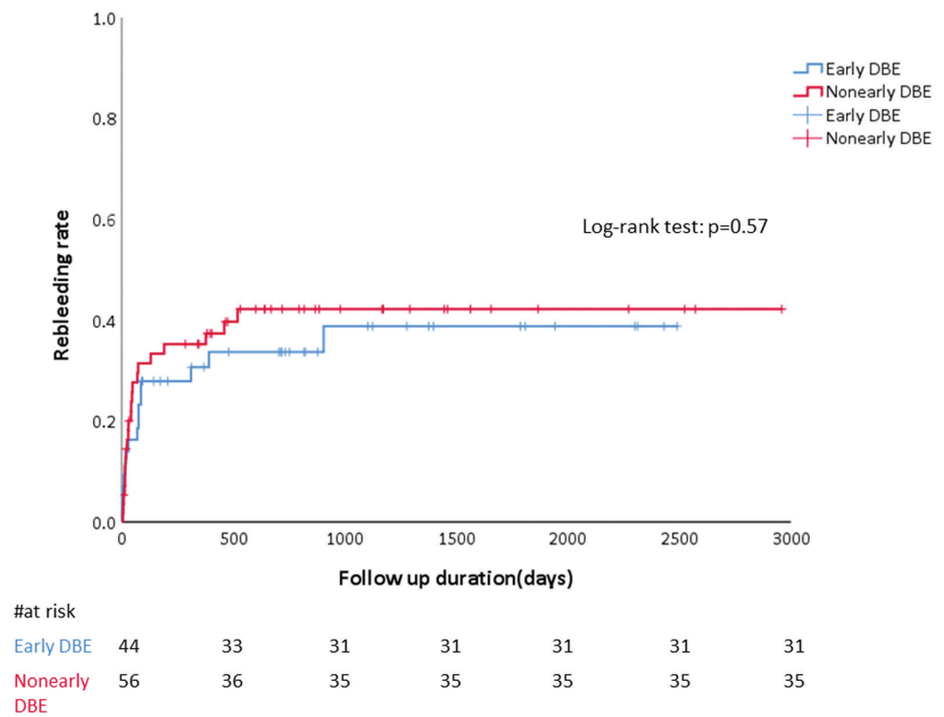

Fig. 1 Kaplan-Meier curve analysis for long-term rebleeding rate according to the timing of double-balloon enteroscopy. DBE = double-balloon enteroscopy.

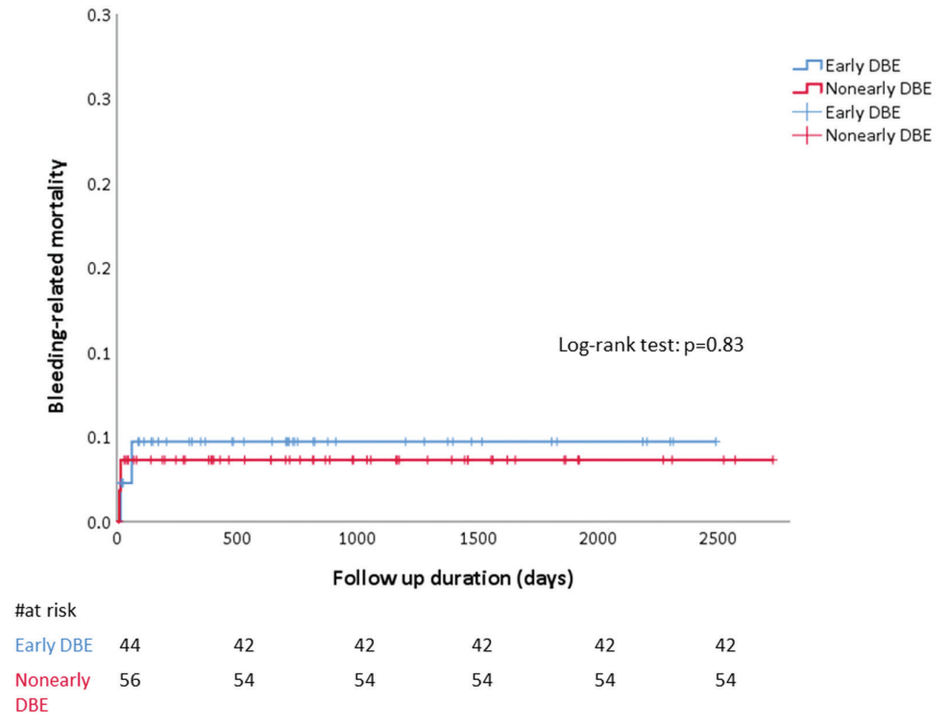

Fig. 2 Kaplan-Meier curve analysis for long-term bleeding-related mortality according to the timing of double-balloon enteroscopy. DBE = double-balloon enteroscopy.

Table 4

Double-balloon enteroscopy findings and therapeutic procedures in patients with overt small bowel bleeding

	Total n = 100	Early DBE n = 44	Nonearly DBE n = 56	*p*
	n (%)	n (%)	n (%)	
Lesions				0.94
Angioectasia	45 (45%)	18 (40.9%)	27 (48.2%)	
Ulcer	20 (20%)	10 (22.7%)	10 (17.9%)	
Tumor	14 (14%)	6 (13.6%)	8 (14.3%)	
Diverticulum	7 (7%)	4 (9.1%)	3 (5.4%)	
Polyp	3 (3%)	1 (2.3%)	2 (3.6%)	
Intervention method				0.85
Hemoclipping	19 (19%)	10 (22.7%)	9 (16.1%)	
APC	27 (27%)	12 (27.3%)	15 (26.8%)	
APC + hemoclipping	12 (12%)	4 (9.1%)	8 (14.3%)	
EMR	4 (4%)	2 (4.5%)	2 (3.6%)	
Polypectomy	1 (1%)	0	1 (1.8%)	
Surgery	7 (7%)	5 (11.4%)	2 (3.6%)	0.13

APC = argon plasma coagulation; DBE = double-balloon enteroscopy; EMR = endoscopic mucosal resection.

by hemoclipping (19%) and the combination of hemoclipping and APC (12%). Four patients (4%) underwent endoscopic mucosal resection, and one patient (1%) received polypectomy. The therapeutic procedure taken did not differ significantly between the early and nonearly DBE groups (p = 0.85) (Table 3). Other than endoscopic intervention, a total of seven patients underwent surgical resection after DBE due to tumor or Meckel diverticulum.

4. DISCUSSION

In this study, we found that early DBE did not result in better clinical outcomes, including rebleeding rate and mortality rate, compared with nonearly DBE. Regarding long-term outcome, there was also no difference between early DBE and nonearly DBE in long-term bleeding-related morality and rebleeding rate. In previous studies, only a few studies addressed the rebleeding rate and mortality rate. Moreover, this is the first study to compare the clinical outcome between early (≤14 days) and nonearly (>14 days) DBE with a long follow-up duration. Some studies have focused on the outcomes of emergent DBE before with conflicting results. Aniwan et al[19] found that the rebleeding rate was nonsignificantly lower after emergent DBE than after nonemergent DBE (10% vs 29%, p = 0.08) with a mean follow-up period of 16.3 months. Silva et al[25] found that rebleeding was

lower after urgent single-balloon enteroscopy than after nonurgent single-balloon enteroscopy (17.6% vs 45.9%, p = 0.04). However, obscure gastrointestinal bleeding-related 30-day mortality did not differ between urgent and nonurgent single-balloon enteroscopy.[25] Vascular lesions (eg, angiodysplasia or Dieulafoy lesions) or ulcers, which were the most common findings in enteroscopy, were sometimes self-limited, making conservative supportive management with nonearly enteroscopy a potential management strategy in patients with suspected small bowel bleeding.[26] Accordingly, the timing of enteroscopy was not related to mortality or rebleeding rate in this study.

In most studies and meta-analyses, the diagnostic yield was higher when device-assisted enteroscopy was performed earlier, ranging from 53.3% to 100% after early device-assisted enteroscopy and 30.4% to 65.1% after nonearly device-assisted enteroscopy.[18] Regarding therapeutic yield, the outcome was better when device-assisted enteroscopy was performed earlier. However, the diagnostic yield in our study was near 90% in both the early and nonearly DBE groups, and the therapeutic yield was similar in both groups, which was higher than that in previous studies. As device-assisted enteroscopy was not covered by National health insurance in Taiwan before May 2022, all enteroscopies in this study were self-paid in that both patients and physicians might avoid performing enteroscopies in less severe bleeding scenarios or patients with low prediction finding rates. The diagnostic yield in this study was consistent with a previous Taiwan DBE study.[27] Furthermore, if a negative finding was noted or the insertion was limited on the initial insertion route, we performed the opposite route of insertion to complete the study. In the setting of bidirectional enteroscopy, the endoscopist could have more opportunity to explore the proximal or distal ileum, which might contribute to a higher diagnostic yield. A previous retrospective study, which also combined both routes if there were negative findings on the initial route, also showed high diagnostic and therapeutic yields.[28] Despite high diagnostic and therapeutic yields, our clinical practice may require more procedure time and be labor intensive.

In the management of suspected small bowel bleeding, the ESGE recommended capsule endoscopy as the first-line examination in patients with suspected small bowel bleeding before device-assisted enteroscopy. The optimal timing is within 14 days in the 2015 version[6] and 48 hours in the 2022 version.[8] In addition, ESGE also suggested a sequential approach with a diagnostic examination followed by device-assisted enteroscopy that limits the utilization of urgent device-assisted enteroscopy in the clinical setting. In addition, National Health Insurance reimbursed capsule endoscopy was indicated after two sets of negative findings on colonoscopy and upper gastrointestinal tract endoscopy in Taiwan, which might defer the timing of enteroscopy. Additionally, early colonoscopy within 24 hours was not recommended and was even related to an increased risk of rebleeding and hospital readmissions in patients with acute lower intestinal bleeding. Therefore, the time period from bleeding to the decision to perform enteroscopy may be at least 5 to 7 days. Double-balloon enteroscopy, which takes a relatively long procedure time, requires two operators and anesthesiologists for sedation and time for schedule arrangement. Unlike urgent esophagogastroduodenoscopy or colonoscopy, it may take longer than 14 days from the onset of bleeding to enteroscopy after detailed inspection of capsule endoscopy sequential diagnostic examination, and supportive management.

We also compared clinical outcomes, including diagnostic yield, therapeutic yield, mortality and rebleeding rate, between the urgent (≤7 days) and nonurgent (>7 days) groups. Most outcomes were comparable between the two groups. However, the urgent group (within 7 days) had a worsened 30-day mortality rate. Given the great discrepancies between the number of patients who underwent urgent enteroscopy and nonurgent enteroscopy, these results should be interpreted with caution. In a previous study, evaluating the optimal timing of esophagogastroduodenoscopy for patients with acute upper gastrointestinal bleeding, patients receiving urgent endoscopy also had greater risk of death than patients receiving early endoscopy, although statistically non-significant.[12]

In our study, angioectasia was the most common finding in DBE, which was consistent with previous literature.[19,27,29] Bollinger et al[30] demonstrated that more than half of patients (60%) with angioectasias had more than one location at the same time. Hence, despite one active bleeding angiodysplasia already found, detailed inspection of the entire gastrointestinal tract was still important to minimize the possibility of missing lesions, which may influence the long-term rebleeding outcome. On the other hand, blood trickled out of angioectasia in most cases, and the vascular lesions were sometimes self-limited under conservative management.[26] Adequate intravenous fluid supplementation and maintaining an adequate level of hemoglobin were important for stabilizing hemodynamic status and clinical condition. Despite no consensus on blood transfusion in patients with small bowel bleeding, we obey the same strategies in upper and lower gastrointestinal bleeding, which uses restrictive red blood cell (RBC) thresholds (7 g/dL) for patients with a hemodynamically stable status and without acute coronary syndrome.[31–34]

The primary strength of this study included the identification of clinical outcomes after different timings of DBE in patients with overt small bowel bleeding. We demonstrated that the short-term mortality rate and rebleeding were not associated with the timing of DBE. In addition, we also followed those patients for a long period and first demonstrated that the long-term bleeding-related mortality and rebleeding rate were not significantly different between early and nonearly enteroscopy. Based on these findings, for hospitals that were incapable of performing urgent enteroscopy, physicians could offer the best supportive management (including CT angiography, drugs, blood transfusion) for patients with suspected small bowel bleeding before further enteroscopy without influencing the clinical outcome.

There are some limitations in our study. First, this is a retrospective study, and the timing of DBE might have been affected by selection bias. Those patients with severe bleeding tended to be likely to receive early enteroscopy, which might influence the opportunity to identify active bleeding lesions. However, the diagnostic yield in this study was comparable between early and nonearly enteroscopy. Multivariate analysis was also conducted to adjust for potential confounding factors. Second, this is a single tertiary center study, and whether the results can be applied to other hospitals warrants further notice. Finally, we did not perform a cost-effectiveness analysis between the groups, which warrants further studies.

In conclusion, the timing of enteroscopy did not influence the clinical outcome, including the short-term mortality rate, short-term rebleeding rate, long-term mortality rate, and rebleeding rate, in patients with suspected overt small bowel bleeding.

ACKNOWLEDGMENTS

The study was supported by grants from the Ministry of Science and Technology, Taiwan (MOST 110-2628-B-075-011 and NSTC 112-2628-B-075-009), Taipei Veterans General Hospital (V112C-088 and V112E005-4).

This study project is reviewed by the institutional review board of tertiary medical center.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A236, http://links.lww.com/JCMA/A237, and http://links.lww.com/JCMA/A235.

REFERENCES

1. Katz LB. The role of surgery in occult gastrointestinal bleeding. *Semin Gastrointest Dis* 1999;10:78–81.
2. Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG clinical guideline: diagnosis and management of small bowel bleeding. *Am J Gastroenterol* 2015;110:1265–87.
3. May A, Nachbar L, Ell C. Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. *Gastrointest Endosc* 2005;62:62–70.
4. Perez-Cuadrado E, Pons V, Bordas JM, Llach J, Menchén P, Pellicer F, et al. Small bowel endoscopic exploration Spanish GI Endoscopy Society recommendations. *Endoscopy* 2012;44:979–87.
5. Beyna T, Arvanitakis M, Schneider M, Gerges C, Böing D, Devière J, et al. Motorised spiral enteroscopy: first prospective clinical feasibility study. *Gut* 2021;70:261–7.
6. Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 2015;47:352–76.
7. Enns RA, Hookey L, Armstrong D, Bernstein CN, Heitman SJ, Teshima C, et al. Clinical practice guidelines for the use of video capsule endoscopy. *Gastroenterology* 2017;152:497–514.
8. Pennazio M, Rondonotti E, Despott EJ, Dray X, Keuchel M, Moreel T, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) guideline—update 2022. *Endoscopy* 2023;55:58–95.
9. Teshima CW, Kuipers EJ, van Zanten SV, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis. *J Gastroenterol Hepatol* 2011;26:796–801.
10. Barkun AN, Almadi M, Kuipers EJ, Laine L, Sung J, Tse F, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the international consensus group. *Ann Intern Med* 2019;171:805–22.
11. Guo CLT, Wong SH, Lau LHS, Lui RNS, Mak JWY, Tang RSY, et al. Timing of endoscopy for acute upper gastrointestinal bleeding: a territory-wide cohort study. *Gut* 2022;71:1544–50.
12. Lau JYW, Yu Y, Tang RSY, Chan HCH, Yip HC, Chan SM, et al. Timing of endoscopy for acute upper gastrointestinal bleeding. *N Engl J Med* 2020;382:1299–308.
13. Anvari S, Lee Y, Yu J, Doumouras AG, Khan KJ, Hong D. Urgent versus standard colonoscopy for management of acute lower gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials. *J Clin Gastroenterol* 2020;54:493–502.
14. Sengupta N, Feuerstein JD, Jairath V, Shergill AK, Strate LL, Wong RJ, et al. Management of patients with acute lower gastrointestinal bleeding: an updated ACG guideline. *Am J Gastroenterol* 2023;118:208–31.
15. Tsay C, Shung D, Stemmer Frumento K, Laine L. Early colonoscopy does not improve outcomes of patients with lower gastrointestinal bleeding: systematic review of randomized trials. *Clin Gastroenterol Hepatol* 2020;18:1696–1703.e2.
16. Nigam N, Ham SA, Sengupta N. Early colonoscopy for diverticular bleeding does not reduce risk of postdischarge recurrent bleeding: a propensity score matching analysis. *Clin Gastroenterol Hepatol* 2019;17:1105–11.e1.
17. Yamamoto H, Ogata H, Matsumoto T, Ohmiya N, Ohtsuka K, Watanabe K, et al. Clinical practice guideline for enteroscopy. *Dig Endosc* 2017;29:519–46.
18. Estevinho MM, Pinho R, Fernandes C, Rodrigues A, Ponte A, Gomes AC, et al. Diagnostic and therapeutic yields of early capsule endoscopy and device-assisted enteroscopy in the setting of overt GI bleeding: a systematic review with meta-analysis. *Gastrointest Endosc* 2022;95:610–25.e9.
19. Aniwan S, Viriyautsahakul V, Rerknimitr R, Angsuwatcharakon P, Kongkam P, Treeprasertsuk S, et al. Urgent double balloon endoscopy provides higher yields than non-urgent double balloon endoscopy in overt obscure gastrointestinal bleeding. *Endosc Int Open* 2014;2:E90–5.
20. Robles EPC, Conesa PB, Delgado PE, Nava LEZ, Andrés BM, Agudo JLR, et al. Emergency double-balloon enteroscopy combined with real-time viewing of capsule endoscopy: a feasible combined approach in acute overt-obscure gastrointestinal bleeding? *Dig Endosc* 2015;27:338–44.
21. Yin A, Zhao L, Ding Y, Yu H. Emergent double balloon enteroscopy in overt suspected small bowel bleeding: diagnosis and therapy. *Med Sci Monit* 2020;26:e920555.
22. Uchida G, Nakamura M, Yamamura T, Furukawa K, Kawashima H, Honda T, et al. Systematic review and meta-analysis of the diagnostic and therapeutic yield of small bowel endoscopy in patients with overt small bowel bleeding. *Dig Endosc* 2021;33:66–82.
23. Tu CH, Kao JY, Tseng PH, Lee YC, Chiang TH, Chen CC, et al. Early timing of single balloon enteroscopy is associated with increased diagnostic yield in patients with overt small bowel bleeding. *J Formos Med Assoc* 2019;118:1644–51.
24. Tanaka S, Mitsui K, Yamada Y, Ehara A, Kobayashi T, Seo T, et al. Diagnostic yield of double-balloon endoscopy in patients with obscure GI bleeding. *Gastrointest Endosc* 2008;68:683–91.
25. Silva JC, Pinho R, Ponte A, Rodrigues A, Rodrigues J, Gomes AC, et al. Does urgent balloon-assisted enteroscopy impact rebleeding and short-term mortality in overt obscure gastrointestinal bleeding? *Scand J Gastroenterol* 2020;55:1243–7.
26. Perez-Cuadrado-Robles E, Perez-Cuadrado-Martinez E. The role of emergency endoscopy in small bowel bleeding: a review. *GE Port J Gastroenterol* 2016;23:84–90.
27. MY S, Lin WP, Chiu CT. Experience of double balloon enteroscopy. *J Chin Med Assoc* 2018;81:225–29.
28. Sun B, Rajan E, Cheng S, Shen R, Zhang C, Zhang S, et al. Diagnostic yield and therapeutic impact of double-balloon enteroscopy in a large cohort of patients with obscure gastrointestinal bleeding. *Am J Gastroenterol* 2006;101:2011–5.
29. Hermans C, Stronkhorst A, Tjhie-Wensing A, Kamphuis J, Balkom BV, Dahlmans R, et al. Double-balloon endoscopy in overt and occult small bowel bleeding: results, complications, and correlation with prior videocapsule endoscopy in a tertiary referral center. *Clin Endosc* 2017;50:69–75.
30. Bollinger E, Raines D, Saitta P. Distribution of bleeding gastrointestinal angioectasias in a Western population. *World J Gastroenterol* 2012;18:6235–9.
31. Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF; Guideline Development Group. Blood transfusion: summary of NICE guidance. *BMJ* 2015;351:h5832.
32. Oakland K, Jairath V, Murphy MF. Advances in transfusion medicine: gastrointestinal bleeding. *Transfus Med* 2018;28:132–9.
33. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11–21.
34. Oakland K, Chadwick G, East JE, Guy R, Humphries A, Jairath V, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut* 2019;68:776–89.