Efficacy of Early Video Capsule Endoscopy for Acute Overt Lower Gastrointestinal Bleeding with Colonic Diverticulosis: A Prospective Observational Study

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Lower gastrointestinal bleeding · Presumptive colonic diverticular bleeding · Diagnostic yield · Capsule endoscopy

Abstract

Background/Aims: Although most patients with presumptive colonic diverticular bleeding (CDB) do not undergo a small bowel investigation in clinical practice, no prospective study supports this management. We evaluated the utility of early small bowel capsule endoscopy (CE) after negative colonoscopy results. Methods: This prospective study evaluated the diagnostic yield of early small bowel CE (≤3 days from visit) for consecutive patients with acute-onset hematochezia, when colonoscopy found colonic diverticulosis but did not identify the definite bleeding source (n = 51; presumptive CDB). As a matched control for comparing clinical outcomes, presumptive CDB patients without CE (n = 51) were retrospectively extracted. Results: On CE for the prospective cohort, the rates of total positive findings, P2 findings (high bleeding potential according to the P classification), and blood pooling in the colon were 57%, 12% (ulceration, 8%; angioectasia, 4%), and 24%, respectively. The rates of rebleeding within 30 and 365 days were 16% and 29% in the prospective cohort with CE, respectively, and were not significantly different from those in the retrospective cohort without CE (10% and 25%, respectively). In addition, thromboembolism and mortality within 30 and 365 days were not significantly different between those with and without CE. Conclusion: Early CE detected a suspected small bowel bleeding source in 12% of acute-onset presumptive CDB patients but did not significantly improve major clinical outcomes. Therefore, routine CE is unnecessary for presumptive CDB patients after colonoscopy (UMIN000026676).

Introduction

The most common diagnosis among patients in Western and Eastern countries with acute overt lower gastrointestinal bleeding (LGIB) is presumptive colonic diverticulitic bleeding (CDB) [1, 2]. In this diagnosis, the colonic diverticulosis is the candidate bleeding source, but...
the bleeding sources are not definitely diagnosed in colonoscopy (CS). In clinical practice, most patients do not undergo a small bowel investigation, although they may have a small bowel bleeding source. The reason is that small bowel bleeding is considered very rare, compared to CDB. Another reason is that small bowel endoscopies, including capsule endoscopy (CE), are time-consuming and the procedures can be performed in limited institutions. However, occasionally, we must decide whether to examine the small bowel in presumptive CDB patients, as those patients often suffer from early rebleeding and usually take nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin [3, 4], which are risks for small bowel ulcerations [5]. Information on the prevalence of small bowel bleeding sources would be beneficial to manage presumptive CDB.

Several studies have reported a high diagnostic yield of early CE for acute overt GIB patients [6–10]. However, the prevalence of small bowel bleeding sources and the efficacy of early CE remain unknown in presumptive CDB patients. Previous prospective studies included an extremely small number of presumptive CDB patients (n = 6) or lacked information on the colonic diverticulosis [6, 8, 9]. A retrospective study only selected patients who underwent small bowel CE [7, 10]. Therefore, small bowel CE data are needed for consecutive patients with acute LGIB.

To address these issues, this prospective study investigated the utility of early small bowel CE for presumptive CDB patients after negative CS results, regarding diagnostic yield and the contribution to reducing rebleeding, thromboembolisms, and mortality. The results of this study will help decide on whether to perform early CE in clinical practice.

Materials and Methods

Study Design, Setting, and Participants

The study flowchart is shown in Figure 1.

A Prospective Cohort with Early Small Bowel CE

This prospective study was performed between March 2017 and November 2021 at a single referral university hospital (The University of Tokyo Hospital, Tokyo, Japan). Written informed consent was obtained from all participants. This study was conducted according to the guidelines of the Declaration of Helsinki, was approved by the Ethics Committee of The University of Tokyo (Approval No. 11478), and was registered at UMIN Clinical Trials Registry (UMIN000026676, March 23, 2017).

Consecutive outpatients aged ≥20 years with moderate to severe hematochezia within 24 h of arrival were eligible and whose definitive bleeding source had not been identified by early CS (≤3 days of admission). Definitive bleeding sources detected by CS included lesions with active bleeding, a visible vessel or an adherent clot, and lesions, such as tumors, colitis, and discrete ulcers [11]. Patients were not eligible if contrast-enhanced computed tomography (CT) revealed an obvious source of bleeding before CE, irrespective of colonoscopic findings. Major inclusion criteria were three or more occurrences of hematochezia within 8 h, hemorrhagic shock, or requiring a transfusion [12].

Exclusion criteria included hematemesis or coffee-ground vomitus; upper gastrointestinal bleeding (UGIB) diagnosed using a nasogastric tube or upper endoscopy; poor bowel preparation for CS; diagnosis of UGIB within the past 10 days; Crohn’s disease; abdominal surgery within the past 10 days; suspected perforation or peritonitis; suspected intestinal obstruction; swallowing disorder; pacemaker or other electromedical devices; end-stage malignant disease; severe cardiac failure; severe respiratory failure; pregnancy; and those who could not undergo surgery according to their adverse general condition when a complication occurred [8, 12]. Among enrolled patients, those with colonic diverticulosis in CS who underwent CE within 3 days from their visit were included in the analysis.

Historical Control without Small Bowel CE

Acute-onset patients with presumptive CDB but who did not undergo CE were retrospectively extracted as a historical control group for the secondary outcomes. These patients were emergently admitted to the same hospital from January 2010 to December 2016. Informed consent of these patients was carried out by the opt-out method at our hospital’s website. To select patients, we first identified those with acute-onset hematochezia whose definitive bleeding source was not detected by early CS (≤3 days of admission), by reviewing the electronic medical record system of our hospital. Then, we excluded patients with UGIB, <365-day follow-up, who underwent the CE procedure, and who did not have colonic diverticulosis in CS. After exclusion, presumptive CDB patients who did not undergo CE remained. Finally, to minimize confounding effects, a historical control group was randomly selected with a ratio of 1:1 to the prospective cohort, matched for age-category, and NSAIDs including aspirin, thienopyridine, and anticoagulant use.

Study Procedure for a Prospective Cohort with CE

Before CE, all patients underwent total CS with full bowel preparation within 3 days of admission. Oral bowel preparation for the CS was performed using 2–4 L of a solution containing polyethylene glycol on the day of the CS. All colonoscopies were performed using an electronic video endoscope (Olympus Optical, Tokyo, Japan) with the water-jet device to visualize the colon. Patients were required to fast from hospitalization and take 40 mg simethicone orally to prevent the formation of gas bubbles before CE [13].

Early CE performed within 3 days of admission reportedly has a higher diagnostic yield than CE performed after 3 days of admission [14–16]. Therefore, CE performed within 3 days of admission was defined as early CE in this study. We used the PillCam™ SB3 CE device (Medtronic, Minneapolis, MN, USA). CE recording stopped when the capsule reached the colon 8 h after ingestion or when the battery ran out more than 8 h after ingestion. Two expert endoscopists (AT and YA, >500 CE reviews each), who had the patients’ clinical background information, reviewed the CE images.
Patients received further endoscopic procedures, such as esophagogastroduodenoscopy (EGD) or double-balloon enteroscopy (DBE), depending on the suspected CE findings. Additional CS was performed for clinical rebleeding in patients without significant CE findings. An endoscopic intervention was performed when endoscopic procedures showed stigmata of recent hemorrhage.

All patients were followed up until death or 365 days from study enrollment. Clinical outcomes such as rebleeding, thromboembolisms, and mortality were monitored once every 3 months by hospital visit during the follow-up period or by a telephone interview from a researcher.

Outcome Measures

The primary outcome measure was the diagnostic yield of small bowel CE in presumptive CDB patients. The clinical significance of small bowel lesions was described according to the P classification (P0–2) [17]. P0 lesions (no bleeding potential) included visible submucosal veins, diverticula without the presence of blood, and nodules without a mucosal break. P1 lesions (uncertain bleeding potential) included red spots on the intestinal mucosa and small or isolated erosions. P2 lesions (high bleeding potential) include angioectasia, ulceration, tumors, and varices. Blood pooling without a definite bleeding source was also included in the positive CE findings [8].

The secondary outcome measures included complications related to CE, and rebleeding, thromboembolisms, and mortality within 30 and 365 days were compared between presumptive CDB patients with CE and historical control without CE. Complications related to CE included capsule retention, perforation, bowel obstruction, and bleeding. Capsule retention was defined as a capsule remaining in the gastrointestinal tract for 15 days (or less if medical, endoscopic, or surgical intervention was deemed necessary) [18]. Rebleeding was evaluated after the initial endoscopic investigation and was defined as overt bleeding with any of the following: hemorrhagic shock, need for transfusion, identification of blood pooling on further CS, definitive bleeding source in the lower gastrointestinal tract, or extravasation identified in the colorectal region on a contrast-enhanced CT scan [10, 12]. Thromboembolisms included acute coronary syndromes, stroke, pulmonary embolism, and deep vein thrombosis.
Table 1. Baseline patient characteristics

| Characteristics                                      | Patients with CE (n = 51) | Patients without CE (n = 51) | p value |
|------------------------------------------------------|---------------------------|-----------------------------|---------|
| Age ≥70 years                                        | 28 (54.9)                 | 28 (54.9)                   | 1.000   |
| Male sex                                             | 31 (60.8)                 | 32 (62.8)                   | 0.839   |
| BMI ≥25, kg/m²                                     | 19 (37.3)                 | 17 (33.3)                   | 0.679   |
| Current drinker                                      | 26 (51.0)                 | 23 (45.1)                   | 0.552‡‡ |
| Current smoker                                       | 6 (11.8)                  | 2 (3.9)                     | 0.269‡‡ |
| Syncope†                                             | 7 (13.7)                  | 4 (7.8)                     | 0.525‡‡ |
| Diarrhea                                             | 0 (0)                     | 2 (3.9)                     | 0.495‡‡ |
| Abdominal tenderness                                 | 6 (11.8)                  | 2 (3.9)                     | 0.269‡‡ |
| NSAIDs including aspirin**                           | 26 (51.0)                 | 26 (51.0)                   | 1.000   |
| Thienopyridines§                                      | 2 (3.9)                   | 2 (3.9)                     | 1.000‡‡ |
| Other antiplatelet drugs**                           | 2 (3.9)                   | 5 (9.8)                     | 0.436‡‡ |
| Anticoagulants§                                      | 3 (5.9)                   | 3 (5.9)                     | 1.000   |
| Corticosteroid***                                    | 8 (15.7)                  | 1 (2.0)                     | 0.031‡‡ |
| Proton pump inhibitor                                | 20 (39.2)                 | 15 (29.4)                   | 0.297   |
| Heart rate ≥100/min                                  | 12 (23.5)                 | 8 (15.7)                    | 0.318   |
| Systolic blood pressure ≤100, mm Hg                  | 6 (11.8)                  | 4 (7.8)                     | 0.741‡‡ |
| Hemoglobin ≤8.0, g/L                                 | 4 (7.8)                   | 5 (9.8)                     | 1.000   |
| WBC <10 × 10^3/μL                                    | 39 (76.5)                 | 46 (90.2)                   | 0.109‡‡ |
| Platelets ≤150 × 10^3/mL                            | 11 (21.6)                 | 6 (11.8)                    | 0.184   |
| PT-INR ≥1.5                                         | 3 (5.9)                   | 1 (2.0)                     | 0.617‡‡ |
| BUN/Cr ratio ≥30                                    | 5 (9.8)                   | 15 (29.4)                   | 0.023‡‡ |
| Diabetes mellitus                                    | 12 (23.5)                 | 9 (17.7)                    | 0.463   |
| Cerebrovascular disease                              | 7 (13.7)                  | 8 (15.7)                    | 0.780   |
| Dementia                                             | 1 (2.0)                   | 4 (7.8)                     | 0.362‡‡ |
| Connective tissue disease                            | 7 (13.7)                  | 1 (2.0)                     | 0.060‡‡ |
| Myocardial infarction                                | 8 (15.7)                  | 8 (15.7)                    | 1.000   |
| Congestive heart failure                             | 3 (5.9)                   | 2 (3.9)                     | 1.000‡‡ |
| Ulcer disease                                        | 7 (13.7)                  | 6 (11.8)                    | 0.767   |
| Chronic kidney disease                               | 11 (21.6)                 | 8 (15.7)                    | 0.445   |
| Peripheral vascular disease                          | 2 (3.9)                   | 1 (2.0)                     | 1.000‡‡ |
| Liver cirrhosis                                      | 2 (3.9)                   | 3 (5.9)                     | 1.000‡‡ |
| Malignancy                                           | 12 (23.5)                 | 10 (19.6)                   | 0.630   |
| History of LGB                                       | 19 (37.3)                 | 7 (13.7)                    | 0.006   |
| CS ≤1 day from visit                                 | 37 (72.6)                 | 48 (94.1)                   | 0.007‡‡ |
| Blood pooling in the colon on CS                     | 9 (17.7)                  | 20 (39.2)                   | 0.016   |
| Blood pooling in the terminal ileum on CS            | 5 (9.8)                   | 3 (5.9)                     | 0.715‡‡ |
| CE ≤1 day from visit                                 | 32 (62.7)                 | –                           | NA      |
| CE ≤1 day from CS                                    | 48 (94.1)                 | –                           | NA      |
| Total visualization of small bowel by CE             | 44 (86.3)                 | –                           | NA      |
| Blood transfusion before CE                          | 18 (35.3)                 | –                           | NA      |
| Blood transfusion during CE                          | 30 (58.8)                 | 18 (35.3)                   | 0.017   |
| Mean length of hospital stay, days (±SD)             | 8.5±5.3                   | 9.4±5.0                     | 0.124   |

Data are presented as n (%). Medication use was defined as intermittent or regular oral administration within 2 weeks before admission. SD, standard deviation; CE, capsule endoscopy; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; WBC, white blood cell; PT-INR, prothrombin time-international normalized ratio; BUN, blood urea nitrogen; Cr, creatinine; LGB, lower gastrointestinal bleeding; CS, colonoscopy; NA, not available. * BMI was calculated as weight divided by height squared (kg/m²). † Syncope included a transient altered mental status defined as a Glasgow coma scale score ≤14 or a history of syncope. ** NSAIDs included nonaspirin NSAIDs (loxoprofen, diclofenac, naproxen, etodolac, zaltoprofen, meloxicam, lornoxicam, and celecoxib) and low-dose aspirin (enteric-coated aspirin or buffered aspirin). Patients with CE included nonaspirin NSAIDs (n = 15) and low-dose aspirin (n = 15, duplicated). Patients without CE included nonaspirin NSAIDs (n = 6) and low-dose aspirin (n = 20). *** In patients undergoing CE, corticosteroid was used for rheumatoid arthritis (n = 2), eosinophilic granulomatosis with polyangiitis (n = 1), myasthenia gravis (n = 1), systemic lupus erythematosus (n = 1), dermatomyositis (n = 1), interstitial nephritis (n = 1), and post-heart transplantation (n = 1). Patients in CE included nonaspirin NSAIDs (n = 5) and low-dose aspirin (n = 1). ¶ Thienopyridine included clopidogrel and ticlopidine. ¶¶ Other antiplatelet drugs included dipyridamole, cilostazol, sarpogrelate hydrochloride, ethyl iodosapentate, dilazep hydrochloride, limaprost alfadex, and beraprost. § Anticoagulants included warfarin, dabigatran etexilate, rivaroxaban, apixaban, and edoxaban. ‡‡ Analyzed using Fisher’s exact test.
**Table 2. Results of early CE (n = 51)**

| CE findings                                                                 | n (%)                  |
|-----------------------------------------------------------------------------|------------------------|
| **Total of positive findings**                                              | 29 (56.9, 42.8–70.9)   |
| Stomach                                                                     | 1 (2.0)                |
| Polyp and blood without definite bleeding source                           | 1 (2.0)                |
| Duodenum                                                                    | 1 (2.0)                |
| Erosion                                                                     | 1 (2.0)                |
| Small bowel                                                                 | 16 (31.4, 18.2–44.6)   |
| P2 lesion                                                                   | 6 (11.8, 2.6–20.9)     |
| Ulceration*                                                                | 4 (7.8)                |
| Angioectasia                                                                | 2 (3.9)                |
| P1 lesion (erosion)                                                         | 8 (15.7, 5.4–26.0)     |
| P0 lesion (small diverticulum)                                              | 2 (3.9, −1.6–9.4)      |
| Small bowel lesion followed by DBE after CE                                | 3 (5.9)                |
| Colon                                                                       | 12 (23.5, 11.5–35.6)   |
| Blood pooling without definite bleeding source*                             | 12 (23.5)              |
| No blood and no lesion                                                      | 22 (43.1)              |
| **Final diagnosis of potential bleeding source**                            |                        |
| Colonic diverticulosis and small bowel ulceration                           | 3 (5.9)                |
| Colonic diverticulosis and Meckel’s diverticulum                           | 1 (2.0)                |
| Colonic diverticulosis and small bowel angioectasia                        | 2 (2.0)                |
| Colonic diverticulum**                                                      | 44 (86.3)              |
| Small bowel ulceration (definitive)                                        | 1 (2.0)                |
| Complication related to CE                                                  | 0 (0)                  |

CI, confidence interval; DBE, double-balloon enteroscopy. * Duplicated: one patient had ulcerations in the small bowel and blood pooling without a definite bleeding source in the colon. ** Definitive diagnosis (n = 1) and presumptive diagnosis (n = 43). †† Analyzed using Fisher’s exact test.

**Statistical Analysis**

Pearson’s χ² or Fisher’s exact test was used to compare the proportions, as appropriate. The Wilcoxon rank-sum test was used to compare medians of continuous variables. Individual odds ratios and 95% confidence intervals were computed for each variable using logistic regression analysis or exact logistic regression analysis, as appropriate. p values <0.05 were considered significant. Statistical analyses were performed with STATA version 14 software (StataCorp, College Station, TX, USA).

**Results**

**Patient Characteristics**

A Prospective Cohort with Early Small Bowel CE

Of the 60 enrolled patients, 51 patients who underwent CE within 3 days from their visit (male, 61%; mean age, 70.3 years; range, 38–87 years) were included in the analysis, and nine were excluded (Fig. 1). As shown in Table 1, NSAIDs, including aspirin, were used in 51% of patients. Blood pooling in the terminal ileum was identified in CS in 10% of patients. CE was performed within 1 day from the CS in 94% of patients, and the total visualization of small bowel by CE was achieved in 86% of cases. Contrast-enhanced CT was performed before CE in 14% of cases but did not reveal any obvious source of bleeding.

A Historical Control Group without Small Bowel CE

Of the 178 patients with acute-onset hematochezia whose definitive bleeding source was not detected by CS, 95 patients with a colonic diverticulum did not undergo CE, and 83 were excluded (Fig. 1). Of these 95 patients, 1:1 matching with our prospective cohort extracted 51 presumptive CDB patients. As shown in Table 1, the historical control had a significantly higher proportion of patients with a blood urea nitrogen (BUN)/creatinine (Cr) ratio ≥30, blood pooling in the colon in CS, and a significantly lower rate of a history of LGIB, compared to the prospective cohort. However, these two groups were similar to other basic characteristics.

**Primary Outcome**

Diagnostic Yield of Early CE

Table 2 describes the early CE findings. In total, the rate of positive findings by CE was 57% (29/51), including...
2% in the stomach, 2% in the duodenum, 31% in the small bowel, and 24% in the colon (one patient was duplicated). The rate of P2 findings was 12% (6/51), and the most prevalent P2 lesion was ulceration, as shown in Figure 2. Among patients with a diverticulum in the cecum or the ascending colon (\(n=49\)), the rate of blood pooling in the terminal ileum in CS was higher in patients with than in those without a P2 lesion (40% vs. 7%, \(p = 0.043\), online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525314).

The rate of small bowel lesions followed by DBE after CE was 6%. Table 3 shows the additional procedures of patients with positive CE findings. DBE was performed in 3 patients, and a small bowel ulceration (\(n = 1\)), Meckel’s diverticulum (\(n = 1\)), and no significant lesion (\(n = 1\)) were detected. EGD was performed in 1 patient and revealed that gastric polyps do not produce acute hematochezia. No additional endoscopy was performed during admission in patients without any CE findings.

**Secondary Outcomes**

**Safety**

None of the patients developed complications related to CE.

**Rebleeding, Thromboembolisms, and Mortality**

The rates of rebleeding within 30 days were 16% and 10% for presumptive CDB with CE (\(n = 51\)) and presumptive CDB without CE (\(n = 51\)), respectively, and the rates of rebleeding within 365 days were 29% and 25%, respectively. Rebleeding, thromboembolisms, and mortality within 30 and 365 days were not significantly different between these two groups (Fig. 3).

**Discussion**

To our knowledge, this is the first study to prospectively evaluate the utility of early CE after negative CS results in patients with acute-onset hematochezia, mainly for presumptive CDB. CE detected a suspected small bowel bleeding source in 12% of acute-onset presumptive CDB patients but did not significantly improve major clinical outcomes. Among patients with a diverticulum in the cecum or the ascending colon, the rate of blood pooling in the terminal ileum in CS was higher in patients with than in those without P2 lesions (40% vs. 7%).

Several prospective studies have reported the efficacy of early CE for acute overt GIB. In a prospective study of early CE in 20 patients with acute GIB after negative upper endoscopy results, patients with fresh-red rectal blood (highly suggestive of LGIB) were excluded [8]. In a randomized controlled trial (RCT) comparing CE with angiography for acute overt obscure GIB, 30 patients with acute melena or hematochezia underwent early CE, but detailed information on the melena or hematochezia and the presence of colonic diverticulosis was lacking [6]. In another RCT comparing CE with standard care for acute GIB, early CE was performed in 11 patients with hematochezia, which included only 6 patients with colonic diver-
Table 3. Baseline characteristics and further procedures on patients with positive CE findings (n = 29)

| Age, sex | Nonaspirin NSAIDs use† | Antithrombotic drug use | Corticosteroid use | CE finding [P classification of small bowel lesions] | Location | Procedure after CE | Final diagnosis of potential bleeding source | Treatment | Rebleeding |
|----------|------------------------|-------------------------|-------------------|-----------------------------------------------------|----------|------------------|----------------------------------------------|-----------|-----------|
| 81, F    | −                      | −                       | −                 | Polyp and blood without definite bleeding source (Fig. 2a) | Stomach | EGD              | Colonic diverticulosis*                       | Observation | −         |
| 77, F    | −                      | Aspirin                | −                 | Erosion                                              | Duodenum | −                | Colonic diverticulosis                        | Observation | −         |
| 79, F    | −                      | −                      | −                 | Angioectasia [P2] (Fig. 2b)                          | Small bowel | −                | Colonic diverticulosis and small bowel angioectasia | Observation | + (Within 365 days) |
| 68, F    | −                      | −                      | −                 | Angioectasia [P2] (Fig. 2c)                          | Small bowel | −                | Colonic diverticulosis and small bowel angioectasia | Observation | −         |
| 78, M    | +                      | Aspirin                | −                 | Ulceration [P2] (Fig. 2d)                            | Small bowel | −                | Colonic diverticulosis and small bowel ulceration | NSAID discontinuation | + (Within 365 days) |
| 69, F    | +                      | −                      | −                 | + (Myasthenia gravis)                                | Small bowel and colon | −                | Colonic diverticulosis and small bowel ulceration | NSAID discontinuation | −         |
| 63, M    | −                      | −                      | −                 | + (Post-heart transplantation)                       | Ulceration [P2] (Fig. 2f) | Small bowel | DBE              | Colonic diverticulosis and small bowel ulceration | Observation | −         |
| 63, M    | −                      | −                      | −                 | Ulceration [P2] (Fig. 2g)                            | Small bowel | DBE              | Small bowel ulceration (Definitive)            | Endoscopic intervention | + (Within 30 days) |
| 61, M    | −                      | −                      | −                 | Small diverticulum [P0]                              | Small bowel | CS and DBE      | Colonic diverticulosis and Meckel’s diverticulum | Observation | + (Within 30 days) |
| 61, M    | −                      | −                      | −                 | Small diverticulum [P0]                              | Small bowel | −                | Colonic diverticulosis                        | Observation | + (Within 30 days) |
| 74, M    | −                      | Aspirin                | −                 | Erosion [P1]                                         | Small bowel | CS               | Colonic diverticulosis (Definitive)            | Colonoscopic intervention and aspirin discontinuation | + (Within 30 days) |
| 81, F    | +                      | −                      | + (Rheumatoid arthritis)                             | Erosion [P1] | Small bowel | −                | Colonic diverticulosis                        | Observation | −         |
| 80, F    | −                      | −                      | −                 | Erosion [P1]                                         | Small bowel | −                | Colonic diverticulosis                        | Observation | −         |
| 75, F    | −                      | Aspirin                | −                 | Erosion [P1]                                         | Small bowel | −                | Colonic diverticulosis                        | Observation | −         |
| 84, F    | −                      | −                      | + (Interstitial nephritis)                             | Erosion [P1] | Small bowel | −                | Colonic diverticulosis                        | Observation | −         |
| 61, M    | −                      | Aspirin                | −                 | Erosion [P1]                                         | Small bowel | CS               | Colonic diverticulosis                        | Aspirin discontinuation | + (Within 30 days) |
| 71, F    | +                      | −                      | + (Dermatomyositis)                                   | Erosion [P1] | Small bowel | −                | Colonic diverticulosis                        | NSAID discontinuation | −         |
| 75, M    | −                      | Aspirin                | −                 | Erosion [P1]                                         | Small bowel | −                | Colonic diverticulosis                        | Observation | −         |
### Table 3 (continued)

| Age, sex | Nonaspirin NSAIDs use† | Antithrombotic drug use | CE finding [P classification of small bowel lesions] | Location | Procedure after CE | Final diagnosis of potential bleeding source | Treatment | Rebleeding |
|----------|------------------------|-------------------------|------------------------------------------------------|----------|-------------------|-----------------------------------------------|-----------|------------|
| 57, M    | +                      | −                       | Blood pooling without bleeding source                | Colon    | CS                | Colonic diverticulosis                        | NSAID discontinuation | −          |
| 73, M    | − Aspirin              | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Observation | −          |
| 66, M    | − − −                  | −                       | Blood pooling without bleeding source                | Colon    | CS and Contrast-enhanced CT | Colonic diverticulosis                        | Observation | + (Within 30 days) |
| 51, M    | − − −                  | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Observation | + (Within 365 days) |
| 65, M    | − − −                  | −                       | Blood pooling without bleeding source                | Colon    | CS                | Colonic diverticulosis                        | Observation | + (Within 30 days) |
| 75, M    | + Rivaroxaban          | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | NSAID discontinuation | −          |
| 63, F    | + − −                  | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Observation | −          |
| 87, F    | + Cilostazol           | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Discontinuation of NSAID and cilostazol | −          |
| 54, M    | − − −                  | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Observation | −          |
| 69, M    | − − −                  | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Observation | −          |
| 58, M    | − − −                  | −                       | Blood pooling without bleeding source                | Colon    | −                 | Colonic diverticulosis                        | Observation | −          |

M, male; F, female; CE, capsule endoscopy; EGD, esophagogastroduodenoscopy; DBE, double-balloon enteroscopy; NSAIDs, nonsteroidal anti-inflammatory drugs; CT, computed tomography. *EGD revealed that gastric polyps did not have the potential for acute hematochezia. **Ulcerations in the small bowel and blood pooling without a definite bleeding source in the colon. †Nonaspirin NSAIDs included loxoprofen, diclofenac, naproxen, etodolac, zaltoprofen, meloxicam, lornoxicam, and celecoxib.
ticulosis [9]. In a retrospective study of acute LGIB patients, only 3% of presumptive CDB patients (9/344) underwent CE; therefore, the utility of CE could not be evaluated [10]. The most unique point in our prospective study was that 51 consecutive patients with presumptive CDB underwent early CE. Thus, the results of this study support the management of presumptive CDB patients and whether to perform CE.

CE has a relatively low likelihood of identifying P2 lesions in the small bowel in presumptive CDB patients. For them, blood pooling in the terminal ileum in CS supports the decision to perform CE, because a total of 40% (2/5) of the presumptive CDB patients with blood pooling in the terminal ileum had P2 lesions in the small bowel. Blood pooling in the terminal ileum indicates not only bleeding from the small bowel but also reflux from the colonic bleeding in clinical practice, but this finding seemed important. We could not find any other factor that would recommend CE (online suppl. Table 1). NSAIDs, including aspirin, are not predictors of P2 lesions, although 75% of P2 lesions were ulcerations, possibly because NSAID use is a risk factor for CDB [3, 4] and small bowel ulcerations [5]. Therefore, it is ineffective for presumptive CDB patients who use NSAIDs to consistently undergo CE. In addition, CE would not be highly recommended even for those who present with recurrent LGIB (i.e., history of LGIB), those with BUN/Cr ratio $\geq 30$, patients with connective tissue diseases, and those on corticosteroids. However, 1 patient using a corticosteroid after heart transplantation had an ulcerative lesion in the small bowel despite no use of NSAIDs, including aspirin. Although the etiology of the lesion was unclear, post-transplantation patients suffer small bowel lesions such as post-transplant lymphoproliferative disorder or graft-versus-host disease.

Interestingly, CE detected blood pooling in the colon in 24% of patients with colonic diverticulosis. Blood pooling was detected by CE within 1 day of the CS. This indicates the utility of CE for managing presumptive CDB and the natural course of presumptive CDB. First, CE denies

Fig. 3. Patient outcomes after negative CS results. a Rates of 30-day outcomes in groups with or without CE. b Rates of 365-day outcomes in groups with or without CE. ‡Analyzed using Fisher’s exact test.
UGIB and small bowel bleeding for these patients, enabling physicians to focus on colonic bleeding, although CE may miss small bowel lesions as a result of automatic capture. EGD could be avoidable during admission. In addition, when rebleeding occurred in these patients, physicians could simply choose repeated colonoscopies as the additional endoscopic investigation, and not EGD or DBE. Second, considering that all patients underwent total CS with oral bowel preparation and the water-jet device before CE, rebleeding occurred at the earliest time after CS in one-fourth of presumptive CDB patients.

Meckel’s diverticulum in the small bowel was found in 1 patient and diagnosed by DBE, not by CE. This result was consistent with a previous study of Meckel’s diverticulum in which balloon-assisted enteroscopy diagnosed 85% of Meckel’s diverticulum cases, whereas CE diagnosed 36% of cases [19]. This indicates one of the limitations of the present study that small bowel bleeding was not completely excluded even when CE did not detect significant findings.

Additional CE for presumptive CDB patients did not improve major clinical outcomes in the short or long term, such as rebleeding, thromboembolisms, and mortality, in the analysis using our matched cohort. One reason is that rebleeding risks for CDB and small bowel ulcerations were reduced after discontinuing NSAIDs [20, 21]. We presume that small bowel ulcerations in CDB patients may be simultaneously cured by discontinuing the drug, even when CE was not performed. The rates of rebleeding within 365 days (patients with CE, 29%; without CE, 25%) were consistent with previous CDB studies (20–35%) [22–24].

The main limitations of our study were the relatively small sample size and the nonrandomized design. A sample size estimate could not be performed because our study was strongly based on an exploratory design. We showed the utility of early CE after negative CS results in this study. However, only an RCT could determine whether the procedure improves clinical outcomes of acute-onset presumptive CDB. In addition, the retrospective extraction of patients without CE for a control group could cause selection bias, because a few patients with CE were excluded. To evaluate selection bias, we reviewed presumptive CDB patients in our retrospective cohort with CE (n = 18) or without CE (n = 95), before matching them with a prospective cohort (online suppl. Table 2). The rate of blood transfusion during admission was higher in patients with CE (78%) than in those without CE (47%), suggesting that severe patients in the retrospective cohort likely undergo CE. This review of the retrospective cohort emphasized that CE rarely found P2 lesions (6%) despite the inclusion of severe patients and that our prospective assessment in this study was meaningful.

Conclusion

CE detected suspected a small bowel bleeding source in 12% of acute-onset presumptive CDB patients but did not significantly improve major clinical outcomes. Therefore, routine CE is unnecessary for presumptive CDB patients after CS.

Statement of Ethics

Written informed consent was obtained from all participants. This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of The University of Tokyo (Approval No. 11478).

Conflict of Interest Statement

The following author disclosed financial relationships: M. Fujishiro – Speaker for Olympus and Fujifilm; research grant from Olympus, HOYA Pentax; and Fujifilm. All other authors disclosed no financial relationships.

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Author Contributions

Tomonori Aoki and Atsuo Yamada designed the study; Tomonori Aoki, Atsuo Yamada, Ryota Niikura, and Ayako Nakada performed CE; Tomonori Aoki and Atsuo Yamada interpreted the data and performed statistical analysis; Tomonori Aoki drafted the article; Atsuo Yamada critically revised; Ryota Niikura, Ayako Nakada, Nobumi Suzuki, Yoku Hayakawa, Yoshihiro Hirata, Kazuhiro Koike, and Mitsuhiro Fujishiro prepared the manuscript. All authors read and approved the submitted version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.
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