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Capsule Endoscopy in Patients with Suspected Crohn's Disease and Negative Endoscopy

Background and Study Aims: The aim of the present study was to assess the value of capsule endoscopy in the diagnostic work-up of patients in whom there is a clinical suspicion of small bowel Crohn's disease that cannot be confirmed using traditional techniques.

Patients and Methods: A total of 21 patients (14 men, seven women; mean age 43 ± 8 years) with a clinical and biochemical suspicion of Crohn's disease were included in the study. Conventional imaging work-up, including upper and lower endoscopy, as well as a small-bowel follow-through, was carried out in all of the patients.

Results: Pathological findings were not observed in 12 of the 21 patients (57%). In the other nine patients (43%), lesions supporting the diagnosis of Crohn's disease were seen. The most frequent findings were located in the distal ileum and included aphthae, lineal and serpiginous ulcers, and fissures. Four patients had lesions in the jejunum. One patient showed erosions in the distal duodenum, jejunum, and ileum. No adverse effects of the technique were observed in any of the patients.

Conclusions: Capsule endoscopy is a valuable diagnostic tool in patients with suspected Crohn's disease that has not been confirmed using standard imaging techniques.

Introduction

Crohn's disease is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract. When it is located in the colon, terminal ileum, or upper digestive tract, endoscopy with biopsies is used to establish a diagnosis, but when it only affects the small bowel (20–30% of the cases), barium radiology is the technique most widely used to confirm the diagnosis [1,2]. However, there is a group of patients, especially in early stages of the disease, in whom a small-bowel follow-through may not detect subtle lesions – making it more difficult to establish a diagnosis and therefore to offer appropriate therapy [3–5].

Advances in electronics and miniaturization have recently made possible the development of wireless endoscopy in the form of a small device that can be swallowed by the patient. This capsule endoscope provides images of the digestive tube in a noninvasive fashion [6,7]. Preliminary studies carried out in animals and hu-

mans have demonstrated the safety of the capsule, the high quality of the images recorded, and the sensitivity of the technique for detecting lesions in the small bowel – better than the sensitivity of push enteroscopy [8–11]. The present study was designed to analyze the value of capsule endoscopy in a group of patients with symptoms suggesting incipient Crohn's disease affecting the small bowel, in whom conventional radiological and endoscopic techniques had not identified pathological findings.

Patients and Methods

Patients

A total of 21 patients (14 men, seven women; mean age 43 ± 8 years) with chronic diarrhea (>6 months), diffuse abdominal pain, fever, or weight loss were included in the study. The patients' clinical and analytical data are shown in Table 1. None of the patients had been taking nonsteroidal anti-inflammatory

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Table 1 Clinical and biochemical data for included patients

	n	%
Patients	21	
Mean age (years)	43 ± 8	
Mean bowel movements per day	4.05 ± 0.86	
Patients with diarrhea	21	100.0
Patients with abdominal pain	21	100.0
Patients with loss of weight	11	52.4
Patients with fever	7	33.3
Patients with hemoglobin < 10 g/dl	9	42.9
Patients with leukocytes > 12 000/μl	9	42.9
Patients with CRP > 0.8 mg/dl	8	38.1

CRP: C-reactive protein

drugs (NSAIDs). Antigliadin antibodies, stool culture, and examinations for ova and parasites were negative, and thyroid hormones were within normal values in all of the patients. Small-bowel follow-through examinations had been carried out in all the patients when stenotic lesions were not seen. Colonoscopy with biopsies were normal in all cases, except for one patient who had an erythematous and tarnished mucosa in the rectum and sigmoid; on histological examination, this was classified as unspecific colitis. Ileoscopy with biopsy was carried out in 17 patients, in whom the terminal ileum was examined as far as possible (10.29 ± 3.74 cm), with no macroscopic abnormalities being identified. Histological examination showed minimal changes in six patients (nos. 4, 7, 11, 17, 18, and 19) and normal mucosa in 11 cases (nos. 1, 3, 5, 6, 8, 9, 13, 14, 15, 16, and 20). It was not possible to intubate the terminal ileum, despite several attempts, in four patients (nos. 2, 10, 12, and 21). Informed consent was obtained in all cases before the capsule endoscopy technique was used.

Capsule Endoscopy

A wireless capsule video was used (M2A, Given Imaging, Yoqneam, Israel), which is easily swallowed by all patients, after a 6-h fast. Patients are seated when they swallow the capsule, but are invited to lie down immediately for 10 min after ingestion so that images from the cardia can be obtained. Following a pre-established scheme, eight external sensors are placed on the abdominal wall, which collect all the photographs and record them in a Holter system that the patient carries in a belt for a period of 7–8 h. The recorded data are then downloaded to a computer and analyzed using a specialized program (Rapid). The identification of sections of the small intestine (jejunum and ileum) is approximate, based on the macroscopic appearance of the mucosa and the time lapse since passage of the pylorus.

Statistical analysis. The results are shown in percentages or average values plus or minus standard deviation, according to each case. The nonparametric Mann–Whitney U test was used for comparative statistical analysis of transit time in the groups of patients with or without pathological findings. Statistical significance was set at $P < 0.05$.

Results

Capsule endoscopy was carried out in all 21 patients included in the study. In nine patients, the images were compatible with Crohn's disease of the small bowel. The most frequently found lesions were aphthae (erythematous mucosa with a white central area) and lineal or irregular ulcers; fissures in the mucosa were also seen (Figure 1). The nine patients with pathological findings had ileal lesions. Four of them also had lesions in the jejunum, and one had abnormalities in the distal duodenum, jejunum, and ileum (Table 2). In patient no. 7, gastroscopy had been carried out 4 months before the capsule endoscopy, and no duodenal lesions had been identified. Due to capsule-endoscopic findings of duodenal fissures and aphthae, a repeat gastroscopy with biopsy was carried out, which was diagnostic of Crohn's disease. Enteroscopy was offered in the four patients (nos. 1, 10, 12, and 18) in whom jejunal lesions were observed with capsule endoscopy. Three patients refused the exploration, and no abnormalities were seen in the enteroscopy carried out in the fourth patient. In the nine patients with capsule-endoscopic diagnosis of Crohn's disease, standard therapy with prednisone and mesalazine was initiated. At the time of writing, all of the patients are still in clinical remission (without diarrhea, fever, or abdominal pain) or analytical remission 3 months later.

The average cardiac transit time in the 21 patients was 1.15 ± 1.63 min, with a pyloric transit time of 51.32 ± 65.98 min and an ileocecal valve transit time of 5.21 ± 1.77 h (312.6 ± 106.2 min). There were no statistically significant differences in these times between patients without findings and those with images suggesting Crohn's disease (Table 3).

The capsule reached the colon and was excreted uneventfully in all patients. There were no adverse effects caused by the technique. In one case, the capsule's lamp did not switch on when it was removed from the box, and it was returned to the manufacturer and replaced. In another case, the capsule transmitted for only 4 h – although it had already reached the cecum, so that this did not affect the analysis. Other minor technical problems were also noted, such as various interruptions in transmission in two patients, although all of these lasted less than 50 min and occurred after the device had already reached the colon.

Discussion

Since endoscopic examination of the entire small bowel has remained elusive using traditional methods, investigation of disorders located in this area of the gastrointestinal tract is currently the main indication for capsule endoscopy. Obscure gastrointestinal bleeding (OGB) is currently the main reason for using wireless endoscopy, since radiological studies with barium cannot show flat or slightly elevated lesions, such as angiodysplasias, which are the main cause of OGB [12,13]. Push enteroscopy provides a sensitivity of 20–60% for this indication [14–16]; however, the limitations of this technique impede identification of the bleeding lesion when it is located in distal areas of the small bowel. The first use of wireless endoscopy in these patients was reported by Appleyard et al. [9] and included four patients with OGB in whom the bleeding site was identified with capsule en-

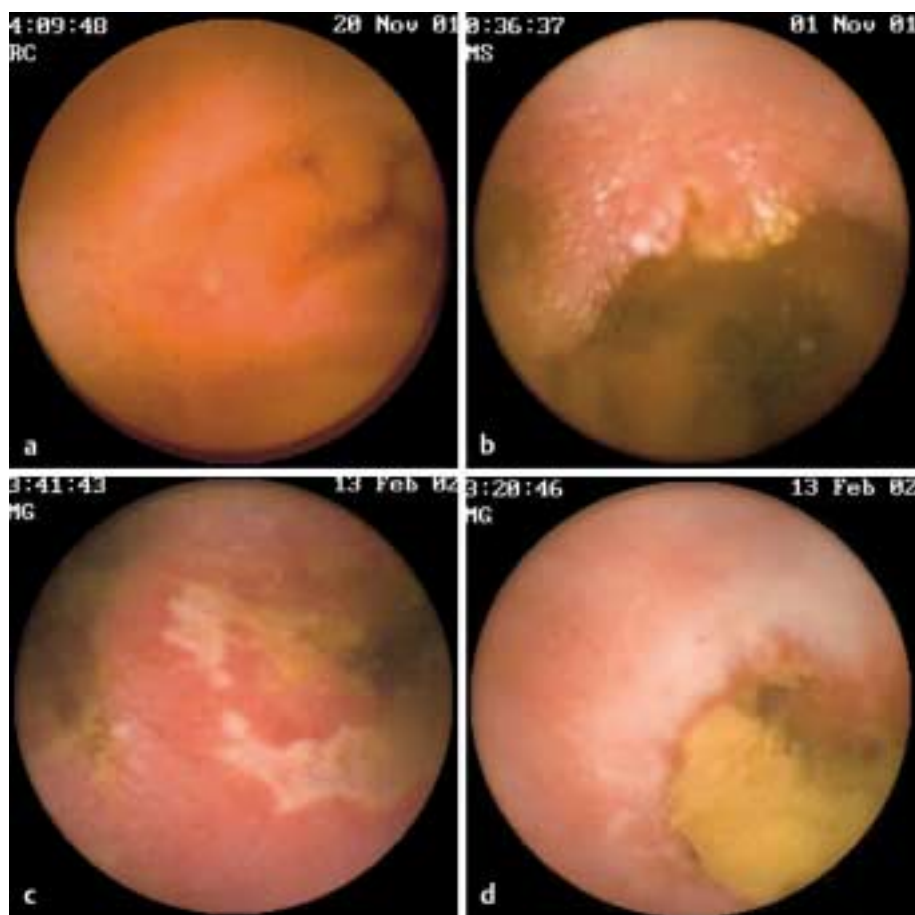


Figure 1 Capsule-endoscopic findings compatible with small-bowel Crohn's disease. **a** Ileal aphtha. **b** Duodenal fissure **c, d** Ileal ulcers.

Table 2 Morphology and location of the findings observed with capsule endoscopy

Patient	Location of lesions			Type of lesion		
	Duodenum	Jejunum	Ileum	Aphthae	Fissures	Ulcers
1	-	X	X (D)	X	X	-
2	-	-	X (D)	X	-	X
7	X	X	X (P)	X	-	X
10	-	X	X(D)	X	-	X
12	-	X	X (P, D)	X	X	X
15	-	-	X (P)	X	-	X
18	-	X	X (P, D)	X	-	X
19	-	-	X (P)	-	-	X
20	-	-	X (P)	X	-	-

D: distal; P: proximal

doscopy. Two reports have been published on capsule endoscopy in patients with OGB. Lewis and Swain [11] compared capsule endoscopy with push enteroscopy in these patients, with diagnostic yields of 55% (11 of 20) and 30% (six of 20), respectively, but the difference between the two did not quite reach statistical significance ($P=0.0625$). In a prospective controlled trial, Ell et al. [10] also compared the two techniques. Definite bleeding sites were diagnosed by push enteroscopy in nine patients (28%), while capsule endoscopy detected a definite source in 21 of the 32 patients (66%) ($P<0.001$).

Table 3 Transit times of capsule endoscopy in patients with and without abnormal findings

Transit times	Global (n = 21)	Patients without findings (n = 12)	Patients with pathological findings (n = 9)	P
Cardial	1.08 ± 1.64 min	0.75 ± 0.94 min	1.73 ± 2.40 min	0.375
Pyloric	40.67 ± 52.77 min	24.22 ± 32.69 min	70.46 ± 70.10 min	0.070
Ileocecal valve	5.0 ± 1.69 h	4.91 ± 1.90 h	5.09 ± 1.52 h	0.800

Capsule endoscopy thus appears to be a very useful tool in the study of patients with OGB. It has also been suggested that capsule endoscopy may be of value in other small-bowel disorders, such as inflammatory bowel disease, benign and malignant tumors, NSAID enteropathy, or digestive lesions in patients with systemic diseases (such as acquired immune deficiency syndrome or graft-versus-host disease). Among the disorders that affect the small bowel, one of the more attractive indications for capsule endoscopy is Crohn's disease. Up to 20–30% of patients with Crohn's disease only present with lesions in the small bowel, particularly the ileum [2]. Many studies have shown that diagnosis in these patients is delayed in comparison with patients who present with cecal lesions [3–5]. Patients with distal ileal lesions can often be diagnosed with colonoscopy and ileoscopy, but when the disease involvement is more proximal or intubat-

ing the ileocecal valve is not possible, radiography (small-bowel follow-through or enteroclysis) is the only imaging tool available. Both techniques, especially enteroclysis, allow diagnosis in many cases, although the results mainly depend on the quality of the exploration [17,18]. Enteroclysis requires nasojejunal intubation and higher doses of radiation than small-bowel follow-through, and is not available in all medical centers [19,20]. However, patients with occult lesions may not be identified, especially if there are overlapping intestinal loops [18]. Although this is a small group of patients, the situation therefore still represents a serious challenge for the clinician.

Push enteroscopy with biopsy has been suggested as a new diagnostic tool in these patients [3,21]. Pérez-Cuadrado et al. [21] studied eight patients in whom there was a high suspicion of Crohn's disease. Enteroscopy carried out in all of them confirmed the diagnosis in 50% of cases. As in the present study, traditional endoscopy and small-bowel follow-through did not show any abnormalities. In a series of 20 patients in whom a diagnosis was not achieved with radiographic studies, Lescut et al. [22] identified Crohn's disease in 65% after intraoperative enteroscopy of the entire bowel. However, this is an invasive technique, associated with a significant rate of complications. Capsule endoscopy is a noninvasive technique that allows the study of the entire small bowel and does not require sedation. As a disadvantage, it is not possible to take biopsies in suspicious areas with capsule endoscopy. However, the finding of noncaseating granulomas may not be seen in 60–70% of endoscopic biopsies from patients with incipient Crohn's disease [23–25], since even if granulomas are present, the chances of finding them in biopsies depend on their frequency and size, the number of slides examined, and the number of sections on each slide. Moreover, the presence of these granulomas does not allow infectious diseases to be completely ruled out [24]. Thus, in most cases, the diagnosis is based on clinical, biochemical, radiographic, and endoscopic data, with a compatible histological report.

Costamagna et al. [26] prospectively compared the clinical outcomes of the traditional small-bowel follow-through with capsule endoscopy in the diagnostic evaluation of 20 patients with suspected small-bowel disease. Aphthous jejunal and ileal ulcers suggestive of Crohn's disease were observed in three patients, two of whom were being evaluated for recurrent Crohn's disease and the third for obscure bleeding. The small-bowel follow-through examination had been normal in all three patients and only detected an ileal nodularity in one of the patients with suspected recurrent Crohn's. Scapa et al. [27] analyzed their initial experience of capsule endoscopy in 35 patients with suspected small-bowel pathology. In six of 13 patients with clinically suspected Crohn's disease with normal colonoscopy, gastroscopy, and small-bowel follow-through, lesions compatible with Crohn's disease were detected by the capsule. The diagnostic yield (46.15%) was comparable to that obtained in the present study (42.86%), although the patient selection was not the same in the two series.

The role of capsule endoscopy in patients in whom there is a clinical and biochemical suspicion of small-bowel Crohn's disease thus seems clear when ileoscopy is not technically possible. This occurred in four patients in the present study (nos. 2, 10,

12, and 21); lesions compatible with Crohn's disease were only detected by the capsule in three of these patients (nos. 2, 10, and 12). On the other hand, findings suggestive of Crohn's disease could only be observed by capsule endoscopy in six patients with normal ileoscopy (mean explored length of the terminal ileum 10.29 ± 3.74 cm), probably because the most distal part of the terminal ileum was not affected in these cases. Further studies will be needed in order to establish the true role of capsule endoscopy in patients in whom there is a suspicion of small-bowel Crohn's disease who have a normal ileoscopy.

Several cases of capsule retention have been reported, particularly in certain groups of patients. Bhinder et al. [28] found intestinal ulcers and multiple short strictures in four of 46 patients with OGB. All four patients had a history of NSAID use, and the capsule was retained in all cases. Two capsules passed spontaneously, and the other two were removed surgically after 28 and 56 days. These patients had undergone an evaluation prior to capsule endoscopy, including small-bowel series and enteroclysis, but no strictures had been identified. These radiographic procedures thus appear to be necessary, but not sufficient, to rule out intestinal strictures prior to capsule endoscopy. Bhinder et al. [28] conclude that patients should be surgical candidates and that surgical intervention with intraoperative endoscopy should be available for treatment of the findings and recovery of the capsule endoscope. Unsuspected strictures in small-bowel Crohn's disease could also cause retention of the capsule endoscope, although no adverse events were observed in the present study during or after the technique. All six patients with Crohn's disease in the study by Scapa et al. [27] also showed normal excretion of the capsule, and the same was true of the series reported by Costamagna et al. [26]. The number of patients with Crohn's disease who have undergone capsule-endoscopic examinations is obviously still very limited; further studies are needed to assess the risks and contraindications of the technique in this group of patients.

In conclusion, this study showed that capsule endoscopy is a valuable diagnostic tool in patients in whom there is a suspicion of Crohn's disease which has not been confirmed using standard imaging techniques.

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