ORIGINAL ARTICLE

Diagnostic yield and clinical management after capsule endoscopy in daily clinical practice: A single-center experience

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Abstract

Background: Capsule endoscopy is an effective method of examining the small bowel in patients with obscure gastrointestinal bleeding, suspected inflammatory mucosal diseases and neoplasms. We herein evaluate the diagnostic yield of capsule endoscopy and its effect on clinical management in daily clinical practice.

Patients and Methods: One hundred and one capsule endoscopies performed at the Department of Endoscopy and Motility Unit of G. Gennimatas General Hospital of Thessaloniki from May 2007 to February 2009 were retrospectively reviewed. Clinical management following capsule endoscopy findings was evaluated. The most frequent indication was obscure gastrointestinal bleeding (n=56, overt=20).

Results: The overall diagnostic yield was 47.5%**.** The diagnostic yield was 88.9% in patients with overt bleeding who underwent early capsule endoscopy (within 5 days), versus 36.4% in patients who underwent late capsule endoscopy (p=0.028). Moreover, it reached 81.8% in patients with abdominal pain, with/without diarrhea and abnormal biological markers, versus 8.3% in patients with normal biological markers (p<0.0001). Capsule endoscopy was diagnostic in all patients with symptomatic celiac disease. Adenomas were found in 9 of 14 familial adenomatous polyposis patients. Capsule retention (>72 hours) occurred in two patients. Forty-three of 48 (89.6%) patients with positive capsule endoscopy findings that received intervention or medical treatment had positive clinical outcomes.

Conclusions: Capsule endoscopy has an important diagnostic role and contribution in the clinical management during routine clinical practice; however, it remains to be determined which patients are more likely to benefit from this expensive examination. Hippokratia 2010; 14 (4): 271-276

Key words: capsule endoscopy; small bowel; diagnosis; treatment

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Capsule endoscopy (CE) has opened up new horizons for the diagnosis of small-bowel disease; it is a novel technology that facilitates highly effective and noninvasive imaging of the entire small bowel in patients with obscure gastrointestinal bleeding (OGIB), after negative upper and lower gastrointestinal (GI) endoscopy, suspected small bowel Crohn's disease, polyposis syndromes, small bowel tumor detection, unexplained abdominal pain and undiagnosed diarrhea, and has an increasingly important role in the management of celiac disease[1-3] . Several controlled studies in tertiary referral centres have shown that CE has an overall diagnostic yield superior to that of enteroscopy, or radiologic imaging and has a positive impact on the clinical management of the patients who undergo this examination[4-9]. However, as routine clinical practice is somewhat different from controlled trial conditions and the experience on enteroscopy is limited, very few studies have investigated the role of CE in daily practice[10-14]. Moreover, because CE is an expensive modality, more information is needed to determine which patients are more likely to benefit from the method.

Our study evaluates the diagnostic yield of CE, overall and for each indication and its effect on the clinical management in daily practice

Methods

Retrospective chart review was performed on 101 consecutive patients who had undergone CEs at "G. Gennimatas" General Hospital from May 2007 to February 2009. The study was approved by the Hospital's Ethics Committee. Written informed consent was obtained from all patients before CE, after verbal and written explanations about advantages and possible complications of the examination.

Contraindications for CE were the following: pregnancy, children under 10, severe motility abnormalities, or swallowing disorders, known or suspected gastrointestinal obstruction/pseudo-obstruction, strictures of any aetiology, or fistulas, use of narcotics and presence

of implanted pacemaker (although recent data showed that CE could be safely performed in patients with pacemakers after multidisciplinary consultation). All patients received small bowel preparation that consisted of a low-residue diet for 24 hours, fluid intake and ingestion of 4lt polyethylene glucol-based electrolyte solution, 12 hours before the examination. The CE was carried out by using the Olympus Capsule Endoscopy System (Tokyo, Japan). Recording of the CE was disconnected after 8 hours and the capsule images were interpreted by the same endoscopist (PK).

Demographic characteristics, indications, non-steroid anti-inflammatory drugs (NSAIDs) or anticoagulant use, laboratory data, prior diagnostic examinations, capsule findings, interventions, and clinical outcomes following CE were evaluated. Prior diagnostic testing included hematological and biochemical profile, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antigliandin, anti-endomycial and anti-transglutaminase antibodies, upper and lower GI endoscopies, abdominal films, abdominal CT and MRI scans, small bowel follow-throughs, angiographies, red blood cell or Tc scans and surgical interventions.

The indications for CE included overt GI bleeding, occult GI bleeding or unexplained iron deficiency anemia, abdominal pain with/without diarrhoea and abnormal biological markers [increased ESR and CRP and low hemoglobin (Hb) levels], persistent abdominal pain with/without diarrhoea and normal biological markers, suspected Crohn's disease, evaluation of small intestine mucosa in patients with known celiac disease and persisting symptoms and surveillance of patients with familial adenomatous polyposis (FAP).

OGIB was defined as a suspected bleeding from the GI tract without an obvious etiology after a series of diagnostic examinations. Obscure-occult bleeding was defined as recurrent or persistent iron deficiency anemia with positive faecal occult blood test. Obscure-overt bleeding was defined as visible red or altered blood in faeces and drop in Hb below lower limit of the normal range. As clinically significant findings to induce GI bleeding were considered angiodysplasias, ulcerations, tumours, varices and multiple erosions. Those of uncertain relevance including red spots, small isolated erosions, non-bleeding diverticula and nodules without mucosal breaks were considered to not have bleeding potential.

CE retention was defined as a capsule remaining in the digestive system for a minimum of 72 hours or requiring directed therapy to aid passage.

Each patient's file was reviewed and both patient and primary care physician were contacted to assess the current medical status and determine whether a medical treatment or endoscopic or surgical intervention occurred at another hospital. Specific medical therapy comprised anti-inflammatory treatment for Crohn's disease, gluten-free diet or diet with medium chain triglycerides for patients with intestinal lymphangiectasia and treatment for functional abdominal pain. Endoscopic therapy included cauterization of vascular lesions via enteroscope. Biopsies and polypectomies were performed in patients with FAP for staging of duodenal disease according to the Spigelman classification[15]. Surgeons performed segmental small bowel resection for tumour and intractable angiectasias. Positive outcome was based on improvement of symptoms (abdominal pain, diarrhoea) and Hb (decreased need or interruption of blood transfusions or ferrum supplements).

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 13.0, Chicago, IL, USA). The differences in diagnostic yields of CE between the subgroups of the study were analyzed with Chi-square and Fisher's exact tests as appropriate. Any p-value less than 0.05 showed the presence of statistically significant difference.

Results

A total of 101 CE examinations were performed (44 men, 57 women, mean age 51.48±16 years) from May 2007 to February 2009. Most patients had extensive prior diagnostic tests, and all patients underwent upper and lower endoscopies. Moreover, evaluation included CT of the abdomen (34/101), small bowel follow-through (47/101), angiography (3/101), red blood cell scan (7/101) and Meckel's scan (1/101). Indications for CE are demonstrated in Table 1. The most frequent indication was OGIB (n=56), subdivided into overt (n=20) and occult (n=36). Other indications included FAP (n=14), abdominal pain with/without diarrhoea and normal biological markers (n=12), abdominal pain with/without diarrhoea and abnormal biological markers (n=11), celiac disease not responding to gluten-free diet (n=5), evaluation of recurrence of previously operated neuroendocrine neoplasm of small intestine (n=2) and fever of unknown origin (n=1).

A complete examination of the small bowel was achieved in all but 2 patients with a mean transit time of 4 hours and 28 minutes. The overall diagnostic yield was 47.5% (48/101) (Table 1). The CE findings are summarized in Table 2. In OGIB the most frequent findings were angiodysplasias that comprised 7.92% (n=8) of cases, followed by ulcers due to NSAIDs use (n=4, 3.96%). The diagnostic yield was higher [88.9% (8/9)] in patients with overt OGIB who had CE during the first 5 days after the bleeding episode (early CE) than in overt bleeders who underwent late (>5 days after bleeding episode) CE (36.4%, p=0.028) (Table 1). Moreover, the diagnostic yield was higher in patients with abdominal pain with/without diarrhea and abnormal biological markers 81.8% (9/11) than in patients with abdominal pain with/without diarrhea and normal biological markers 8.3% (1/12) (p<0.0001) (Table 1). CE was diagnostic 100% (5/5) in patients with symp-

Table 1: Indications for capsule endoscopy and its diagnostic yield.

Indications	No of patients (%)	No of patients with diagnostic CE (diagnostic yield-%)	Significance (P-value)
Obscure GI bleeding	56 (55.44)		
Overt	20 (19.80)	12 (11.88)	0.031[b]
CE performed during 5 days following bleeding episode	9 (8.91)	8(7.92)[a]	
CE performed after 5 days following bleeding episode	11(10.89)	4(3.96)	
Occult	36 (35.64)	11 (10.89)	
Abdominal pain with/without diarrhea and normal biological markers	12 (11.88)	1 (0.99)	<0.0001
Abdominal pain with/without diarrhea and abnormal biological markers	11 (10.89)	10 (9.90)	
Evaluation of symptomatic known celiac disease	5 (4.95)	5 (4.95)	
Fever of unknown origin with increased ESR and CRP	1 (0.99)	-	
Prior resected neuroendocrine neoplasms	2 (1.98)	-	
Familial adenomatous polyposis	14 (13.86)	9 (8.91)	
Total	101 (100)	48 (47.5)	

[a] shows the presence of statistical significance between CE performed during and after 5 days following overt bleeding episode (p=0.028)

[b] shows the presence of statistical difference of diagnostic yield of CE between overt and occult GI bleeding

p: level of statistical significance 0.05

GI: gastrointestinal

CE:capsule endoscopy

tomatic celiac disease. Moreover, 3 young patients with OGIB and negative antigliandin antibodies were diagnosed as suffering from celiac disease, which was confirmed with biopsy and positive antiendomysial and anti-transglutaminase antibodies.

Although features of mucosal atrophy, mosaic pattern scalloping and stacking of folds appearance were identified in symptomatic patients with celiac disease, none had evidence of complications, ulcerative jejunoileitis or lymphoma, suggesting poor compliance to gluten-free diet. Adenomas were found in 9 (64.3%) and jejunal and ileal adenomas in 7 (50%) and 8 (57.1%) of 14 patients with FAP. The Spigelman stage of duodenal polyposis was associated with the presence of jejunal and ileal adenomas. Negative yields of CE were observed in two patients with possible recurrence of previously resected neuroendocrine tumours of small intestine and in one patient with fever of unknown origin.

Capsule retention occurred in two patients (1.98%), caused by neoplasms, and required surgical intervention with exploratory laparotomy for tumour resection and removal of capsule. Abdominal CT and small bowel follow-through were performed in both patients prior to CE, without revealing any abnormal finding.

Table 3 summarizes the interventions and clinical management of patients with positive findings at CE. Based on the applied interventions, positive clinical outcomes were reported in 43 of 48 (89.6%) patients with positive CE findings.

Discussion

CE is a new technology that has been shown to have superior diagnostic yield compared with other methods of evaluating the small bowel. Since its first clinical use in 2000[16], CE has developed from the exotic to a clinical reality, extending our diagnostic capability in the small intestine, which is of great utility in planning the most appropriate therapeutic strategy.

The present retrospective study assessed the diagnostic yield and mainly the impact of an expensive modality as CE on clinical management and patients' outcome in routine clinical practice and not during prospective controlled studies in tertiary referral centres. In our series of 101 cases, an overall diagnostic yield of 47.5% (48/101) was found and is comparable to the previous studies in the literature[10-14], except the study of Toy et al[17]. In their study of 145 patients the overall diagnostic yield was 69% and was related with stricter criteria to perform the examination. OGIB was the first and remains the most important indication of CE. Several prospective studies have documented the efficacy of CE in identifying the source of previously unexplained blood loss in the small intestine[18-21].

In the present study with 56 cases of OGIB, an overall diagnostic yield of 41.1% (23/56) was found, with intestinal ulcerations due to NSAIDs use or Crohn's disease occurring in 19.6% (11/56) and angiodysplasias in 14.3% (8/56) of all cases. Interestingly, our study demonstrates that timing of CE with respect to the overt bleeding episode can optimize the diagnostic yield. When the ex-

Table 2: Endoscopic findings of CE in relation to indications.

Indications	Endoscopic findings	No of patients (%)
Obscure bleeding	Angiodysplasias	8 (7.92)
	Ileal ulcers (NSAIDs use)	4 (3.96)
	Ileal ulcers (congenital afibrinogenemia)	1 (0.99)
	Celiac disease	3 (2.97)
	Mass lesion	2 (1.98)
	Cecal diverticulum	1 (0.99)
	Portal gastrophathy	1 (0.99)
	Jejunal varices	1 (0.99)
	Radiation enteritis	1 (0.99)
Abdominal pain with/without diarrhea	Ileal ulcers (NSAIDs use)	1 (0.99)
and normal biological markers		
Abdominal pain with/without diarrhea	Idiopathic intestinal lymphangiectasia	2 (1.98)
and abnormal biological markers	Ileal ulcers (Crohn's disease)	5 (4.95)
	Ileal ulcers (NSAIDs use)	1 (0.99)
	Mucosal edema (SMVT)	1 (0.99)
	Capsule retention	1(0.99)
Celiac disease	Mucosal atrophy, mosaic pattern, scalloping	5 (4.95)
FAP	Polyps in small intestine	9 (8.91)
	(duodenum/jejunum/ileum)	(9/7/8)

FAP: familial adenomatous polyposis

SMVT: superior mesenteric vein thrombosis

amination was performed early after overt bleeding (≤5 days), the diagnosis was achieved in 88.9% of patients (8/9). On the contrary, when CE was performed after 5 days from the bleeding episode the diagnostic yield significantly fell to 36.4% (4/11) (p=0.028). Our data about time referral for CE in OGIB are in accordance with Pennazio et al findings[21], who showed that if the reason for the referral was ongoing obscure–overt bleeding, the diagnostic yield of CE was significantly higher than in the case of previously-overt bleeding, or in the case of obscure-occult bleeding; a reverse relationship observed between findings and time after last bleeding episode. The longer the time from last bleed, the lower the diagnostic yield. In our study the diagnostic yield in obscure-occult bleeding was 36% (11/36), lower than obscure-overt bleeding 60% (12/20) (p=0.031). Of the patients with obscure GI bleeding and positive CE findings, 78.3% (18/23) had a surgical or endoscopic intervention, discontinuated the NSAIDs use or received anti-inflammatory treatment for Crohn's disease and had a positive clinical outcome (Table 3). Taking into account the high cost of CE (740 Euros plus additional payment of the reviewer of the examination), we believe that in patients with OGIB and NSAIDs use, it is preferable to discontinue the NSAIDs treatment and repeat the laboratory data before proceeding to CE. Moreover, in two patients with OGIB, CE revealed the lesions to be located in the stomach and cecum, respectively. Therefore, careful repeat upper and lower GI endoscopy, as supported by other investigators[1,17-19] should be performed before evaluation of the small intestine with CE, and the video images of upper and lower GI tract should be carefully reviewed by endoscopists with experience in GI bleeding. Nevertheless, comparing the diagnostic yield of CE in OGIB to other diagnostic modalities, CE appears to be superior to other techniques in diagnosing the source of bleeding; the yield for CE is 63% and 67% compared with 28% for push enteroscopy and 8% for barium study[22].

Use of CE for the evaluation of abdominal pain is debated[23]. In particular, CE appears to be unhelpful in the evaluation of patients with abdominal pain, with/without diarrhoea and normal biological markers**;** in the present series one patient (8.5%, 1/12) had positive findings. In contrast CE revealed positive findings in 91% (Table 1) patients with/without abdominal pain, but with abnormal biological (p<0.0001). Therefore, in accordance to other studies[24], CE is not suggested as diagnostic modality in the investigation of patients with functional abdominal pain.

Table 3. Patients' interventions and outcomes based on findings of capsule endoscopy.

Type of lesion	No of patients	Intervention	Positive Outcome
Jejunal/ileal angiodysplasias	5	cauterization	yes
Jejunal/ileal angiodysplasias	3	no	no
Jejunal/ileal ulcers due to NSAIDs use	6	discontinuation of NSAIDs	yes
Ileal ulcers due to Crohn's disease	5	anti-inflammatory drugs	yes
Ileal ulcers in congenital afibrigenemia	1	operation due to perforation	yes
Duodenal/jejunal/ileal celiac disease	7	gluten-free diet	yes
Duodenal/jejunal/ileal celiac disease	1	no compliance to gluten-free diet	no
FAP (duodenum/jejunum/ileum)	9 (9/7/8)	endoscopic resection	yes
Idiopathic intestinal lymphangiectasia	2	specific diet	yes
Mass lesion	2	operation	yes
Cecal diverticulum	1	operation	yes
Portal gastropathy	1	no	no
Radiation enteritis	1	no	no
Jejunal varices	1	TIPS	yes
Capsule retention due to multifocal ileal carcinoids	1	operation	yes
Capsule retention due to ileal wall infiltration by genital cancer	1	operation	yes
Mucosal edema due to superior mesenteric vein thrombosis	1	anticoagulants	yes

FAP: familial adenomatous polyposis

TIPS: transjugular intrahepatic portosystemic shunt

In 5 patients with known celiac disease who were complaining for persisted symptoms despite gluten-free diet, CE demonstrated findings of active celiac disease and no complications, suggesting poor compliance to gluten-free diet. Moreover, in three patients with occult OGIB and negative antigliandin antibodies, CE showed celiac disease, emphasizing the low sensitivity and specificity of antigliandin antibodies in relation to anti-endomysial and anti-transglutaminase antibodies. A good correlation of CE findings with histology has been reported in a small series[25,26]. CE can also be able to demonstrate conditions such as adenocarcinoma, lymphoma or ulcerative jejunoileitis, which can complicate the celiac disease course[23]**.** Of note, searching for celiac disease particularly in older adults, duodenal mucosa may be normal in appearance on CE in about 2/3 of patients with iron deficiency anemia, but classic abnormalities of celiac disease are present distally[27]. Viewing aforementioned data, we believe that underwater high-resolution endoscopy, which is a simple and very sensitive method[28,29], provides an optimized view of the villi, with the advantages of biopsies and should be preceded CE in patients suspected for active celiac disease. This underwater view is present most of the time during CE making it possible to diagnose villous atrophy. Notably, when an atrophic pattern is detected by CE, the patient has a high probability of having celiac disease[30]**.**

CE detected adenomas in 9/14 (64.3%) of patients with FAP, and Spigelman stage of duodenal polyposis was associated with the presence of jejunal and ileal adenomas. Importantly, the findings of CE had no impact on the further clinical management of all FAP patients. The resected adenomas were in the second part of duodenum and had been diagnosed with conventional endoscopy. In this respect, although CE is accurate in the detection of polyps it is not reliable for sizing and determining localization of polyps[9,31]. In particular, the duodenum appears to be a potential blind point of CE because the capsule passes quickly with tumble leading to inadequate examination; in FAP patients CE underestimated the total number of polyps and did not reliably detect larger polyps in that portion[32]. In this study CE altered patients management in 89.6% of cases with positive CE findings. This was mostly in the form of therapeutic enteroscopy in patients with OGIB. In addition, in the inflammatory bowel disease, immunosuppressive therapy was initiated in the majority of patients as a result of the CE findings. In patients with NSAIDs enteropathy, discontinuation of NSAIDs use resulted in improvement of their hematological profile. A small proportion of patients also underwent surgery for resection of vascular abnormalities or tumors (Table 3).

In this study, capsule retention occurred in two patients (1.98%) caused by neoplasms. As in our series, the reported overall frequency of capsule retention is usually 1%-2%[33,34]. Apart from small bowel tumors, retention risk is also high in patients with known Crohn's disease, radiation enteritis and NSAID strictures. Because retention is defined as the indefinite presence of a capsule in the small bowel, this is different from slow transit, incom-

plete transit or regional transit abnormalities. In latter cases, the capsule stays in the ileum but ultimately passes *via* peristalsis. It is advisable to perform abdominal radiographs within two weeks to identify capsule retention if the capsule did not enter the colon. Therapeutic intervention can be instituted anytime unless the patient becomes symptomatic; as in our cases, retention can cause symptoms of small bowel obstruction leading to need for endoscopic or surgical removal of the capsule[35].

In conclusion, small bowel CE has an important diagnostic role and contributes in patients' clinical management during daily clinical practice; however, more information is needed to determine which patients are more likely to benefit from this expensive examination.

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