

When Crohn's Disease is in Remission, More Patients Complete Capsule Endoscopy Study But Less Lesions are Identified

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ABSTRACT

Background and Aims: Wireless capsule endoscopy (WCE) is used in Crohn's disease (CD) to define disease extent. We aimed to define WCE detection rate of small bowel ulcerative lesions and completion rate in CD patients. **Patients and Methods:** A total of 102 consecutive CD patients, who successfully passed patency capsule, were matched to 102 controls. WCE was performed in both patients (in acute phase and CD clinical remission) and controls. **Results:** Eighty-six (84%) controls versus 62 (61%) patients in the acute phase ($P = 0.003$) and 96 (94%) in remission ($P = 0.02$) completed WCE study. Gastric passing time was 48 ± 66 min in controls, 66 ± 82 min in CD acute phase ($P = 0.03$) and 30 ± 21 min in remission ($P = 0.07$). Small bowel passing time was 276 ± 78 min in controls, 299 ± 78 min in the acute phase of CD ($P = 0.04$) and 248 ± 89 min in remission ($P = 0.01$). Mean capsule endoscopy Crohn's disease activity index (CECDAI) score was 14 ± 6 in acute small bowel CD, 12 ± 7 in acute small-large bowel CD ($P = 0.08$) and 2 ± 2 in both CD types while in remission ($P = 1.00$). Small bowel ulcerative lesions in the acute phase were more frequently in distal small bowel. Aphthous ulcers were frequent a month after entering clinical remission and tend to disappear gradually later on. No ulcerative lesions were present in deep remission. Patency capsule is rather safe to exclude small bowel obstruction. **Conclusions:** (1) A high percentage of patients with active CD do not complete small bowel study with WCE. (2) Small bowel ulcerative lesions in clinical remission were less severe, although at least 6 months are needed in order for them to disappear.

Key Words: Active Crohn's disease, Crohn's disease in remission, patency capsule, small bowel, wire capsule endoscopy

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Crohn's disease (CD) is an inflammatory bowel disease (IBD) of multifactorial etiology, which can strike anywhere from mouth to anus. It involves the small bowel proximal to the terminal ileum in 4-65% of the patients^[1] and terminal ileum in 75-85%.^[2] Wireless capsule endoscopy (WCE) permits direct visualization of the small bowel lumen and its diagnostic yield for early CD is 77%. The method is not feasible in patients with

bowel stenosis or severe ulcerative disease and it is mainly used for mapping disease extent or diagnosing difficult CD cases.^[1,3-8]

Today CD treatment is decided on the base of clinical and biochemical criteria.^[9] Nevertheless a broader utilization of WCE to judge effectiveness of CD treatment is expected in the future. Thus WCE studies that focus, apart from the acute phase, on its rate of completion and its findings in early and deep remission are needed.

We performed a prospective evaluation of patients with CD to define: (1) detection rate of small bowel lesions by WCE during the acute phase of CD and in remission (early and deep clinical remission). (2) Complete examination rate during the acute phase of CD and in remission.

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PATIENTS AND METHODS

This prospective study included CD patients, aged over 18 years, attending our inflammatory bowel disease (IBD) outpatient clinic between January 2006 and December 2008. CD diagnosis was established based on clinical, biochemical, endoscopic, and histological criteria according to the European consensus for the diagnosis and management of CD.^[10] Thus, all patients had full endoscopic evaluation (esophagogastroduodenoscopy and ileocolonoscopy) with multiple biopsies, abdominal computed tomography (CT) scan and at least 12 months clinical follow-up.

Each patient was matched to a control based on age, gender, smoking, and alcohol consumption. Controls had never been diagnosed as having IBD or presented related symptoms. They were evaluated for chronic diarrhea, chronic abdominal pain of unknown origin, and overt bleeding or iron deficiency anemia with negative endoscopic evaluation.

Before WCE study, a patency capsule (Agile, Given Imaging, Yoqneam Israel) was given to every subject selected for the study. Patency capsule propel throughout the bowel was followed with daily abdominal X-rays until successful expulsion of an intact capsule or until completing 72 hours since swallowing of patency capsule, with the capsule still visible on abdominal X-rays. Because we used patency capsule, prior abdominal operation, diabetes mellitus or previous episode of bowel obstruction were not necessarily exclusion criteria. We included patients with pacemakers but excluded those with any mental condition precluding compliance, pregnant women or patients who were taking nonsteroidal antiinflammatory (NSAIDs) drugs during the past 3 months before WCE.

WCE was performed twice in CD patients: (a) in CD acute phase, defined by CDAI >220 and C-reactive protein (CRP) >10 mg/l and (b) at least 15 days after CDAI has dropped below 150, assuming that patient's general condition continues to improve. Thus definition of remission was based on CDAI and global clinical assessment. At the time of 'on remission study': (1) no patient had more than three bowel movements daily. (2) No blood was present in stools. (3) Patients had no or minimal abdominal pain and had started to regain weight. (4) No patient presented extra-intestinal manifestations or active fistulizing disease. Time to perform on remission WCE study was determined by social security fund permission policy. Time to allow repeat WCE study ranges between 1 and 12 months between different funds. No patient treatment changed after entering remission and since on remission study performed.

The work undertaken conformed to provisions of the Declaration of Helsinki (as revised in 2000). The study protocol had the approval of the Scientific Council of our Hospital, standing for Ethics Committee. All patients gave and signed written informed consent, before entering the study.

Capsule endoscopy procedure

After overnight fasting and bowel cleaning with 4 L of polyethylene glycol solution (Fortrans, Beaufour Ipsen, France), WCE (Pillcam SB, Given Imaging, Yoqneam Israel) was performed as described previously.^[1,3] Whenever wireless capsule failed to enter the cecum within the 8 hours of the WCE study, we followed the patient with daily X-rays until capsule expelled in stool, starting 48-hours after capsule ingestion.

Two independent gastroenterologists experienced in the field of WCE blinded to the clinical presentation and the finding of a previous WCE (in case of a repeat study) analyzed the data of WCE, using well-defined criteria and a dedicated scoring system to describe the degree of severity of CD manifestations. Findings considered pathologic and indicating CD affection in WCE were those known from conventional endoscopy including erythema, aphthous and ulcerous lesions, fissures, mucosal hemorrhage edema, (pseudo)-polyps, and local villi denudation. We split the small bowel in two halves, as the limit between jejunum and ileum cannot be defined accurately. In case that capsule did not reached the cecum we calculated jejunum-ileum margin: (a) based on small bowel morphology and (b) if small bowel morphology was inconsistent and terminal ileum has been reached we increased small bowel passing time by 10% and calculated the two halves adequately. Capsule endoscopy Crohn's disease activity index (CECDAI score) was retrospectively applied in all patients,^[11] to ensure better findings homogeneity. CECDAI lesions were graded: 1 = erythema and mucosal edema, 2 = sumucosal hemorrhages and tissue granularity, 3 = aphthous ulcers, including minor ones, 4 = small discrete ulcers up to 6 mm in diameter, 5 = large ulcerative lesions; while disease extent was defined: 1 = lesions in one area (less than 1/3), 2 = lesions in more than one areas (between 1/3 and 2/3), 3 = almost universal lesions (involving more than 2/3).

Quality of bowel preparation was graded using a 10-grade visual scale: 1-3 poor, 4-6 fair, 7-8 good, 9-10 excellent. Grading was done separately in the proximal and distal small bowel and the ratio was calculated for the final report. Bowel preparation was graded as 10 if the picture was completely clear, without a single bubble and as 1 if small bowel mucosa was hardly visible through bowel contents.

Statistical analysis

The Mac Nemar test was used when comparing group

differences. Wilcoxon pair test was used to determine differences between mean values a P value < 0.05 was considered to be statistically significant.

RESULTS

Patients

In the study period, 133 patients with CD consented to perform WCE. Of them 102 (77%) successfully passed patency capsule and entered final analysis. The rest, had enterocolitis that revealed stenosis in 23 (74%) and extensive ulcerative lesions without obvious stenosis in 8 (26%). Forty-seven (46%) patients who passed patency capsule had CD restricted in the small bowel (SB-CD), 18 (18%) in the large bowel (LB-CD), while 37 (36%) had both small and large bowel lesions (SBLB-CD). To enter remission 62 (61%) patients received corticosteroids, 32 (31%) corticosteroids in addition to azathioprine and 8 (8%) infliximab.

Mean age of CD patients, who successfully passed patency capsule, was 43 ± 16 years. Forty-seven (46%) were male, 4 (4%) consumed alcohol daily, 40 (39%) were active smokers, and 13 (13%) were ex-smokers. Their body mass index was 24 ± 4 . Mean CD duration was 5.3 ± 2.8 years. CD in remission was less severe than active disease [Table 1].

Time interval between the acute phase WCE study and in remission study was 2-3 months in 27 CD patients (26%, 14 SB-CD, 11 SBLB-CD, and 4 LB-CD patients), 3-6 months in 20 patients (20%, 10 SB-CD, 8 SBLB-CD, and 1 LB-CD patients), and 6-12 months in 55 patients (54%, 23 SB-CD, 18 SBLB-CD, and 15 LB-CD patients).

Patients were matched to 112 controls. One hundred and two (91%) of them passed patency capsule and entered the study. In the rest enterocolitis revealed bowel stenosis in 2 (20%). Three controls with normal enterocolitis who failed to pass patency capsule had a history of abdominal operation, four diabetes mellitus and one Parkinson disease.

Thirty (29%) controls that passed patency capsule were evaluated for chronic diarrhea, 16 (16%) for bleeding with negative endoscopy, 49 (48%) for iron deficiency anemia with negative endoscopy and 7 (7%) for chronic abdominal pain. Mean age of controls was 43 ± 13 years ($P = 1.00$), 48 (47%) were male ($P = 0.89$), 5 (5%) consumed alcohol daily ($P = 0.73$), 40 (39%) were active smokers ($P = 1.00$), and 13 (13%) were ex-smokers ($P = 1.00$). Their body mass index was 25 ± 5 , $P = 0.16$.

Study completion-gastric/small bowel passing time

A complete small bowel study achieved: in 86 (84%) controls;

62 (61%) patients with active CD ($P = 0.003$) and 96 (94%) in remission ($P = 0.02$). WCE study completion was less probable in patients with acute phase SB-CD and SBLB-CD, while it was more probable in the same subgroups when CD was in remission [Table 2a].

Gastric passing time (GPT) was 48 ± 52 min and small bowel passing time (SBPT) was 276 ± 79 min in controls that completed the study. In active CD GPT was 66 ± 82 min ($P = 0.03$) and SBPT was 299 ± 78 ($P = 0.04$). In CD remission, GPT was 30 ± 21 min ($P = 0.007$) and SBPT 248 ± 89 ($P = 0.01$). In the acute phase GPT was longer in SB-CD and SBLB-CD patients and SBPT in SB-CD patients [Table 2b]. In remission GPT was shorter in all CD subgroups and SBPT in SB-CD and SBLB-CD patients [Table 2b].

The quality of cleansing decreased toward the ileocecal valve. Despite receiving the same cleansing formulation, quality of preparation in the jejunum was 9.3 ± 0.4 in controls,

Table 1: Disease related characteristics of patients with CD

Characteristics	Active CD (n=102) (%)	In remission CD (n=102) (%)	P
Mean CD duration	5.3±2.8 years		
Mild small bowel stenosis	14 (14)	9 (9)	0.27
Small bowel inflammation	84 (83)	33 (32)	<0.0001
Fistulizing CD	6 (7)	0	0.01
Extraintestinal manifestations	27 (26)	0	<0.0001
Joint inflammation	16 (16)	0	<0.0001
Ocular manifestations	4 (4)	0	0.04
Skin complications	9 (9)	0	0.002
Mean CDAI	284±46	88±51	<0.0001
Mean CRP (mg/L)	87±33	8±4	<0.0001

CRP: C-reactive protein, SD: Standard deviation, CDAI: Crohn's disease activity index, CD: Crohn's disease

Table 2a: Rates of WCE study completion in various CD subgroups

Disease activity	SB-CD (n=47)	SBLB-CD (n=37)	LB-CD (n=18)	Controls (n=102)
Acute phase				
Study completion (%)	23 (48)	25 (68)	14 (78)	86 (84)
P	<0.0001	0.03	0.73	
In remission				
Study completion (%)	44 (94)	35 (95)	17 (94)	86 (84)
P	0.19	0.19	0.44	
P*	<0.0001	0.003	0.15	

SB-CD: Small bowel CD, SBLB-CD: CD involving both small and large bowel, LB-CD: Large bowel CD, SD: Standard deviation. P values express comparison between patients and controls, while P^* between acute phase and remission study in each disease subgroup. CD: Crohn's disease, WCE: Wireless capsule endoscopy

Table 2b: Gastric passing time and small bowel passing time in various CD subgroups (in min)

Disease activity	SB-CD (n=47)	SBLB-CD (n=37)	LB-CD (n=18)	Controls (n=102)
Acute phase				
GPT	68±80	58±61	77±115	48±52
<i>P</i>	0.04	0.17	0.04	
SBPT	313±68	298±68	278±77	276±79
<i>P</i>	0.02	0.10	0.46	
In remission				
GPT	29±20	35±24	22±14	48±52
<i>P</i>	0.008	0.07	0.02	
<i>P*</i>	0.0008	0.02	0.03	
SBPT	248±85	236±115	273±92	276±79
<i>P</i>	0.03	0.01	0.44	
<i>P*</i>	<0.0001	0.003	0.43	

SB-CD: Small bowel CD, SBLB-CD: CD involving both small and large bowel, LB-CD: Large bowel CD, SD: Standard deviation. *P* values express comparison between patients and controls, while *P** between acute phase and remission study in each disease subgroup. CD: Crohn's disease

Table 3a: Severity of WCE findings in proximal and distal small bowel in CD patients with active disease

Small bowel lesions	SB-CD patients n=47 (%)	SBLB-CD patients n=37 (%)	<i>P</i>
Proximal SB big ulcers	1 (2)	0	0.37
Distal SB big ulcers	7 (15)	3 (8)	0.34
Proximal SB small ulcers	3 (6)	5 (14)	0.27
Distal SB small ulcers	27 (57)	14 (38)	0.07
Proximal SB aphthous ulcers	28 (60)	25 (68)	0.45
Distal SB aphthous ulcers	47 (100)	37 (100)	1.00
No lesions in proximal SB	6 (13)	5 (14)	0.91
No lesions in distal SB	0	0	

SB: Small bowel, SB-CD: Small bowel CD, SBLB-CD: CD involving both small and large bowel. CD: Crohn's disease, WCE: Wireless capsule endoscopy

Table 3b: Severity of WCE findings in proximal and distal small bowel in CD patients in remission

Small bowel lesions	SB-CD patients n=47 (%)	SBLB-CD patients n=37	<i>P</i>
Proximal SB big ulcers	0	0	
Distal SB big ulcers	0	0	
Proximal SB small ulcers	0	0	
Distal SB small ulcers	0	0	
Proximal SB aphthous ulcers	5 (11)	6 (16)	0.45
Distal SB aphthous ulcers	11 (30)	11 (30)	0.51
No lesions in proximal SB	28 (60)	20 (54)	0.61
No lesions in distal SB	21 (45)	13 (35)	0.38

SB: Small bowel, SB-CD: Small bowel CD, SBLB-CD: CD involving both small and large bowel. CD: Crohn's disease, WCE: Wireless capsule endoscopy

9.8 ± 0.3 in active CD (*P* < 0.0001) and 9.2 ± 0.6 in CD remission (*P* = 0.08). While in the ileum it was 7.3 ± 1.5 in controls, 9.1 ± 1.8 in active CD (*P* < 0.0001) and 7.1 ± 1.9 in CD remission (*P* = 0.20).

Small bowel lesions

In the acute phase, small bowel ulcerative lesions were found in all SB-CD and SBLB-CD patients, but no LB-CD patient. In the latter, cecal ulcerative lesions were present in 8 (57%) patients who completed the study. Large bowel ulcerative lesions in WCE were also found in 22 (88%) SBLB-CD patients who completed the study. Mean CECDAI score was 14 ± 6 in SB-CD and 12 ± 7 in SBLB-CD patients (*P* = 0.08). Mean number of ulcerative lesions was 8.1 ± 4.5 in the proximal and 21 ± 9.4 in the distal small bowel (*P* < 0.0001). There was close correlation between CECDAI score and CDAI (*P* = 0.02) or CRP (*P* = 0.005).

There was no difference between SB-CD and SBLB-CD patients with acute phase CD concerning frequency and distribution of small bowel ulcerative lesions [Tables 3a and 4] and CECDAI score [Table 4].

When WCE study performed within a month after entering remission (time interval between the two studies 2-3 months), all SB-CD and SBLB-CD (*n* = 13) patients with small or large ulcers in the acute phase study presented aphthous ulcers in 'remission' study (but no larger lesions), as well as 5/10 (50%) patients with aphthous ulcers in the acute phase study. When time interval between the two studies was 3-6 months, 4/9 (44%) SB-CD or SBLB-CD patients with small or large ulcers in the acute phase study had aphthous ulcers in 'remission' study. Nevertheless, no patient with aphthous ulcers in the acute phase study had ulcerative lesions in 'remission' study. No ulcerative lesions were found in SB-CD and SBLB-CD patients (*n* = 40) with long-term remission (more than 6 months). Mean number of ulcerative lesions was 3.6 ± 0.7 in the proximal and 6.9 ± 1.2 in the distal small bowel when WCE study performed within a month after entering remission, 1.8 ± 0.6 in the proximal and 3.5 ± 0.9 when WCE study performed 3-6 months after the acute phase study. Later on no ulcerative lesions were found. Mean CECDAI score was 4 ± 2 both in SB-CD and SBLB-CD patients in 'remission' study (*P* = 1.00). There was no difference between SB-CD and SBLB-CD patients in remission concerning the frequency and distribution of small bowel ulcerative lesions [Tables 3b and 4] and CECDAI score [Table 4].

Side effects-capsule expulsion

No side effects were recorded within 30 days of WCE. In acute phase of CD, the capsule was successfully expelled in all but one CD patient in 2.1 ± 0.6 days. In one patient, capsule was impacted in an extensively ulcerated area and was finally expelled in 5 days on 60 mg prednisolone daily. It should be noted that patency capsule was not visible in two consecutive X-rays and the patient reported passing intact patency capsule. In remission, the capsule was successfully expelled in 0.8 ± 0.2 days.

Table 4: Comparison of patients with CD in the active phase and in remission

Small bowel lesions	SB-CD patients n=47	SBLB-CD patients n=37	P
Active phase			
CECDAI score	14±6	12±7	0.08
Mean number of ulcerative lesions in proximal SB	8.1±4.8	8.2±4.3	0.92
Mean number of ulcerative lesions in distal SB	21.6±9.6	20.2±9.1	0.50
In remission			
CECDAI score	4±2	4±2	1.00
Mean number of ulcerative lesions in proximal SB	1.5±0.3	1.4±0.4	0.19
Mean number of ulcerative lesions in distal SB	2.6±0.5	2.5±0.4	0.32

SB: Small bowel, SB-CD: Small bowel CD, SBLB-CD: CD involving both small and large bowel, CECDAI score: Capsule Endoscopy Crohn's Disease Activity Index, SD: Standard deviation. CD: Crohn's disease

DISCUSSION

In our hospital-based study, we found that presence of ulcerative lesions during acute phase CD slowed down capsule propulsion through the stomach and the small bowel and therefore prevented complete small bowel examination in a significant percentage of patients. In remission, capsule passing through both the stomach and the small bowel was a little faster than controls, without affecting WCE completion rate. We found that ulcerative lesions tend to disappear gradually after entering clinical remission. Larger lesions fade out within the first month, but aphthous ulcers might persist up to 6 months after treatment initiation. Finally we found that patency capsule is very effective to exclude bowel stenosis. Nevertheless, it can be rarely overlooked in plain abdominal X-rays.

Our study included a rather large CD population diagnosed on the basis of strict criteria^[10] and despite being a hospital-based one, included about 20% of the estimated national CD population.^[12] We also performed for the first time a comparison of GPT and SBPT, as well as 'acute phase' and in remission WCE findings. Moreover, although socioeconomic factors determined 'in remission' study and that study did not take place in a fixed time point, it gave a rough idea about ulcerative lesion healing in CD patients.

Although, we excluded NSAIDs use, 14% of CD patients and 22% of controls presented more severe ulcerative lesions in the proximal small bowel, a disease pattern compatible to NSAIDs enteropathy.^[13,14] A significant drawback was the high percentage of CD patients (23%) with stenotic disease who failed to pass patency capsule and excluded from the study. The rate of patient exclusion due to bowel stenosis was not

different in other WCE studies.^[1-8] Nevertheless, it introduced some biases concerning WCE findings interpretation.

Completion rates in our study, as in most previous reports (53-58%),^[1,15,16] in patients with active CD were low. Early reports have described high rates of cecum visualization (91%), in mixed populations, including mainly patients in CD remission.^[17] Passing patency capsule does not guaranty a quick propel through the small bowel. Taking into consideration long SBPT and capsule expulsion time, due to the presence of small bowel ulcerative lesions, more than 8 hours are needed in order to visualize the entire small bowel. In contrast, because completion rates in SB-CD and SBLB-CD are not different, large bowel inflammation does not affect completion rate.

In the active phase, GPT (66 min) was not different than GPT in Eliakim *et al.*, study (68 min).^[4] Moreover, SBPT, was within the limits of SBPT in Golder *et al.*, (323 min),^[16] Eliakim *et al.*, (243 min),^[4] and Eftymiou *et al.*, (278 min)^[7] studies. Any deviation in SBPT mirrors mingle of different CD subtypes in the study population. In remission, healing of ulcerative lesions suppressed inflammatory factors produced in terminal ileum, such as tumor necrosis factor alpha or interleukin-6, and decreased SBPT and GPT.^[18] Because cytokines influencing bowel motility are more extensively produced in the small bowel,^[19] SBPT in SB-CD (313 min) has higher than LB-CD (278 min). Herrerias *et al.*,^[6] and Eftymiou *et al.*,^[7] found no difference between SBPT in active disease and in remission. Nevertheless, both included CD patients who have just entered clinical remission, with multiple ulcerative lesions in the small bowel and therefore still under the influence of inflammatory cytokines.

Previous studies have demonstrated that the correlation between CRP and disease activity can be inconsistent.^[20] Recently, strong correlation between CECDAI and fecal calprotectin has been described.^[21] We have found a strong correlation between clinical severity as judged by CDAI and CECDAI and objective disease parameters such as CRP, as well as WCE findings.

Until recently we knew that within the first month after entering clinical remission, large ulcers tend to heal, while smaller lesions still persist.^[7] Selecting 3 time points to perform WCE, we found that ulcerative lesions in CD subjects tend to heal gradually and aphthous ulcers persist in 50% of CD patients 6 months after entering remission. Occupational biases, leading our selection, are expected to be minor.^[22]

Since up to 50% of tertiary center CD patients may have a previous operation^[17] and at least 25% have small bowel stenosis,^[23] capsule retention rate is high (up to 30%).^[24]

Intensive treatment can relieve capsule impaction in more than 25% of the cases.^[23] Nevertheless, the majority of those cases usually require endoscopic or surgical intervention.^[25] Barium contrast studies failed to prevent capsule retention in up to 7% of CD cases, without any prior history of bowel obstruction.^[24] Second generation patency capsule seems to perform at least as effectively as radiological studies to exclude small bowel stenosis.^[26] We therefore decided to give patency capsule, before WCE. Nevertheless, we have not avoided a case of temporary capsule retention, as patency capsule was invisible in plain abdominal X-rays.

In conclusion, a high percentage of patients with active CD do not complete capsule endoscopy. Inflammatory lesions delay capsule transit through the stomach and the small bowel. In remission both GPT and SBPT are accelerated and a high percentage of patients complete the study. Nevertheless fewer lesions are found and therefore study utility is questionable. It seems that the best time to perform WCE is early after entering clinical remission and before endoscopic lesions disappear. More studies are needed to define the best time to perform WCE, as the cost of the study is rather high.

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