Factors associated with the clinical impact of capsule endoscopy in patients with overt obscure gastrointestinal bleeding

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Running title: Capsule endoscopy in obscure gastrointestinal bleeding

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Abstract

Background and Study Aims: Capsule endoscopy (CE) does not necessarily identify positive findings in patients with overt obscure gastrointestinal bleeding (OGIB). We aimed to identify factors predictive of positive CE findings and those of re-bleeding after negative CE in overt OGIB.

Patients and Methods: We retrospectively analyzed 68 patients who underwent CE for overt OGIB. CE findings, therapeutic interventions, and clinical course after CE were reviewed. Clinical variables associated with positive CE findings and those associated with re-bleeding after negative CE findings were investigated.

Results: Positive CE finding was found in 36 (53%) patients. Marked decrease in hemoglobin value [OR; 18.8, 95%CI; 3.4-152.0] and earlier CE examination within a week after the last episode of bleeding [OR; 8.0, 95%CI; 2.2-35.9] were factors associated with positive CE findings. Nine (28%) of 32 patients with negative CE findings re-bled. Marked decrease in hemoglobin value was more frequent in patients with re-bleeding than those without (p=0.07).

Conclusion: Patients with massive and overt OGIB are best candidates for CE. Earlier CE, virtually within a week, contributes to the better diagnostic yield of the procedure. Careful follow-up seems necessary for patients with massive bleeding even in cases of negative CE findings.

Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent bleeding with negative esophagogastroduodenoscopy (EGD), ileocolonoscopy, and small bowel radiography [1]. Since the source of OGIB is frequently located beyond the reach of conventional enteroscopy, diagnostic workup for patients with OGIB had been a matter of dilemma for gastroenterologists until the development of capsule endoscopy (CE) [2] and double (DBE) or single balloon enteroscopy [3]. The clinical advantage of CE has been particularly advocated in patients with OGIB [4], and the diagnostic yield of CE in OGIB has been reported to range from 30% to 80% [5-11], the value of which is higher than those obtained by push enteroscopy [12,13], small bowel radiography [13,14], and computed tomography (CT) [15,16]. Based on these findings, CE has been defined as the examination of choice for patients with OGIB after negative EGD and colonoscopy [4,11].

OGIB is subdivided into overt OGIB and occult OGIB [1]. Overt OGIB is defined as recurrent or persistent, visible bleeding with negative endoscopic or radiological workups. Occult OGIB shows recurrent or persistent iron deficiency anemia or positive fecal occult blood test without any detectable source of bleeding [1]. Because overt OGIB manifests acutely with occasionally life-threatening clinical course, the diagnostic yield of CE should be improved especially for the condition.

In the present study, we investigated clinical variables, which are predictive of positive diagnostic yield of CE among patients with overt OGIB. We also analyzed clinical characteristics of patients with a higher risk of re-bleeding after negative CE findings in order to establish the better clinical impact of CE.

Materials and methods

Patients

Between May 2004 and January 2008, 118 patients underwent CE at our institution for suspected small intestinal pathology after the conventional workup

including EGD, ileocolonoscopy, and either abdominal CT scan or small bowel radiography. Among them, 76 patients with recurrent or persistent visible GI bleeding were initially recruited for the present investigation. Six patients, who were examined by CE for possible concurrent intestinal bleeding, were excluded from the analysis. The sources of bleeding in those six patients were colonic angioectasia (2 patients), colonic diverticulosis, marked diffuse antral vascular ectasia, gastroduodenal stomal ulcer, and gastric ulcer (each in a patient). Other two patients were also excluded because of the lack of follow-up data. The remaining 68 patients were the subjects for the present investigation.

The study protocol was approved by the ethical committee at Kyushu University hospital, and the study was conducted in accordance with the Helsinki Declaration. No patient had contraindications for CE, such as pregnancy, known stricture or fistula of the small intestine, an inability to swallow, or equipment of electromedical devices. Written informed consent was obtained from all participants prior to the examination.

Assessment of clinical data

Clinical data of each subject was obtained by reviewing the checklist form that had been completed at the time of CE. Clinical data included the indication for CE, the onset and duration of overt OGIB, the type of bowel preparation, the lowest hemoglobin (Hb) value and the decrease in Hb value (ΔHb) after the onset of symptoms until CE, underlying diseases (liver cirrhosis, chronic renal failure, and heart diseases), and the application of anti-coagulant therapy. Liver cirrhosis was diagnosed based on the laboratory tests and morphologic characteristics under CT scan or ultrasonography. Chronic renal failure was defined as positive when patients were under regular hemodialysis or peritoneal dialysis. The heart diseases included severe valvular disease and congestive heart failure.

The time interval from the latest overt GI bleeding until CE was divided into either within 3 days, 4-7 days, or ≥8 days. A cut-off value of 8.0 g/dl, which was also

regarded as an indication for blood transfusion, was used for the classification of the lowest Hb value. Also, the severity of bleeding was determined by the decrease in Hb value from the baseline value (ΔHb). When ΔHb was greater than 5.0 g/dl, the bleeding was regarded to be massive. The baseline Hb value prior to bleeding was verified in 66 patients. In the remaining 2 patients, the Hb value after the improvement of OGIB was regarded as the baseline Hb value, because their Hb values prior to bleeding were unavailable.

CE examination

All patients underwent CE after hospitalization. After an overnight fast for 12 hours, each patient was prepared by magnesium citrate or by simethicone [17]. During a period from May 2004 until December 2005, patients were administered simethicone; thereafter, a bowel preparation by magnesium citrate. CE was then carried out in accordance with the manufacture's recommendation. Each subject was prepared with sensor arrays and data recorder, and instructed to swallow the capsule with a small amount of water. In 10 patients with poor performance status, the capsule was inserted into the duodenum with the guide of EGD. CE images were recorded for the subsequent 8 hours. Patients were allowed to drink clear liquid and eat light meals 2 hours and 4 hours after capsule ingestion, respectively. In order to decrease gastric retention of the capsule, patients were instructed to keep walking, sitting, or recumbent in the right lateral position within the first 2 hours of the examination. No physical restriction was intended during the remaining 6 hours.

All the digital video image streams were downloaded to the Given Imaging Reporting and Processing of Images and Data (RAPID) system and they were assessed by an experienced CE observer (ME) [17-19]. The video images were analyzed at an average speed (15~20 frames/sec) with concurrent manual inspection for close assessment under Multiview system.

Assessment of diagnostic yield of CE

The outcome of CE was determined according to the definition reported by Costamagna et al [14] with a slight modification. CE findings were initially classified as either 'positive', 'possibly positive', or 'no' findings. A finding, which definitely explained clinical symptoms and which was proven by other examinations (DBE, small bowel radiography, or CT) or surgery was regarded as positive finding. A finding, which presumably explained clinical symptoms but remained to be verified by further examination, was regarded as possibly positive finding. Nonspecific mucosal changes including minute red spots were regarded to be no findings. The positive diagnostic yield was calculated according to the number of subjects with either positive or possibly positive findings.

Clinical outcome after CE

Clinical information after CE was collected by reviewing patients' clinical charts and by telephone contacts with patients, their families, or the referring physicians in May 2008. The information included additional diagnostic procedures, final diagnosis, the modality of treatment (none, medical, endoscopic, or surgical), recurrent episodes of bleeding, and the length of follow-up after CE. Based on these data, clinical outcome according to CE findings and to therapeutic interventions was analyzed retrospectively.

Statistical analysis

Parametric data were expressed as mean±SD, and compared between the groups using the Mann-Whitney U test. The nonparametric data were expressed as frequencies, and were compared between the groups using Fisher's exact probability test or chi-squared test where appropriate. Logistic regression analysis was applied for the analysis of factors associated with the diagnostic yield of CE. The cumulative rate of re-bleeding after CE was calculated by the Kaplan-Meier method, and it was compared among the groups by the Log-rank test. A p value of less than 0.05 was regarded as statistically significant for each test.

Results

Demographic data

Demographic data of the patients were indicated in Table 1. The patients comprised 36 males and 32 females with the ages ranging from 9 to 91 years (mean±SD; 62±19 years). The time interval from the latest bleeding until CE ranged from 0 to 104 days (mean±SD; 13±18 days). The lowest Hb levels ranged from 4.3 to 11.9 g/dl (mean±SD; 7.3±1.9 g/dl), and 61 patients (90%) had been treated by blood transfusion prior to CE. The preceding EGD and ileocolonoscopy showed esophagogastroduodenal or colorectal lesions in 30 patients. The endoscopic diagnoses included scarred gastric or duodenal ulcer (9 patients), colonic diverticula (6 patients), colonic angioectasia (6 patients), mild diffuse antral vascular ectasia (5 patients), esophageal varices (3 patients), gastric varices (1 patient), portal hypertensive gastropathy (1 patient), and colitis (1 patient). These lesions were presumed to be irrelevant to the latest overt OGIB. Seventeen patients had been under anti-coagulant therapy (warfarin potassium in 6 patients, aspirin in 4 patients, both warfarin potassium and aspirin in 4 patients, ticlopidine hydrochloride in 2 patients, and both sarpogrelate hydrochloride and cilostazol in a patient).

The capsule did not reach the cecum in 17 patients (25%) within the examination time. In the patients, however, neither retrograde DBE nor small bowel radiography revealed additional findings. CE related complications were not observed in the patients.

CE findings

CE identified the source of GI bleeding in 36 patients (53%), 16 of whom had ongoing overt bleeding (portal hypertensive enteropathy in 6 patients, angioectasia in 6 patients, metastatic tumor in 2 patients, enteropathy of Schönlein-Henoch purpura in a patient and ileal polyp in a patient). The identified sources of GI bleeding included vascular lesions in 23 patients (angioectasias in 12 patients, portal hypertensive enteropathy in 10 patients, and arteriovenous malformation in a

patient), inflammatory lesions in 6 patients (ileal ulcer in 2 patients, non-steroidal anti-inflammatory drugs enteropathy in 2 patients, stomal ulcer in a patient, and enteropathy of Schönlein-Henoch purpura in a patient), tumors in 6 patients (metastatic tumors in 3 patients, gastrointestinal stromal tumor in 2 patients, and ileal polyp in a patient), and Meckel's diverticulum in a patient.

Factors associated with diagnostic yield of CE

Table 2 compares the diagnostic yield of CE in patients classified by clinical characteristics. Univariate analyses showed the time interval and the ΔHb value were significantly different between patients with positive CE findings and those with negative CE findings. There were also trends towards differences in the lowest Hb value (p=0.08), the prevalence of liver cirrhosis (p=0.07), and the type of bowel preparation (p=0.09) between the two groups. A multivariate analysis revealed ΔHb≥5 g/dl [odds ratio (OR); 18.8, 95% confidence interval (CI); 3.4-152.0] and CE within 7days after the last bleeding [OR; 8.0, 95%CI; 2.2-35.9] to be independent factors associated with the diagnostic yield of CE.

Clinical outcomes after CE

Of the 36 patients with positive CE findings, therapeutic interventions were applied to 28 patients. The intervention included medications (propranolol hydrochloride in 6, prednisolone in 2, and mesalazine in 1) or cessation of medications (aspirin in 2 and loxoprofen in 1) in 12 patients, endoscopic intervention in 9 patients (argon plasma coagulation in 6, hemoclip in 2 and polypectomy in 1), and surgery in 7 patients. No therapeutic intervention was allowed in the remaining 8 patients, because of the difficulty in endoscopic intervention in 3, refusal of treatment in 3, and poor general condition in 2 patients. In those patients, the follow-up data during a period from 1 to 46 months after CE (mean±SD; 15±12 months) were available. Repeated overt GI bleeding occurred in 8 patients during periods ranging from 1-24 months (mean±SD; 5.6±7.5 months); 3 patients had angioectasia, 3 patients had portal hypertensive enteropathy, a patient had Behçet

disease and a patient had metastatic tumor. Therapeutic intervention had been applied to 3 of the eight patients (propranolol hydrochloride, prednisolone, and argon plasma coagulation each in a patient), whereas no therapeutic intervention had been performed in the remaining 5 patients. The cumulative risk of re-bleeding was significantly different between patients with therapy and those without therapy (p=0.0001) (Figure 1).

Thirty-two patients with negative CE findings were followed up during periods ranging from 1-44 months (mean±SD; 20±14 months). In 5 of 6 patients with incomplete CE, retrograde DBE was subsequently performed, which failed to identify small intestinal pathology. The examination was not attempted in the remaining one patient because of his poor general condition. Of the 32 patients, 9 patients re-bled during periods ranging form 1-30 months (mean±SD; 14±12 months) (Figure 1). Repeated examinations identified the source of bleeding in 5 patients (Meckel's diverticulum, esophageal varices, gastric dieulafoy ulcer, gastric angioectasia, and colonic angioectasia, each in a patient). In the remaining 4 patients, however, repeated examination failed to identify the source of GI bleeding.

As for the risk of re-bleeding in negative CE patients, the univariate analyses showed that patients with ΔHb value ≥5 g/dl tended to have a higher rate of re-bleeding than those with less ΔHb value (p=0.07) (Table 3). Although anti-coagulant therapy was more frequent in patients with re-bleeding than in those without re-bleeding, the difference did not reach a statistical significance (p=0.19).

Discussion

Previous literatures have shown that the diagnostic yield of CE in patients with OGIB is favorable when compared to radiological modalities including small bowel radiography [13,14,16], CT scan [15,16], mesenteric angiography [20,21], and scintigraphy [22]. However, clinical characteristics that are relevant to the diagnostic yield of CE have been scarcely investigated to date [10,23-28]. Because there is

heterogeneity in clinical characteristics between overt and occult OGIB, we enrolled only patients with overt OGIB and identified clinical features that are predictive of better diagnostic yield of CE in those patients.

We have shown an obvious decrease in Hb value to be the most significant factor that influenced on the diagnostic yield of CE. This result seems to conform partly to the finding reported by Estévez et al. [28], who indicated the best candidates for CE to be overt OGIB, which required blood transfusion. However, 90% of our subjects in fact had blood transfusion prior to CE. Since the indication for blood transfusion is determined on the basis of patients' physical condition and clinicians' decision, it seems preferable to have an objective definition in the selection of patients for CE. On the other hand, we did not find a close association between the lowest Hb level and the diagnostic yield of CE. This negative result may be a consequence of low baseline Hb values in our subjects, because 23 of 68 patients had underlying liver cirrhosis or chronic renal failure.

Recent investigations have indicated the optimal timing of CE in OGIB to be within the first few days after bleeding with an acceptable maximum time duration being two weeks [4,10,23-25]. In accordance with the previous results, the present study also showed the prompt application of CE to be a factor that contributed to the better diagnostic yield of CE. This result seems reasonable, since a delay in the use of CE can allow the healing of bleeding site [10]. In addition, CE images of active bleeding are most distinctive for the localization of bleeding site especially in overt OGIB. Based on our results, earlier use of CE is mandatory, and the acceptable time duration seems to be within a week for the better diagnostic yield of CE in overt OGIB.

We have recently compared two preparations, magnesium citrate and simethicone, for CE in patients without active bleeding, and found better fluid transparency in patients prepared with the former than in those with the latter [17]. Our prior analysis also showed a positive association between the diagnostic yield

and fluid transparency, thus indicating magnesium citrate to be a preferable bowel preparation for CE [17]. In addition, a recent meta-analysis by Rokkas et al [29] demonstrated a significant improvement of purgative preparation on the diagnostic yield of CE as well as small bowel visualization quality. Thus, bowel preparation by purgatives seems to contribute to the better diagnostic yield of CE. In the present investigation, however, bowel preparation did not affect the diagnostic yield of CE in patients with OGIB. The insignificant result may be explained by the fact that CE identified ongoing overt bleeding in 16 of our 36 patients with positive findings. Because ongoing overt bleeding is presumed to be detected by CE regardless of the image quality, the role of bowel preparation seems to have been underestimated in our OGIB patients. Actually, fresh blood was observed under CE in 54% (7/13) of patients treated by simethicone and 39% (9/23) of patients treated by magnesium citrate, respectively (data not shown).

Among the underlying diseases, liver cirrhosis was suggested to be a possible predictive factor for positive CE findings. Multiple angioectasia or diffuse mucosal changes compatible with portal hypertensive enteropathy [30] were in fact detected in 10 of our 13 cirrhotic patients, 6 of whom had ongoing overt bleeding. Although there may be an argument that the prevalence of portal hypertensive enteropathy in our cirrhotic patients was high, recent articles have reported equivalent values of prevalence, up to 60~70%, of portal hypertensive enteropahty among cirrhotic patients [30-33]. In addition, it has been suggested that severe cirrhosis is not a sine qua non condition for the occurrence of portal hypertensive enteropathy [31]. Although further analyses are necessary to identify mucosal lesions of a higher risk for overt bleeding, portal hypertensive enteropathy should be considered in cirrhotic patients with negative bleeding source under conventional endoscopy.

The clinical impact of CE on the diagnosis and therapeutic intervention has recently been discussed [23-28,34-37]. In the present study, positive CE findings were identified in 36 patients, in 28 of whom therapeutic interventions were

conducted. The re-bleeding rate after therapeutic interventions in the present study (10.7%) was slightly higher than those in the previous reports (6~10%) [35,37]. Such an unfavorable result may be a consequence of the use of anti-coagulation therapy or the types of therapeutic intervention [38]. In fact, recurrent bleeding after CE occurred in 6 of 9 patients with either anti-coagulation therapy or medical intervention. Nevertheless, the cumulative risk of re-bleeding in our patients after therapeutic interventions was significantly lower than those without any interventions. It thus can be assumed that active therapeutic intervention should be considered in overt OGIB, in which responsible intestinal pathology is confirmed under CE.

The management of patients with OGIB without any significant finding under CE remains to be determined [39]. Contrary to the report by Lai et al. [39], the rate of re-bleeding in our CE-negative patients was high (28% vs. 5.6%). Furthermore, patients with an obvious decrease in Hb value had a trend toward a higher rate of re-bleeding after negative CE. Since a recent study by Viazis et al [40] also indicated marked drop in hemoglobin value (≥ 4g/dl) and the change of bleeding pattern were predictive factors of positive findings under second-look CE, patients manifesting massive bleeding at the initial episode may be candidates that require close follow-up even after negative CE. However, we believe that a repeated CE is not the first choice in the case of second bleeding, because five of the 9 patients had the bleeding site outside the small intestine. Since CE is an expensive and time-consuming method, it should be necessary to take clinical symptoms and laboratory data into consideration in the selection of appropriate endoscopic modalities when re-bleeding occurs after negative CE [35].

The current study has several limitations. In the first place, it was a retrospective, single center study. However, clinical data of the patients were obtained by checklist forms, which had been completed at the time of CE. We thus believe that the possible bias in data analyses caused by the retrospective nature

could be minimized. In the second place, the number of subjects was relatively small. However, we focused on the analysis of patients with overt OGIB to exclude heterogeneity in patients' characteristics. Third, a longer observation period seems to be necessary to draw a strong conclusion as to the fate of CE-negative OGIB. However, we believe that our results showed the natural history of overt OGIB during an intermediate period of observation [34-37].

In conclusion, the current study demonstrated that patients with a history of massive bleeding are candidates for evaluation of the bowel by CE, although an early application of CE seems necessary for better diagnostic yield. Even though CE is negative in such patients, careful observation is warranted in consideration of a high risk of re-bleeding.

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