Tech Coloproctol (2014) 18:277–283
DOI 10.1007/s10151-013-1054-3

ORIGINAL ARTICLE

Role of capsule endoscopy Pillcam COLON 2 in patients with known or suspected Crohn's disease who refused colonoscopy or underwent incomplete colonoscopic exam: a case series

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Received: 9 April 2013 / Accepted: 24 July 2013 / Published online: 21 August 2013

Abstract
Background Almost 70–80 % of patients with Crohn's disease and virtually all patients with ulcerative colitis have colorectal mucosa involvement. Colon capsule endoscopy is an interesting option for patients unable or unwilling to undergo colonoscopy. We report our experience with the second-generation colon capsule PillCam® COLON 2 in the detection of significant lesions in patients with known or suspected Crohn's disease, who refused colonoscopy or underwent incomplete colonoscopic exam.
Methods We have retrospectively reviewed the results of capsule endoscopy in 6 patients who refused colonoscopy ($n = 3$) or underwent incomplete colonoscopic exam ($n = 3$) between March 2011 and October 2012. In all patients, a CT scan was obtained before capsule endoscopy to rule out significant stenosis.
Results In our series of 6 patients, 4 had both small bowel and colonic involvement. The use of the PillCam® COLON 2 capsule allowed a thorough examination and evaluation of the mucosal lesions with high acceptability, the method being perceived as noninvasive by the patients. No adverse events related to the capsule or bowel preparation were recorded.
Conclusion In this patient population, PillCam® COLON 2 capsule endoscopy was safe. The capsule findings had an important impact on treatment decisions and patient management.

Keywords Capsule endoscopy · PillCam COLON 2 · Crohn's disease · Colonoscopy refusal · Incomplete colonoscopy

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Introduction

Almost 70–80 % of patients with Crohn's disease (CD) and virtually all patients with ulcerative colitis (UC) have colorectal mucosa involvement [1].

Endoscopy remains the best test for diagnosing inflammatory bowel disease (IBD) because of its high sensitivity in the detection of mucosal lesions and its ability to provide biopsies, which are usually required for diagnosis [2].

Since its introduction into clinical practice, small bowel capsule endoscopy (SBCE) has been used in the diagnosis of IBD and has been responsible for significant progress in the evaluation of such patients [3]. It is a sensitive test for the diagnosis of mucosal changes, but its findings are nonspecific and have to be interpreted with caution and in the correct clinical setting as there may be subtle changes in the small intestine of up to one-fifth of normal individuals. Care should also be taken to exclude lesions due to nonsteroidal anti-inflammatory drugs (NSAIDs) because they can mimic findings of CD [3]. Other lesions such as vasculitis, lymphoma, ischemic or infectious lesions should also be ruled out.

A meta-analysis has shown that SBCE has a significantly higher diagnostic yield for small bowel lesions when compared with small bowel follow through or computed tomography (CT) enterography in patients with either suspected or known CD [4].

Currently, capsule endoscopy is considered a valuable tool to diagnose or exclude CD. A high index of clinical suspicion (digestive symptoms plus either extra-intestinal manifestations, inflammatory markers or abnormal imaging studies) together with suggestive capsule findings increases the diagnostic yield [5].

In the era of mucosal healing as a therapeutic target, capsule findings may be equally important for monitoring disease evolution and treatment efficacy.

Colon capsule endoscopy could be used to identify mucosal changes in the colorectal mucosa. Recently, the European Society of Gastrointestinal Endoscopy (ESGE) published updated and extensive guidelines for CCE outlining the indications, bowel preparation, reporting standards and level of evidence [6].

According to the guidelines, there are insufficient data to support the use of CCE for diagnostic work-up or in the surveillance of patients with suspected or known IBD (Evidence level 4, Recommendation grade D), further studies being necessary to validate its role.

To date, the use of CCE in IBD has been evaluated in only three series of UC patients. One study evaluated PillCam® COLON (Given Imaging Ltd, Yokneam, Israel) capsule endoscopy in the detection of the severity and extent of active UC, in comparison with conventional colonoscopy in 26 patients. There was significant correlation between the severity and extent of UC on CCE and traditional colonoscopy [7].

The primary endpoint of the second study was the accuracy of CCE in assessing colonic inflammation (defined as the presence of exudation, ulcers, erythema, erosions and edema in the mucosa), using colonoscopy as the gold standard. The sensitivity of CCE in detecting active colonic inflammation was 89 % (95 % confidence interval (CI) 80–95), and specificity was 75 % (95 % CI 51–90) [8].

In this preliminary experience, CCE yielded encouraging results regarding detection of active UC with substantial agreement with colonoscopy [7, 8]. However, in a recent European study on UC, disease extent was underestimated by CCE compared to colonoscopy [9]. The disease activity assessment did not differ statistically between investigators ($p = 0.26$ and $p = 0.1$, respectively) with similar acceptance of both procedures [9].

Colon capsule endoscopy seems a safe and useful procedure to monitor mucosal healing in ulcerative colitis although, at this stage, CCE cannot be recommended to replace conventional colonoscopy in the management of this condition.

There is little evidence about the role of CCE in patients with CD

A second-generation, improved, colon capsule endoscopy system (PillCam® COLON 2) was developed to increase sensitivity for detecting colorectal lesions. The PillCam® COLON 2 capsule is slightly longer than the first-generation capsule, 11.6 × 31.5 mm. It has been designed to work for at least 10 h, and it has a variable frame rate (from 4 to 35 frames/second) in order to correctly visualize the mucosa when accelerated by peristalsis. The angle view was increased to 172°. Using both capsule lenses, the field of vision covers almost 360° of the colonic surface. To save battery energy, PillCam® COLON 2, instead of entering a "sleep" mode like the first-generation capsule, continues to work at a low rate of 14 images per minute until small bowel images are detected. The capsule then turns into the adaptive frame rate mode. The new data recorder (DR3) is smaller and more ergonomic, with a liquid crystal display allowing real-time view. It allows a bidirectional communication with the capsule and also is friendlier and easier for the patient to use, providing automatic visual and audio signals for procedure activities (boost administration). A recent study using second-generation colon capsule PillCam® COLON 2 showed a sensitivity of almost 90 % for detection of significant colonic lesions [10].

It can be expected that better results can be obtained using PillCam® COLON 2 in IBD patients. One of the main advantages is that the recording can be started in the stomach, and a picture of the entire digestive tract mucosa can be obtained.

We report our experience with the second-generation colon capsule PillCam® COLON 2 in detection of significant lesions in patients with known Crohn's disease or strongly suspected of having Crohn's disease, who refused colonoscopy or underwent incomplete colonoscopic exam.

Materials and methods

Procedure, colon preparation and cleanliness estimation

All the investigators reading the capsule videos had extensive experience in digestive endoscopy, had previous experience using the small bowel capsule and were instructed to review the entire examination recording. The study was approved by the hospital ethics committee.

Participating patients received written and oral explanations of the procedure, including the capsule impaction risks. The details of colonic preparation were explained. This consisted of a low-residue diet starting 48 h before investigation and a clear liquid diet 24 h before ingestion. Four liters of split-dose polyethylene glycol (PEG) Fortrans® (Macrogol 4000, Ibsen, France) was administered in the evening and 2 h prior to capsule ingestion. Since in Romania, oral sodium phosphate is not available, PEG was used as booster. Upon capsule exits from the stomach, a

first liter of PEG was administered and a second boost of one liter of PEG was administered (if needed) 3 h after the first one. Colon cleanliness was graded using a 2-point scale in each of the five colon segments (cecum, right colon, transverse colon, left colon and rectum), and then, a general estimate of the entire colon was made. This 2-point scale was a development of the original 4-point scale used in previous studies and grades preparation as inadequate (poor or fair on the 4-point scale) or adequate (good or excellent on the 4-point scale) [11].

Results

Patients

Six consecutive patients, 4 women and 2 men, mean age 46 years (range 24–66 years) were enrolled in the study. The details are summarized in Table 1.

Capsule endoscopy was proposed to the patients as an alternative after incomplete colonoscopy or if the patient refused the colonoscopy examination. The main indication for colonoscopy was suspected Crohn's in four patients and long standing Crohn's in two patients.

Three patients refused colonoscopy, and the other three patients had a previous attempted colonoscopy which failed and were offered the option of a CCE examination (in 2 cases, two previous colonoscopies failed to reach the cecum).

Careful history and clinical examination was done to exclude other causes for gastrointestinal lesions mimicking Crohn's disease use of nonsteroidal anti-inflammatory drugs, vasculitis, lymphoma, bacterial or mycobacterial infections. Symptoms compatible with intestinal obstruction were also carefully assessed. Extensive blood testes, fecal calprotectin and abdominal ultrasound were routinely performed. After the decision to perform CCE, a CT scan was obtained in all patients to exclude significant stenoses.

Findings

The examination recording was set up to start in the stomach in all patients. In this way, the entire digestive mucosa was evaluated.

Colonoscopy refusals

A 66-year-old woman with a history of right hemicolectomy for severe ileocecal Crohn's disease, 2 years prior, presented symptoms of a new flare. She refused a new colonoscopy and had a CCE examination instead. Minor lesions type i-1 according to Rutgeerts classification were seen at CCE in the anastomotic area. She is currently on 5-aminosalicyclic acid (5 ASA) derivatives with significant improvement.

Another patient refusing colonoscopy was a 44-year-old woman referred from a different center for chronic diarrhea and weight loss. Her fecal calprotectin level was seven times higher than normal. Capsule examination revealed multiple aphthoid ulcers in the small bowel. She is currently in clinical remission on azathioprine.

The third patient refusing colonoscopy was a 46-year-old male with weight loss, anemia and chronic diarrhea. He had been treated symptomatically for IBD for several years. CCE revealed small bowel lesions, with deep ulcers in the terminal ileum and ileocecal valve (Fig. 1). The patient was put on 5-ASA and budesonide with significant improvement, but he was lost to follow-up after 6 months.

Incomplete colonoscopies

In the case of suspected Crohn's disease in a 24-year-old woman with diarrhea, weight loss and anemia, two attempted colonoscopies failed to reach the terminal ileum, due to a redundant sigmoid colon so CCE was proposed to the patient. A CT examination showed inflammatory lesions in the terminal ileum but no stenoses. PillCam®

Table 1 Patient details

Patient	Gender	Age (years)	Indication	Colonoscopy	Findings
1	M	46	Diarrhea, weight loss, elevated CRP	R	Deep ulcerations in the terminal ileum and IC valve
2	W	44	Chronic diarrhea, abdominal pain, elevated fecal calprotectin (7xN)	R	Aphthoid ulcers ileum
3	W	66	Surgically treated Crohn's disease	R	Anastomotic lesions
4	M	39	New flare of Crohn's disease	I (2)	Deep ulcers stomach small bowel colon
5	W	24	Anemia, weight loss, chronic diarrhea	I (2)	Deep ulcers terminal ileum, colon
6	W	40	Anemia, chronic diarrhea, weight loss	I	Ulcerations terminal ileum, colon

I Incomplete colonoscopy, *R* refusal of colonoscopy, *IC* Ileocecal, *CRP* C-reactive protein

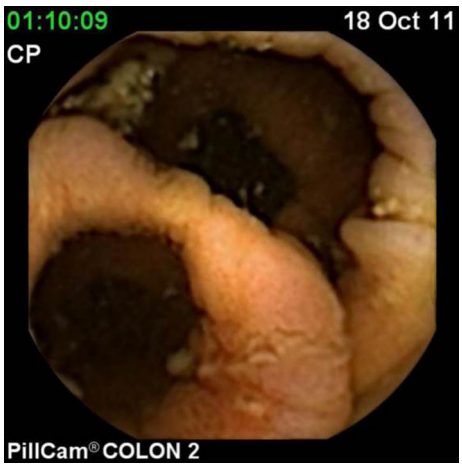

Fig. 1 Deep ulcer and edema in the terminal ileum and ileocecal valve

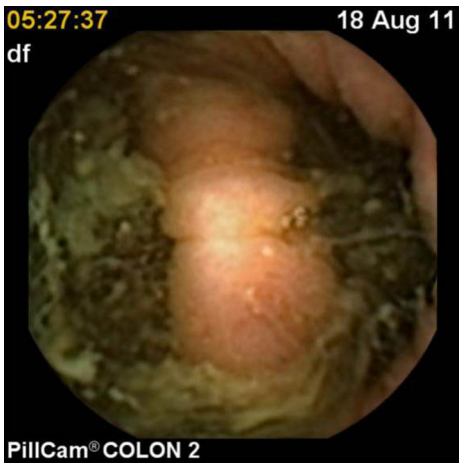

Fig. 3 Colonic aphthoid ulcer

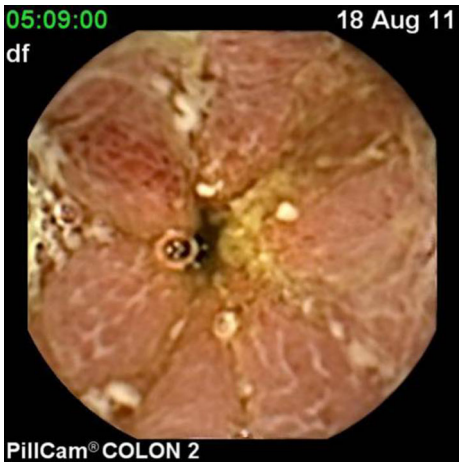

Fig. 2 Terminal ileitis

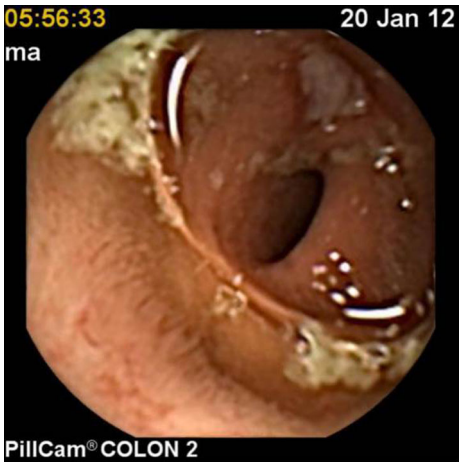

Fig. 4 Ulceration and stenosis in the ileum

COLON 2 showed typical lesions in the terminal ileum and ascending colon (Figs. 2, 3). Budesonide and azathioprine were started and co-administered for 6 months. The patient is currently in clinical and biological remission on azathioprine 2 mg/kg.

A 39-year-old man with longstanding Crohn's disease was admitted for severe anemia, diarrhea and weight loss. He was not on any therapy at the moment, because of a history of non-Hodgkin's lymphoma at the age of 20. Two attempted colonoscopies failed to pass the sigmoid colon. He was offered the opportunity to undergo capsule examination and he accepted. Multiple deep ulcers were seen in the small bowel and colon (Figs. 4, 5, 6). Stenotic lesions were seen in the small bowel. Surprisingly, the strictures were not visible on his previous CT scan. He is in remission on anti-TNF alfa therapy.

In another 40-year-old woman referred for anemia and chronic diarrhea, capsule was proposed after failure of complete colonoscopy. Ulcerations in the terminal ileum

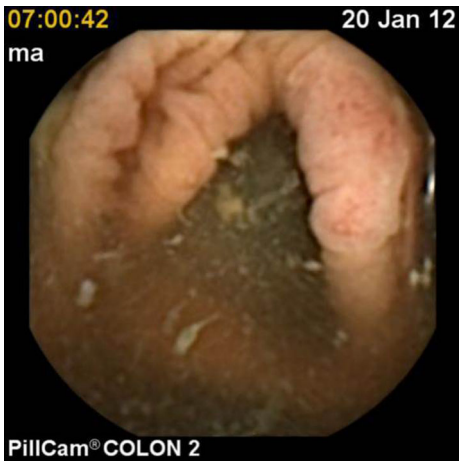

Fig. 5 Erythema and aphthoid ulceration transverse colon

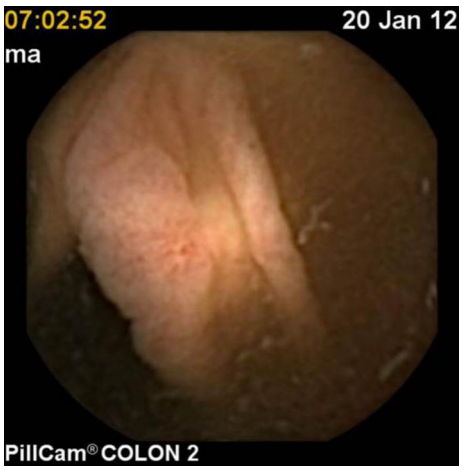

Fig. 6 Edema and aphthoid ulceration transverse colon

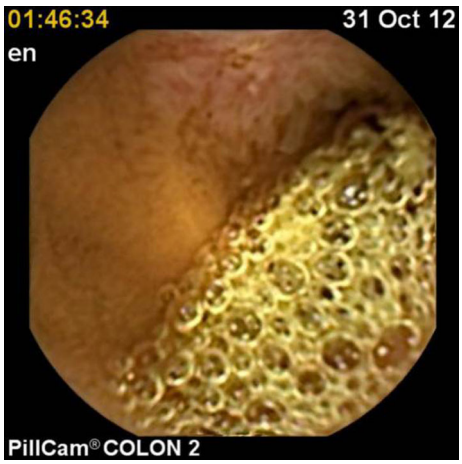

Fig. 7 Ulceration and edema in the ileum

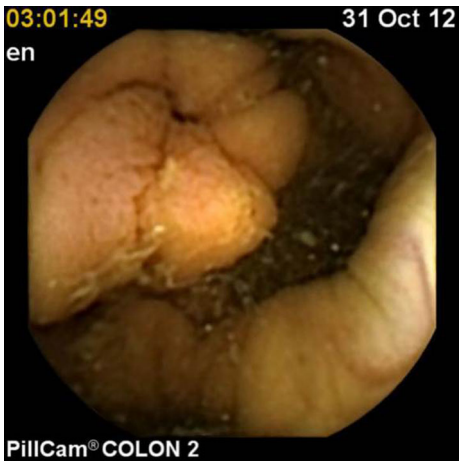

Fig. 8 Ileocecal ulcer

and cecum (Figs. 7, 8) were seen, and therapy with budesonide was started. The patient is currently in clinical and biological remission.

Adverse events

Capsule ingestion went smoothly in all patients

Although none of the patients had a small bowel follow through before CCE, we did not encounter any impaction on stenoses.

No electrolyte disturbances or adverse effects related to bowel preparation were recorded, although most patients had to ingest a total of six liters of PEG (preparation and boosters). No other side effects related to the capsule were encountered.

Discussion

To the best of our knowledge, this is the first report on the utility of PillCam® COLON 2 in patients with known or suspected CD who refused colonoscopy or underwent incomplete colonoscopic exam.

Although the rate of incomplete colonoscopy tends to be lower, it can reach 10 % [12]. After an incomplete colonoscopy, several options are available. Changing the treatment center, the endoscope or the endoscopist is an alternative. The use of imaging tests is an option, especially with the progress of the CT and MRI techniques, which are particularly useful in CD, since they allow an estimation of the extra-intestinal involvement [13].

If a patient refuses colonoscopy, the CT or MRI colonography imaging is an option with radiation exposure remaining a concern for the CT examination despite the evolution of the technique and improvement of examination protocols.

The development of PillCam® COLON by Given Imaging was seen as an alternative to increase the acceptability and safety of a colorectal examination. Although bowel preparation similar to that required before to colonoscopy cannot be avoided, this technique requires no insufflation or sedation, the risks are minimal and the complication rates very low. A complete examination of the mucosa of the digestive tract is possible with PillCam® COLON 2 where recording can be set to start in the stomach.

One of the main problems in capsule endoscopy is capsule retention. The incidence of capsule retention in the general population ranges from 1 to 2.6 %, depending on the indication [14]. That CD is an independent risk factor for capsule retention is confirmed in many studies [15]. The rate of capsule retention was 1.6 % in cases of suspected CD and reached 13 % in patients with known CD [16].

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 retention was reported in asymptomatic patients [17].

Radiologic imaging procedures are often recommended before SBCE to exclude stenoses. However, it is important to note that even in the presence of normal SB radiologic findings, there can still be significant undetected strictures [18].

In an effort to avoid capsule retention, a soluble capsule called patency capsule has been developed (Agile® Patency Sapsule, Given Imaging Ltd, Yokneam, Israel) and showed promising results [19]. However, even after a patency examination, capsule retention might occur [20, 21].

Patients with suspected or known CD should be clearly informed about increased impaction risks despite normal imaging prior to capsule examination [22].

We consider the patients presented in our series who refused colonoscopy or underwent incomplete colonoscopic exam as a special population, very motivated to undergo another examination provided it was not colonoscopy. The impaction risk should be explained and only very motivated patients should be examined.

Colon capsule endoscopy findings had a great clinical impact on the management of our 6 patients, as all are currently receiving therapy. Similar results were obtained in a British study, where the CCE results led to a change in management in the majority of cases of symptomatic IBD [23]. Treatment decisions were based on clinical suspicion and on capsule findings. The choice of therapy was also based on the European Crohn's and Colitis Organization(ECCO) recommendations and on the national protocol for IBD [24]. After a mean follow-up of 14.6 months (range 3–24 months), all patients are in remission.

The majority of patients in our series had ileocecal involvement, and the use of the colon capsule allowed a complete examination of the mucosal lesions in all patients who refused colonoscopy or underwent incomplete colonoscopic exam, with high acceptability, the method being perceived as noninvasive and harmless. In addition, the capsule examination led to a change in clinical management.

Our study has some limitations mainly because of its small number of patients and its heterogenous population. We did not have a control group.

However, the results are promising, and CCE can be a valuable approach to this special category of patients.

Further studies are necessary to validate the best approach to patients with known or suspected Crohn's disease who refused colonoscopy or underwent incomplete colonoscopic exam.

Conclusions

PillCam® COLON 2 is a valuable tool for the evaluation of patients with known/suspected CD who refused colonoscopy or underwent incomplete colonoscopic exam.

Acknowledgments This research was funded by the European Society of Gastrointestinal Endoscopy-Given Imaging research grant awarded to Dr Lucian Negreanu in 2010.

Conflict of interest None.

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