Diagnostic Yield and Clinical Impact of Capsule Endoscopy in Obscure Gastrointestinal Bleeding during Routine Clinical Practice: A Single-Center Experience

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Key Words

Obscure gastrointestinal bleeding • Capsule endoscopy • Clinical impact

Abstract

Objective: This study assessed the diagnostic yield of capsule endoscopy (CE) and its impact on patients with obscure gastrointestinal bleeding (OGIB). **Subjects and Methods:** Between May 2007 and May 2009, 63 patients with OGIB (overt bleeding: 25, and occult blood loss with chronic ferropenic anemia: 38) and normal upper and lower endoscopy were studied by CE. Demographic characteristics, prior diagnostic tests, CE findings, therapeutic interventions, medical treatment and clinical outcomes following CE were evaluated. **Results:** The overall diagnostic yield was 44.44% of patients and included findings of angiectasia in 11 (17.46%) patients, nonsteroidal anti-inflammatory drugs enteropathy in 6 (9.52%) patients, celiac disease in 3 (4.76%) patients, tumors in 2 (3.17%) patients, and a variety of other diagnoses ranging from varices to ulcers (due to congenital afibrinogenemia and amyloidosis). The diagnostic yield was notably higher in overt bleeders (15/25, 60%) compared to occult bleeders (13/38, 34.21%; $p = 0.044$), and in patients with overt

bleeding who had CE within the first 10 days (14/16, 87.5%) after the bleeding episode in comparison to overt bleeders who underwent CE >10 days after the bleeding episode (2/16, 11.1%; $p < 0.0001$). During follow-up (11.8 ± 7 months), CE findings led to specific therapy that resolved the underlying disease or improved the clinical condition in 45 of 63 patients, thus having a positive clinical impact of 71.43%. **Conclusion:** CE has a high diagnostic yield and a positive influence on clinical management in a significant proportion of patients with OGIB. These data further support the role of CE in routine clinical practice.

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Introduction

The introduction of capsule endoscopy (CE) in 2000 was a revolution in the visualization of the small intestine [1]. The noninvasive nature of this procedure, and its safety profile, capability of imaging the entire small bowel and its ability to store images, makes CE the investigative tool of choice for the evaluation of patients with obscure gastrointestinal bleeding (OGIB) [1–4]. Previous studies [5–7] had shown that CE is superior to enteroscopy, small

bowel follow-through and computed tomography in detecting bleeding lesions in the small intestine. Numerous studies have shown that the diagnostic yield of CE ranges from 45 to 75% [4, 8–13]. Moreover, several calculations have been performed to define the impact of CE on the outcome of patients evaluated for OGIB, with impact percentages ranging from as low as 30% to as high as 77.3% [8–16]. However, most of the studies were performed in tertiary referral centers with large experience in CE. Therefore, there is limited experience [14, 17] on the diagnostic yield and clinical impact of CE in patients with OGIB during routine clinical practice.

The aim of this study was to evaluate the diagnostic yield of CE and its effect on the management of patients with OGIB in routine clinical practice.

Subjects and Methods

Between May 2007 and May 2009, a total of 63 patients with OGIB were referred to the Department of Endoscopy and Motility Unit of 'G. Gennimatas' General Hospital, Thessaloniki, Greece, where they underwent CE. The small intestine was examined in all patients as the capsule reached the cecum successfully at the end of its battery life. There were 30 males and 33 females, with a mean age of 54.17 ± 15.4 years (range: 17–86 years) (table 1). Our department is a tertiary referral center in Northern Greece, highly specialized in interventional endoscopy. Obscure gastrointestinal bleeding was defined according to the recently published American Gastroenterological Association (AGA) position statement [18]. Patients were defined as having occult digestive bleeding when they presented with chronic iron deficiency anemia without any clinically evident bleeding episode, no evidence of inadequate iron intake, no excessive gynecological bleeding or evidence of malabsorption. Patients were defined as having overt digestive bleeding when they had a bleeding episode marked by melena, hematochezia or hematemesis. All patients had undergone nondiagnostic upper and lower endoscopy.

Exclusion criteria were: pregnancy, symptoms/signs of bowel obstruction, presence of implanted pacemaker, use of narcotics, and swallowing disorders. Written informed consent was obtained from all patients before CE, after verbal and written explanation about the advantages and possible complications of the examination. Patients remained fasted for 12 h before swallowing the capsule. An oral purge (with 3 liters of polyethylene glycol solution in the evening and 1 liter in the morning) was given before capsule ingestion. A total of 4 liters instead of 2 liters of oral purge was preferred in order to improve the visibility of the small intestines and thus increase the validity and reliability of the test. CE was performed using the Olympus Capsule Endoscopy (Olympus, Tokyo, Japan). Once the system had been set up and the capsule was swallowed, patients were observed for 8 h in the hospital before the system was removed. The recorder was connected to a computer workstation, in which the images were processed and then viewed on a monitor using a specifically designed software package, allowing images to be viewed at various speeds, with facilities for pausing and rewinding. Capsule images were reviewed

by an experienced endoscopist (PK). The reviewer, who was not blinded to the indication of OGIB, interpreted and characterized the lesions at the time of reading in a similar fashion to the CE structured terminology (CEST) previously described and reported in 2005 [19]. A plain abdominal radiograph was performed if the capsule was not expelled 72 h after ingestion. The findings were considered clinically significant if they could be the cause of GI bleeding or iron malabsorption. These included angiectasia, large ulcerations, tumors, varices, multiple erosions and changes suggestive of celiac disease [19]. Findings that were considered not to have bleeding potential included red spots, small isolated erosions, nonbleeding diverticula and nodules without mucosal breaks [19]. All findings on CE were communicated to the referring physicians, and the patients' subsequent management was carried out at the discretion of the referring physician, the patient's decision and our ability to perform specialized endoscopic interventions (single balloon enteroscopy). Clinical and laboratory data collected regarding CE included age, gender, duration of OGIB, type of GI bleeding (obscure-overt vs. obscure-occult), prior endoscopic evaluation, prior radiographic examination (small bowel follow-through, abdominal CT and MRI) or other diagnostic modalities (angiography, ^{99m}Tc -pertechnate scan), hematological and biochemical profile, antigliadin, antiendomysial and antitransglutaminase antibodies and history of nonsteroidal anti-inflammatory drugs (NSAIDs) or antiplatelet use.

Follow-up information was obtained from a review of the inpatient and outpatient charts and by telephone contact with the referring physicians, patients or their families in order to assess the current medical status of the patients and to determine whether medical treatment, or endoscopic or surgical intervention occurred at another hospital. Specific medical therapy included long-acting somatostatin for nonresectable or unsuccessful endoscopically cauterized angiectasia and gluten-free diet. Endoscopic therapy included cauterization of angiectasia. Surgeons performed segmental small bowel resection in patients with a tumor and intractable angiectasia. A positive outcome was determined by the improvement in hemoglobin levels (decreased need or interruption of blood transfusions or iron supplements). The study was approved by the Central Hospital Institutional Review Board.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 13.0, Chicago, Ill., USA). The differences in diagnostic yields of CE between the study subgroups were analyzed with χ^2 and Fisher's exact tests as appropriate. $p < 0.05$ was considered statistically significant.

Results

All the 63 patients swallowed the capsule easily. No adverse events were observed. All except 1 patient excreted the capsule within 72 h (confirmed by a plain abdominal radiograph). The procedure was considered optimal in 61 (96.82%) patients and suboptimal in 2 patients, because the presence of liquid stools did not allow proper visualization especially of the terminal ileum, and the capsule photo rate was lower than normal.

Table 1. Demographic data and clinical characteristics of the study population

	Overt OGIB (n = 25)	Occult OGIB (n = 38)	p ^a
Age, years	56.08 ± 15.35	53.31 ± 15.8	0.495
Sex ratio, M/F	16/9	14/24	0.035
Number of previous diagnostic procedures			
Small bowel series	3	24	<0.001
Computerized tomography	17	29	0.467
Angiography	3	0	0.058
Labeled red blood cell scintigraphy	4	0	0.021
⁹⁹ Tc scintigraphy	2	0	0.154
Medication used			
NSAIDs	6	9	0.977
Antiplatelets (aspirin and/or clopidogrel)	2	8	0.165

^a Level of statistical significance: p < 0.05.

The median time for reviewing the images was 51.4 min (range 42–83 min). Localization of findings was determined by the external localization system supported by the capsule device, the clinician's estimations, and the findings at surgery or enteroscopy, in 14 selected patients. The mean gastric and small-intestinal transit times were 55 ± 73 and 252 ± 64 min, respectively. The presence of fresh blood in the small bowel without a definite source was regarded as a significant but not a diagnostic finding.

Most patients as shown in table 1 had extensive prior diagnostic tests, with all patients having undergone upper and lower GI endoscopy. These tests included CT of the abdomen: 46 (73.01%), small bowel series: 27 (42.86%), angiography: 3 (4.76%), labeled red blood cell scan (n = 4, 6.35%), and ⁹⁹Tc scintigraphy scan: 2 (3.17%) as shown in table 1. Medications suspected to influence the development of OGIB included NSAIDs and antiplatelets in 15 and 10 patients, respectively (table 1). The results of positive CE findings are shown in table 2. The most frequent finding was the presence of angiectasia: 11 (17.46%) (fig. 1), followed by NSAIDs enteropathy: 6 (9.52%), celiac disease: 3 (4.76%) (fig. 2), and tumors: 2 (3.17%). In 2 (3.17%) patients, portal hypertensive gastropathy and a bleeding cecal diverticulum responsible for occult and overt bleeding, respectively, that were missed by upper and lower endoscopy were observed. The abnormalities were located in the jejunum in 12 (19.05%) patients, ileum in 7 (11.11%) patients and jejunum and ileum in 7 (11.11%) patients (table 2). Active small bowel bleeding, without a specific lesion, was seen in 1 patient. In this patient, the diagnosis (bleeding gastrointestinal stromal tumor) was made by

Table 2. CE findings in 63 patients with obscure gastrointestinal bleeding

Findings	Patients
Angiectasia	11
NSAIDs enteropathy	6
Ulcers	3
Multiple erosions	3
Tumors	2
Varices	1
Active bleeding without seeing a bleeding source	1
Portal hypertensive gastropathy	1
Cecal diverticulum	1
Celiac disease findings	3
Congenital afibrinogenemia	1
Ulcers due to amyloidosis	1
Sites of lesions	
Stomach	1
Duodenum	0
Jejunum	12
Ileum	7
Jejunum and ileum	7
Cecum	1

single-balloon enteroscopy and confirmed by laparotomy. The CE findings were considered relevant in 28 patients, resulting in an overall diagnostic yield of 44.44%. For occult bleeders, the diagnostic yield was 34.21% (13/38) and 60% (15/25) in patients with overt bleeding, and the difference was statistically significant (p = 0.044) (table 3). The diagnostic yield was 87.5% (14/16) in patients with overt bleeding who had CE performed during the first 10

Fig. 1. CE showing a large jejunal angiectasia.

Fig. 2. CE showing villous atrophy and scalloped valvulae conniventes.

Table 3. Diagnostic yield of CE in patients with OGIB

	Patients	Positive findings	Negative findings	p ^a
Occult OGIB	38	13	25	0.044
Overt OGIB	25	15	10	
Early CE (<10 days)	16	14	2	<0.0001
Late CE (>10 days)	9	1	8	
Total	63	28	35	

^a Level of statistical significance: p < 0.05.

Table 4. Modifications of treatment according to CE findings

	Patients	Patients with positive CE findings	Positive outcome
Medical treatment			
Discontinuation of NSAIDs	11	5	11
Continuation of NSAIDs plus misoprostol	4	1	4
Iron supplementation	10		4
Change of antiplatelet treatment	10	2	6
Colchicine	1	1	1
Gluten-free diet	3	3	3
Invasive intervention			
Single-balloon enteroscopy plus argon plasma coagulation	7	7	5
Surgical treatment	9	7	9
TIPS placement	2	2	2
Refusal of treatment	6		0
Total	63	28	45

TIPS = Transjugular intrahepatic portosystemic shunt.

days after the bleeding episode, while it was 1/9 (11.1%) for overt bleeders who underwent CE >10 days after a bleeding episode (the result was statistically significant, $p < 0.0001$) (table 3). In 3 (4.76%) patients with iron deficiency anemia and negative anti-gliadin antibodies, endoscopic findings of celiac disease were found on CE, and subsequently confirmed with biopsies from the first and second part of duodenum and positive antiendomysial and anti-transglutaminase antibodies.

Follow-up data were obtained in 59 of the 63 (93.65%) patients in the study. The mean follow-up time was 11.8 ± 7 months (range 1–23). In general, CE findings led to a specific therapy that resolved the underlying disease or improved the clinical condition in 45 of 63 patients, thus having a positive clinical impact of 71.43% (table 4). More specifically, after positive CE results, 16 patients underwent further invasive examinations (7 single-balloon enteroscopy with/without argon plasma coagulation, 7 surgical operations, and 2 TIPS placement). In 15 patients with a history of NSAIDs use, with/without enteropathy, discontinuation of NSAIDs (11 patients) or administration of misoprostol (4 patients) (table 4) resulted in improvement in the hematological profile. Two patients with angiectasia who were receiving antiplatelet treatment (clopidogrel) did not show any improvement of their iron deficiency anemia despite a change in the antiplatelet treatment. The hemoglobin levels normalized with a gluten-free diet in the 3 patients with findings of celiac disease.

Discussion

Both the overt and occult forms of OGIB present a great challenge to the physician. The CE is a major technological revolution for the visualization of the small intestine and is considered the final frontier in diagnostic luminal endoscopy [1, 20]. Its noninvasive nature, safety profile, capability of imaging the entire small bowel and ability to store images makes CE the investigation of choice for the evaluation of small intestinal lesions [20].

The overall yield of CE of 44.44% in our study is within the range of 30–75%, as published previously [8–13]. The yield tended to depend on the definition of positive findings and the type of bleeding investigated. However, the incidence of angiectasia was lower than that reported in other studies (24–60%) [8–17], most probably reflecting the difference between studies performed in routine clinical practice and in prospective studies in tertiary referral centers.

Interestingly, our study suggests that the timing of CE examination with respect to the overt bleeding episode can optimize the diagnostic yield. When the examination was performed early after the overt bleeding (<10 days), a positive diagnosis of 87.5% was achieved. By contrast, when CE was performed greater than 10 days after a bleeding episode, the diagnostic yield fell to 11.1%, which is similar to the findings of Pennazio et al. [8] who showed that if the indication for CE was ongoing obscure-overt bleeding, the diagnostic yield was significantly higher than in patients with a past history of obscure-overt bleeding.

Based on the findings of our study (table 4), we recommend that when there is a history of NSAIDs use in patients with OGIB, it is preferable to suspend the NSAIDs and repeat the hematological tests after several months before proceeding with an expensive examination such as CE (EUR 740 plus the additional cost of the CE reviewer).

In 3 patients with occult OGIB and negative antigliadin antibodies, CE showed findings suggestive of celiac disease, emphasizing the low sensitivity of antigliadin antibodies in comparison to antiendomysial and antitransglutaminase antibodies. A good correlation between CE findings and history of celiac disease has been reported in a few studies [21, 22]. Moreover, in 2 patients with OGIB, CE revealed the lesion to be located in the cecum and stomach, respectively. Therefore, careful repeat upper and lower GI endoscopy, as suggested by other investigators [8–10], should be performed before an evaluation of the small intestine with CE is carried out. Moreover, the video images of the upper and lower GI tract should be carefully viewed by endoscopists with experience in GI bleeding.

In an OGIB study, a positive outcome should be either stoppage of bleeding or resolution of anemia. In the present study, CE had an important clinical impact in 45 (71.43%) patients, as the findings obtained led to specific therapy (medical or interventional) that either resolved the disease or improved the symptoms. However, our results may be biased because the referring physicians may have been inclined to inform us only about the positive clinical results. Large studies are needed to assess the influence of CE on clinical outcomes in routine clinical practice.

Conclusion

Our findings show that CE has an important diagnostic role in OGIB in routine clinical practice; however, further studies on the clinical impact of CE are clearly needed.

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