

ORIGINAL PAPERS

The Role of Capsule Endoscopy in Obscure GI Bleeding: Experience of a Tertiary Center in Romania

Lucian Negreanu¹, Ana Filimon¹, Ana Stemate¹, Theodor Voiosu², Bogdan Mateescu²

Abstract

Obscure gastrointestinal bleeding OGIB represents about 5% of the digestive hemorrhages. The introduction of the endoscopic videocapsule in the current clinical practice caused a major change in the diagnostic and treatment paradigm of these patients. **Aim:** In Romania capsule endoscopy is not reimbursed and although available in many centers is not an investigation readily accessible in all patients. Also, device assisted enteroscopy is performed in few centers only. We present a series of forty patients with obscure GI bleeding and the role of capsule endoscopy in their diagnosis, treatment decision and follow up. **Methods:** This is a retrospective, single center study. Examinations were performed using second and third generation small bowel capsules SB2/SB3 and the second generation of colon capsule PillCam Colon 2. The choice of capsule was arbitrary decided by their availability in the unit at the moment of the examination. **Results:** The source of bleeding was identified in 33 patients (83% of the cases). The most frequent lesions were angiomas in 14 patients, small bowel Crohn's disease in 9 cases and NSAID's enteropathy in 4 cases. Endoscopic therapeutic procedures were used in five patients, three undergone surgery, medical treatment was initiated in 11 patients, gluten free diet in one, and discontinuation of NSAID's in three. **Conclusion:** Capsule endoscopy was useful in the diagnostic and the therapeutic decision in the majority of cases. Angiomas, ileal Crohn's disease and NSAID enteropathy were the main causes for obscure bleeding. Due to capsule endoscopy examination costs, a careful and complete exploration of the patients with routine ileoscopy before capsule is advisable.

Keywords: obscure bleeding, Crohn's disease, angioma, capsule endoscopy

Rezumat

Videocapsula endoscopică are un rol primordial în diagnosticul hemoragiilor digestive de cauză obscură. Investigația se face în tandem cu o enteroscopie (simplu sau dublu balon sau spirală) care permite biopsii sau gesturi terapeutice. Accesul la investigarea cu videocapsulă sau la enteroscopie este limitat în România în câteva centre și terapia pacienților presupune un efort multidisciplinar și uneori multicentric. Este prezentată experiența din două centre terțiare, retrospectiv, cu un număr important de pacienți care au avut leziuni de boală Crohn. Această particularitate este posibil explicată de specializarea în boli inflamatorii a celor două centre.

Cuvinte cheie: hemoragie obscură, videocapsulă, enteroscopie, boala Crohn

¹ Second Department of Internal Medicine and Gastroenterology, Emergency University Hospital, Bucharest, Romania

² Department of Gastroenterology, Colentina Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author:

Lucian Negreanu

Second Department of Internal Medicine, Emergency University Hospital, 169 Splaiul Independenței, 5th District, Bucharest, Romania

INTRODUCTION

Obscure gastrointestinal bleeding OGIB represents about 5% of those patients with gastrointestinal bleeding of any type. It is defined as persistent or recurrent bleeding of unknown origin (i. e., recurrent or persistent iron-deficiency anemia, positive fecal occult blood test, or visible bleeding) with a negative upper and/or lower gastrointestinal endoscopy¹.

In the majority of cases, OGIB originates in the small bowel and can result from a series of conditions, including vascular lesions, tumors, drug induced and immune mediated lesions. It is classified as “overt” when there are manifestations of bleeding such as hematochezia or melena, and as “occult” when fecal occult blood tests are positive or iron deficiency anemia is presumed to be caused by gastrointestinal blood loss^{2,3}.

Over the last decade with the introduction in clinical practice of new diagnostic and therapeutic procedures (i.e. Capsule Endoscopy, Computed Tomographic Enterography, Magnetic Resonance Enterography, and Device Assisted Enteroscopy) the diagnostic and treatment paradigm of patients with obscure gastrointestinal bleed has completely changed⁴.

Capsule endoscopy and device assisted enteroscopy are regarded as complementary methods in the management of OGIB. Their availability is increasing and they now became an integral part of the diagnostic and therapeutic recommendations for OGIB in most parts of the world.

AIM

To present a series of forty patients with obscure GI bleeding and the role of capsule endoscopy in their diagnosis treatment and follow up.

Because in Romania capsule endoscopy is not reimbursed, although available in many centers is not an investigation readily accessible in all patients. Device assisted enteroscopy is performed in only few centers.

PATIENTS AND METHODS

This is a retrospective, single center study.

Starting February 2011 a total of 150 capsule examinations were performed in our unit. Forty patients, 20 women and 20 men, with a mean age of 51.3 years (range 22 – 89) were investigated for obscure gastrointestinal bleeding (Table 1).

The patients were initially investigated in our center or referred from other gastroenterology centers, were they all had upper endoscopies and colonoscopies for the exclusion of other causes of bleeding. After capsule

Table 1. Patients characteristics

Name	Age	Sex	Capsule type	Results
1. VS	56	M	SB2	Angiomas
2. VFS	66	M	SB3	Gastric ulcer
3. VM	25	M	SB3	Crohn 's disease
4. VD	72	M	SB2	Angiomas
5. IV	45	M	SB3	Angiomas
6. HM	76	F	SB3	Angiomas
7. GOL	22	F	SB2	Normal
8. FA	78	F	PC2	Angiomas
9. DC	34	F	SB3	Crohn 's disease stenosis with capsule impaction
10. CD	43	F	PC2	NSAID's ulcartions
11. FD	23	F	PC2	Crohn's disease
12. IB	75	F	PC2	GIST
13. BA		M	SB3	Angiomas
14. CI	72	M	SB3-defect PC2 as rescue	Angiomas
15. CL	34	F	SB3	Normal
16. DA	62	M	SB3	Angiomas
17. SR	34	F	PC2	Angiomas
18. SC	29	F	PC2	Normal
19. SA	74	F	PC2	Angiomas
20. SG	46	F	PC2	Crohn's disease
21. SA	59	M	PC2	Angiomas
22. RA	28	F	SB3	NSAID's ulcerations
23. SI	78	M	PC2	Normal
24. PM	27	M	SB3	Crohn's disease
25. PM	57	M	SB3	Angiomas
26. OF	66	M	PC2	Active bleeding from jejunal ulcer
27. MR	33	F	SB3	Angiomas
28. TS	38	M	PC2	Colon cancer
29. NE	40	F	PC2	Crohn's disease
30. SM	55	F	SB3	Celiac disease
31. TI	45	M	SB3	Crohn's disease
32. OG	89	M	PC2	NSAID's ulcerations
33. MV	62	F	SB3	NSAID's ulcerations
34. DC	35	M	SB3	Peutz Jeghers polyposis
35. BD	76	M	PC2	Normal
36. DA	27	F	PC2	Normal
37. ZC	66	M	SB3	Angiomas
38. BL	41	F	PC2	Normal
39. ZF	62	F	SB3	Crohn's disease
40. MC	31	M	SB3	Crohn's disease

endoscopy we referred the patients needing enteroscopy in another unit, since we lack the equipment.

ETHICAL CONSIDERATIONS

Capsule endoscopy examination protocol, informed consent and examination agreement were approved by the ethics committee of the University Hospital of

Bucharest in 2011 and renewed in 2013. All patients signed an informed consent for the investigation.

PROCEDURE

All types of capsules from Given Imaging (Yokneam Israel) were used in this study: second and third generation small bowel capsule and the second generation of colon capsule PillCam Colon 2. The choice of capsule was arbitrary dictated by their availability in the unit at the moment of the examination. We used the DR3 recorder.

Initially the Rapid reader 7 software was used in this study. Starting 2012 we used a Rapid 8 prototype and from December 2013 the commercial version of Rapid 8.

The preparation consisted in a low-residue diet starting 48 hours before investigation. One liter of polyethylene glycol (PEG) Fortrans® (Macrogol 4000, Ibsen, France) was administered in the evening before capsule ingestion. Capsule ingestion was performed between 9-10 a.m.



Figure 1. Polip ulcerat - sd Peutz Jeghers.



Figure 4. Angiodisplazie.



Figure 2. Ulcer ileal cu sangerare activa.



Figure 5. Sangerare activa exulceratie Dieulafoy.



Figure 3. Angiodisplazie.

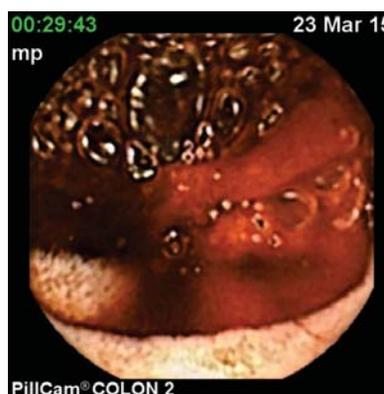


Figure 6. Sangerarea activa din malformatie arteriovenoasa.

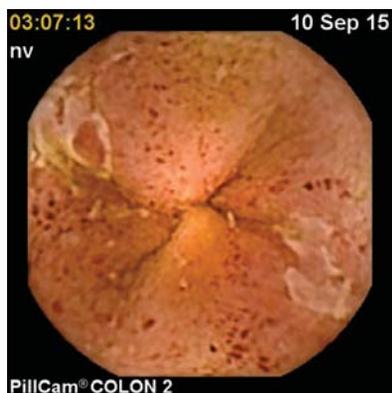


Figure 7. Ileita terminala.



Figure 8. Ileita terminala ulcere adanci hemoragice.

All the investigators reading the capsule videos had extensive experience in digestive endoscopy and with capsule endoscopy.

RESULTS

Forty patients were examined for OGIB, with a mean age of 51.3 years, extreme ages 22-89.

Forty one capsules were used in the study: 20 SB3 capsules, three SB2 capsules and 18 PC2 capsules. A PC2 capsule was used as a rescue after blockage of transmission from a SB3 capsule. In one patient an SB3 examination revealed multiple angiomas after a first negative SB2 in another unit.

Seven patients had a normal examination. Fourteen patients had small bowel angiomas, nine patients had small bowel lesions suggesting Crohn's disease, four had small bowel ulcerations which were linked to chronic NSAID's use, one had celiac disease, one had a gastric ulcer, one had a jejunal GIST, one had an active bleeding from a jejunal ulcer and one had Peutz Jeghers polyps. In one young male patient that had two previous "complete" colonoscopies, addressed for anemia and where capsule examination was performed using a Pillcam colon² capsule, a cecal ulcerated tumor was visualized.

Follow up, clinical decision and treatment

A clinical decision and treatment based on capsule findings was realized in 22 of the patients.

Seven enteroscopies were performed in five patients, four with multiple angiomas one with the Peutz jeghers syndrome. Since in our center enteroscopy is not available we referred the patients to other centers.

One patient had a failed single balloon enteroscopy followed by a spiral enteroscopy which allowed argon plasma coagulation of seven angiomas.

The Peutz Jeghers patient had two single balloon enteroscopy with polypectomy of multiple polyps.

In two patients with multiple angiomas a single balloon enteroscopy with APC and a double balloon enteroscopy with APC were performed in two different centers.

In a patient the single balloon enteroscopy which also failed to reach his vascular lesions and then a surgical ileal resection. He has currently a good clinical status without recurrent anemia.

Another two patients were treated surgically: the jejunal GIST patient undergone resection with excellent results and a right hemicolectomy was performed for the colon cancer patient.

A gluten free diet was prescribed for the celiac disease patient after bioptic and serologic confirmation.

The patient with a gastric ulcer underwent a second endoscopy that confirmed the lesion. One morbid obesity patient had an active severe bleeding of a jejunal ulcer and he died before surgery due to cardiovascular complications. Both patients received proton pump inhibitors.

Discontinuation of NSAID's was possible in three out of four patients.

All the nine patients with Crohn's disease are currently treated and in clinical remission.

Technical failures

We had two technical difficulties: one due to a recorder dysfunction which required replacement with another recorder and one SB3 capsule malfunction which was replaced with a PC2 capsule.

Complications

We had an asymptomatic capsule retention due to a Crohn's disease stenosis. She was completely asymptomatic without any occlusive symptoms or abdominal pain and was addressed for iron deficiency anemia and she had normal upper endoscopy and colonoscopy. After failure to excrete the capsule, the retention was

confirmed by plane radiography two weeks after the examination. The patient refused surgery and started medical treatment with budesonide with capsule elimination after three months.

DISCUSSION

In our study we find lesions that could explain the OGIB in 33 patients (82.5% of cases). In a meta-analysis including 227 studies and including 22840 CE procedures, the diagnostic yield for OGIB was 61%⁵. In another study published subsequently including 911 patients with OGIB, 56% patients had positive finding at CE⁶. Our increased success rate can be explained by the highly selected population (based on global limited access to capsule due to economic reasons) and the small number of patients presented.

As a result of the findings, a specific intervention was made in 66% of patients who had a positive capsule finding. Endoscopic therapeutic procedures were used in five patients, three undergone surgery, medical treatment was initiated in 11 patients, gluten free diet in one, and discontinuation of NSAID's in three patients. This is comparable with other studies⁷.

Negative CE in the setting of OGIB, has been shown to predict the outcome. In fact, the risk of re-bleeding rate after negative CE is very low^{8,9}, and these patients could be managed by a conservative approach. In our group of seven patients with negative capsule findings only three patients (two women, one man) still have mild recurrent iron deficiency anemia.

The particularity of our series is the important number of patients (9/40) who had lesions that were suggestive for Crohn's disease. Currently capsule endoscopy is considered a valuable tool to diagnose or exclude CD. A high index of clinical suspicion (digestive symptoms plus either extraintestinal manifestations, inflammatory markers or abnormal imaging studies) together with suggestive capsule findings is necessary to increase the diagnostic yield¹⁰.

After careful examination associated symptoms such as diarrhea and weight loss were found in all patients. Also inflammation markers and fecal calprotectin were elevated in all nine patients.

The classical indications of VCE in Crohn's disease are indeterminate colitis, Crohn's disease of the small bowel excluding last ileal loop, clinical/endoscopic discrepancy, post surgery and mucosal healing monitoring. Failure/refuse of colonoscopy is an indication for colon capsule in selected patients¹¹.

Ileal involvement was the rule in our patients but unfortunately although a complete colonoscopy was performed in all cases, in none of them the last ileal

loop was visualised. After capsule examination results, Crohn's disease was confirmed by colonoscopy with catheterization of the terminal ileum and biopsies in five cases; for the other four patients the therapeutic decision was based on clinical setting, capsule findings and inflammatory markers. We excluded lesions due to the use of non-steroidal anti-inflammatory drugs (NSAIDs), vasculitis, lymphoma, ischemic or infectious lesions. At the moment all the nine patients are treated and in clinical and biological remission. A careful examination of the data showed that in five out of nine patients the capsule examination could have been avoided if a visualization of the last ileal loop would have been realized during colonoscopy.

The mean age of the nine patients diagnosed with Crohn's disease was 37 years. Similar results were reported in a study of 385 patients with obscure gastrointestinal bleeding, where the young adults (17-40 years) were most likely to have Crohn's disease, small intestine tumors or non-specific enteritis¹².

One of the most feared problems in capsule endoscopy is capsule retention. Crohn's disease is an independent risk factor for capsule retention confirmed in many studies¹³. The rate of capsule retention was 1.6% in cases of suspected CD and peaked as high as 13% in patients with known CD¹⁴. Sometimes obtaining a careful history might be the best single method to detect the possibility of retention according to some experts but this is highly debated since retentions were encountered in asymptomatic patients¹⁵. In our study the retention occurred in an asymptomatic patient that remained asymptomatic for the three months until capsule excretion.

In three patients (7.5%) the lesions discovered by capsule endoscopy were accessible by upper endoscopy (gastric ulcer, celiac disease) and colonoscopy (colon cancer). This is not unusual since lesions in upper or lower GI tract can be missed in as much as about 28% of patients submitted to CE for obscure bleeding¹⁶.

CE may play an important role in identifying the lesions missed at conventional endoscopy and careful evaluation of the images should be realized.

We currently changed our approach to the patients with OGIB. Before recommending an expensive and not reimbursed examination by capsule we make sure that a complete colonoscopy with visualization of the terminal ileum was performed.

CONCLUSIONS

The rate of patients without an explaining lesion was small (13%). Capsule endoscopy was paramount in the therapeutic decision in the majority of cases.

An important number of patients investigated for obscure GI bleeding turned out to have small bowel Crohn's disease in our group.

Due to capsule endoscopy examination costs, a careful and complete exploration of the patients with routine ileoscopy before capsule is advisable.

The access to therapeutic enteroscopy is still limited and close networking between centers is necessary to provide the necessary care for the patients.

Conflicts of interests: none declared.

Author contributions: All authors equally contributed to the article.

References

1. Rockey DC. Occult gastrointestinal bleeding. *N Engl J Med*. 1999 Jul 1;341(1):38-46. PMID:10387941
2. Pennazio M, Eisen G, Goldfarb N; ICCE. ICCE consensus for obscure gastrointestinal bleeding. *Endoscopy*. 2005;37(10):1046-50. PMID: 16189788
3. Raju G, Gerson L, Das A, Lewis B; American Gastroenterological Association. American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. *Gastroenterology*. 2007;133(5):1694-6. PMID: 17983811
4. Rondonotti E, Marmo R, Petracchini M, de Franchis R, Pennazio M. The American Society for Gastrointestinal Endoscopy (ASGE) diagnostic algorithm for obscure gastrointestinal bleeding: eight burning questions from everyday clinical practice. *Dig Liver Dis*. 2013;45(3):179-85. doi: 10.1016/j.dld.2012.07.012. PMID: 22921043
5. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc*. 2010;71:280-286 PMID: 20152309
6. Lepieur L, Dray X, Antonietti M, Iwanicki-Caron I, Grigioni S, Chapat U, Di-Fiore A, Alhameedi R, Marteau P, Ducrotté P, et al. Factors associated with diagnosis of obscure gastrointestinal bleeding by video capsule enteroscopy. *Clin Gastroenterol Hepatol*. 2012;10:1376-1380 doi: 10.1016/j.cgh.2012.05.024 PMID:22677574
7. Estévez E, González-Conde B, Vázquez-Iglesias JL, de Los Angeles Vázquez-Millán M, Pértega S, Alonso PA, Clofent J, Santos E, Ulla JL, Sánchez E. Diagnostic yield and clinical outcomes after capsule endoscopy in 100 consecutive patients with obscure gastrointestinal bleeding. *Eur J Gastroenterol Hepatol*. 2006;18(8):881-8. PMID: 16825907
8. Lai LH, Wong GL, Chow DK, Lau JY, Sung JJ, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *Am J Gastroenterol*. 2006;101:1224-1228. PMID: 16771942
9. Riccioni ME, Urgesi R, Cianci R, Rizzo G, D'Angelo L, Marmo R, Costamagna G. Negative capsule endoscopy in patients with obscure gastrointestinal bleeding reliable: recurrence of bleeding on long-term follow-up. *World J Gastroenterol*. 2013;19:4520-4525 doi: 10.3748/wjg.v19.i28.4520 PMID:23901227
10. Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy*. 2007; 39(10):895-909. PMID: 17968807
11. Bourreille A, Ignjatovic A, Aabakken L, Loftus EV Jr, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, Despott EJ, Fortun PF, Heuschkel R, Kammermeier J, Leighton JA, Mantzaris GJ, Moussata D, Lo S, Paulsen V, Panés J, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger JM, Yamamoto H, Travis S, Colombel JF, Van Gossum A; World Organisation of Digestive Endoscopy (OMED) and the European Crohn's and Colitis Organisation (ECCO). Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy*. 2009;41(7):618-37. doi: 10.1055/s-0029-1214790. PMID:19588292
12. Zhang BL, Chen CX, Li YM. Capsule endoscopy examination identifies different leading causes of obscure gastrointestinal bleeding in patients of different ages. *Turk J Gastroenterol*. 2012;23(3):220-5. PMID: 22798110
13. Höög CM, Bark LÅ, Arkani J, Gorsetman J, Broström O, Sjöqvist U. Capsule retentions and incomplete capsule endoscopy examinations: an analysis of 2300 examinations. *Gastroenterol Res Pract*. 2012;2012:518-718. doi: 10.1155/2012/518718. PMID: 21969823
14. Cheifetz AS, Kornbluth AA, Legnani P, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. *Am J Gastroenterol*. 2006;101:2218-2222. PMID:16848804
15. Karagiannis S, Faiss S, Mavrogiannis C. Capsule retention: a feared complication of wireless capsule endoscopy. *Scand J Gastroenterol*. 2009;44:1158-65.
16. Riccioni ME, Urgesi R, Cianci R, Marmo C, Galasso D, Costamagna G. Obscure recurrent gastrointestinal bleeding: a revealed mystery? *Scand J Gastroenterol*. 2014;49(8):1020-6. doi: 10.3109/00365521.2014.898327. PMID:24945819