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Small Bowel Capsule Endoscopy in Crohn's Disease and Controls: Upper Lesions, Impact and Transit Times in a Tertiary Referral Center

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Abstract

Background and Aims: The role of Small Bowel Capsule Endoscopy (SBCE) in Crohn's Disease (CD) is debated. We aimed to investigate, in a retrospective cohort study, whether using SBCE allows a better assessment of Small Bowel (SB) lesions in CD. The gastric and SB transit times and the impact rate were evaluated in CD patients *vs.* matched non-IBD controls (C).

Methods: All SBCE performed from June 2004 to September 2010 in CD patients referring to our IBD Unit were reviewed. As controls, SBCE images from 40 non-IBD patients (C) matched for gender and age (± 5 yrs) were reviewed. The Given Pillcam SB capsule (Given, Israel) was used. Findings considered: a. CD lesions; b. Upper SB lesions; c. SBCE transit times in minutes (min); d. Impact. Data were expressed as median [range].

Results: CD group included 40 patients (19 males. age 34 [18-70]). In CD, inter individual variations were observed in terms of gastric (29 [3-182] min) and SB transit times (up to the valve: 258 [236-443] min; anastomosis: 285.5 [77-480] min). Transit times showed variations in C also (gastric: 19. [1-435] min) (p=n.s. *vs.* CD; SB: 268 [84-404] min; p=ns *vs.* CD). SBCE detected upper SB lesions in 26/40 (65%) CD, previously undetected in 21/26 (80%). Jejunal stenosis was diagnosed in 1 CD. SBCE retention was observed 1 CD and in no C (impact rate 2.5% *vs.* 0%; p=ns).

Conclusion: SBCE visualizes previously unknown upper SB lesions in a high proportion of CD patients. The impact risk limits its use in CD. The transit times using SBCE shows wide inter individual variations in both CD and non-IBD C.

Keywords: Crohn's disease; Small bowel capsule endoscopy; Non-IBD controls; Upper lesions; Upper and small bowel transit times

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Abbreviations

SBCE: Small Bowel Capsule Endoscopy; CD: Crohn's Disease; IBD: Inflammatory Bowel Disease; Non-IBD C: Non-Inflammatory Bowel Disease Controls; SB: Small Bowel; CTE: CT Enterography or Enteroclysis; MRE: MR Enterography or Enteroclysis

Introduction

Crohn's disease (CD) lesions involve the Small Bowel (SB) in almost two/third of patients. Cross-sectional imaging (MRI and CT enterography, CTE) currently represents the gold standard techniques for assessing SB lesions in CD. Both imaging techniques indeed visualize the bowel wall thickness and extraluminal lesions (i.e. abscesses, fistulae, mesenteric enlargement) related to CD [1]. Small Intestine Contrast Ultrasonography (SICUS) showed, in experienced hands, a high accuracy for assessing SB lesions in CD [2]. Despite these techniques showed a high sensitivity for detecting SB lesions related to CD, superficial mucosal lesions related to the disease may not be detected. Small Bowel Capsule Endoscopy (SBCE) is a relatively new technique able to visualize the entire SB. SBCE showed a higher sensitivity than MRE and CTE for detecting superficial SB lesions related or not to CD (i.e. aphthous ulcers) [3,4]. Major limits of SBCE at this purpose include a high detection rate (up to 13%) of superficial SB lesions also in subjects with no gastrointestinal symptoms [5].

Moreover, SBCE does not allow histological examination of the observed lesions, thus showing a low specificity [4-6]. In clinical management of Inflammatory Bowel Disease (IBD), the use of SBCE

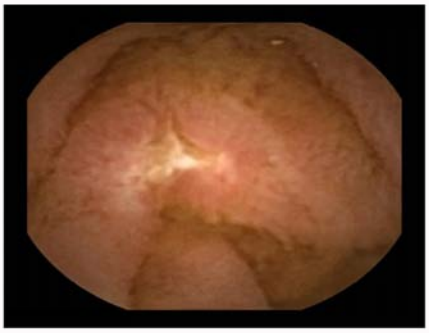

Figure 1: Apthoid ulcer of the small bowel, surrounded by normal mucosa, as visualized by SBCE in one patient with a previous diagnosis of ileal Crohn's Disease (CD), as detected by conventional techniques.

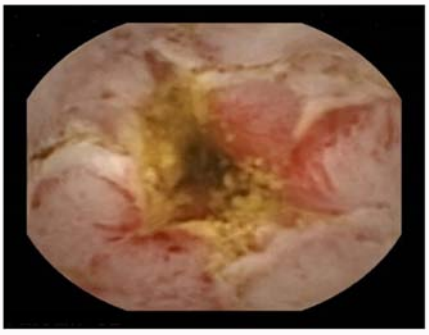

Figure 2: SBCE image showing a jejunal ulcerated stricture, requiring a long term interval before passage of SBCE though the stenosis (2 hr, 25 min), followed by local bleeding (Figure 1). No SBCE impact was observed. This jejunal stricture was not visualized by a SBFT performed in the previous 45 days. Elective SB resection was performed 6 months after SBCE, due to recurrent sub-obstructions leading to steroid-dependence.

is currently indicated in patients with symptoms highly compatible with CD involving the SB, not confirmed by conventional techniques [5]. Although SBCE does not allow the histopathological assessment of the lesions, evidences indicate that a normal finding by using SBCE shows a high negative predictive value for CD involving the SB [5]. Several diagnostic criteria and activity indexes have been proposed in order to assess the severity and extent of CD involving the SB [7-9]. The use of SBCE in the diagnosis of CD is strongly limited by retention risk, requiring surgical removal of SBCE, related to the presence of strictures and/or stenosis. Capsule retention is the most frequent complication when using SBCE, being observed in almost 1% to 2.5% of the general population [10-12]. The retention rate is increased (up to 13%) in patients with an established diagnosis of CD [13], but not in patients with suspected CD without sub/obstructive symptoms [14]. Thus, in patients with an established diagnosis of CD of the SB, it is essential to exclude the presence of strictures. Due to these observations, the usefulness of SBCE for assessing SB lesions in patients with a known diagnosis of CD has been investigated in studies including a limited number of patients. Moreover, while SBCE does not allow the exact definition of the site of the SB lesions, this technique allows the exact assessment of the time interval between SBCE ingestion and visualization of the lesions. SBCE therefore allows the measurement of the time interval between the first duodenal image and the cecum. To our knowledge, the SB transit times using SBCE in patients with CD involving the small bowel (with or without previous surgical resections) and in patients undergoing SBCE for indications different from CD is unknown.

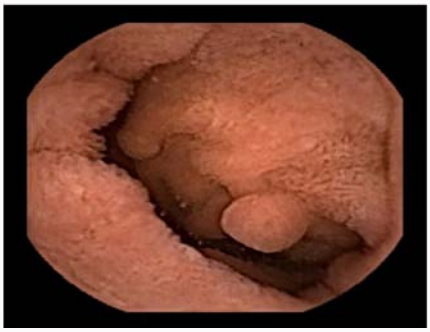

Figure 3: SBCE image showing multiple polyps of the small bowel in one non-IBD Control patient with a known diagnosis of Peutz-Jeghers syndrome.

On the basis of these observations, we aimed to investigate, in a retrospective cohort study, the usefulness of SBCE for evaluating the presence and extent of SB lesions in patients with an established diagnosis of CD. We also aimed to assess the rate of SBCE impact and inter individual variations in terms of gastric and SB transit times in CD patients compared with matched controls requiring SBCE examination for indications not related to CD. Indication for SBCE in the tested population was made according to clinical assessment and to conventional criteria [15-17].

Materials and Methods

Study protocol

In a retrospective, monocentric, cohort study, findings from all SBCE performed from June 2004 to September 2010 in CD patients referring to our IBD referral center were reviewed. In all patients, SBCE was performed in patients with a diagnosis of CD made according to conventional colonoscopy and/or radiology, with SBCE performed according to current conventional criteria and to clinical judgement [15-17]. Indication for SBCE included: assessment of recurrence, unexplained anaemia and/or suspected superficial SB lesions not detected by conventional radiology (SICUS, TCE or MRE). Inclusion criteria considered were as follows: 1. Absence of known gastrointestinal stenosis or history of sub/obstructions; 2. CD of the SB as assessed by CT-enterography/MRI-enterography, SICUS, SB Bowel Follow Through (SBFT) and/or colonoscopy during the last 6 months. Previous surgery for CD did not represent exclusion criteria, only in the absence of overt strictures/stenosis. In order to compare the SB transit times, a control non-IBD population (non-IBD C) matched for gender and age (± 5 years) was also studied. Non-IBD C included patients with a previous SBCE performed in our referral center for clinical indications different from IBD. A written informed consent to perform SBCE was given by each patient and control.

Small bowel capsule endoscopy

SBCE was performed with the Given Pillcam SB capsule system (Given Imaging Limited, Yoqneam, Israel) (16, 18) after one day of a fiber-free diet and bowel preparation (2 L oral solution of polyethylene glycol). Images were reviewed by a single gastroenterologist. In CD patients, all SBCE findings were considered for the analysis. In particular, the visualization of SB lesions compatible with CD in patients with a known diagnosis of CD were reported (i.e. aphthous ulcers, deep ulcers, erosions in the presence of aphthous and/or deep ulcers). Additional SBCE findings reported in each CD and non-IBD C included lesions compatible with CD in the upper SB. As no standard criteria for defining upper SB lesions using SBCE were available, distal SB lesions were considered lesions proximal to the

Table 1: Demographic and clinical characteristics of the 40 Crohn's Disease patients studied by Small Bowel Capsule Endoscopy (SBCE).

	CROHN'S DISEASE PATIENTS N (%)
Gender	
Males	19 (48%)
Females	21 (52%)
Smoking habits	
Yes	12 (30%)
No	20 (50%)
Ex	8 (20%)
Familial IBD	6 (15%)
NSAIDs use	0 (0%)
CD localization before SBCE	
Ileum	25 (62.5%)
Ileum-colon	2 (5%)
Colon	2 (5%)
None	11 (27.5%)
Previous surgical resections	28 (70%)
Indication for SBCE	
Post-operative recurrence	21 (52.5%)
Proximal small bowel lesions	8 (20%)
Anaemia	3 (7.5%)
Evaluation of lesions extent	4 (10%)
Highly suspected CD	4 (10%)

Abbreviations: IBD: Inflammatory Bowel Disease; NSAIDs: Non Steroidal Anti-Inflammatory Drugs; CD: Crohn's Disease; SBCE: Small Bowel Capsule Endoscopy

ileocecal valve or to the ileo-colonic anastomosis. Upper SB lesions were considered as the SB lesions proximal to these areas (jejunum, proximal ileum) [17,19]. In all patients with CD and non-IBD C, additional SBCE findings considered included the gastric transit times and the SB transit times defined as time interval between the first image of the duodenum and the first image of the colon (after the visualization of the ileo-cecal valve or the anastomosis). The transit times were expressed in minutes (min.) the impact rate was also reported in both groups.

At the end of the study, comparison was made between patients with CD and non-IBD C, in terms of gastric transit times, SB transit times and impact rate. The study was approved by the Ethic Committee of the University "Tor Vergata" of Rime, Italy.

Statistical analysis

Results were expressed as median [range]. Statistical analysis included the paired T test for comparing transit times (gastric and SB) detected by SBCE in CD patients *vs.* control population. The inter observer variation when assessing SBCE images was evaluated according to the k statistic.

Results and Discussion

Study population

From June 2004 to September 2010, SBCE was performed in 40 patients with CD (19 males, median age 34 [18-70] years), according to the above reported clinical indications. As control group, 40 non-IBD patients matched for gender and age (± 5 years) with clinical indications to perform SBCE not related to a suspected diagnosis of

Table 2: Demographic and clinical characteristics of the 40 Control patients with no Inflammatory Bowel Disease (IBD).

	CONTROL PATIENTS N (%)
Gender	
Males	18 (45%)
Females	22 (55%)
NSAIDs use	9 (22.5%)
Indication for SBCE	
Anaemia	16 (40%)
Gastrointestinal bleeding	9 (22.5%)
Diarrhoea	7 (17.5%)
Abdominal pain	4 (10%)
Peutz Jeghers syndrome	2 (5%)
Polyposis	1 (2.5%)
Bleu Rubber Nevus Syndrome	1 (2.5%)

Abbreviations: IBD: Inflammatory Bowel Disease; NSAIDs: Non Steroidal Anti-Inflammatory Drugs; SBCE: Small Bowel Capsule Endoscopy

IBD were also studied. Clinical characteristics of patients with CD and non-IBD C are summarized in (Table 1 and 2), respectively.

As shown in (Table 1), in CD group the lesions involved the ileum in 25 out of the 40 (62.5%) patients, the ileum-colon in 2 (5%), the colon in 2 (5%), while 11 (27.5%) patients showed no post-operative recurrence after surgery (including 3 patients with no recurrence after permanent ileostomy). Upper SB lesions (jejunum or proximal ileum) were also detected by conventional techniques in 5 out of these 40 (12.5%) patients. Therefore, conventional techniques detected ileal lesions related to CD in 27 out of the 40 (67.5%) patients enrolled (both the ileum- and colon in 25, the ileum only in 2). Previous intestinal resection was reported by 28 patients (70%).

SBCE findings

CD group: Among the 40 CD patients, SBCE did not visualize the colon in 10 (25%) patients, including 6 patients with previous ileal and/or colonic resection. Upper SB lesions compatible with CD were detected by SBCE in 26 (65%) CD patients. These upper SB lesions detected by SBCE were not visualized by previous conventional imaging techniques in 21 out of these 26 (80%) patients. The detection rate of upper SB lesions was significantly higher when using SBCE than conventional techniques (80% *vs.* 12.5%; $p<0.0001$).

Characteristics of these upper SB lesions, as detected by SBCE included erosions (n=2), aphthous ulcers (n=20), deep ulcers (n=3) or strictures (n=1).

SBCE detected lesions of the ileum compatible with CD in 25 out of the 40 (62.5%) CD patients and in particular, in 25 out of the 27 (93%) patients showing ileal lesions according to conventional techniques. Characteristics of the lesions visualized by SBCE included aphthous ulcers (Figure 1), deep ulcers, erosions or strictures (Figure 2).

In one patient with CD, SBCE images showed a marked jejunal ulcerated stricture, requiring a long term interval before passage of SBCE (2 hrs and 25 mins), followed by local bleeding (Figure 3). This jejunal stricture was not visualized by a previous SBFT performed 45 days before SBCE. In this patient, the presence of the previously undetected jejunal stricture determined a delayed transit time, but not SBCE impact. SBCE indeed passed through the ileostomy

within the next 48 hrs, with no abdominal symptoms. Elective SB resection was performed 6 months after SBCE, due to recurrent sub-obstructions leading to steroid-dependence. Histological analysis of the surgical sample confirmed the presence of an ulcerated jejunal stricture. Among the 40 CD patients, SBCE retention was observed in one patient (2.5%) with both ileo-colonic and ileo-ileal anastomosis. In this patient, SBCE retention did not induce any symptom, being detected by salpingography performed 3 months after SBCE, due to infertility. SBCE retention was confirmed by a plain film of the abdomen. At surgery, SBCE was detected within the "cul de sac" of the side-to-side ileo-ileal anastomosis.

In the tested CD population, the use of SBCE was followed by changes of clinical management in a very low proportion of patients (2 out of 40:5%). In one of these 2 patients a jejunal stricture was detected by SBCE, requiring surgery (see above). In the second patient, showing a post-operative recurrence with >5 aphthous ulcers (Rutgeerts' score 2) (1), SBCE detected multiple ulcers in the proximal SB, not visualized by SICUS. After SBCE, the patient was treated with azathioprine due to the extent of the lesions.

Non-IBD controls: The colon was not visualized in 8 out of 40 (20%) non-IBD patients. None of the 40 non-IBD C developed SBCE retention (retention rate in CD vs. non-IBD C: 2.5% *vs.* 0%; p=n.s.). SBCE detected SB lesions not related to CD in 8 out of the 40 (20%) non-IBD C patients. Lesions detected by SBCE in non-IBD C included: angiodysplasia (n=2; associated with erosions in 1), erosions (n=2), ulcers (n=1), multiple polyps (n=2; Peutz-Jeghers=1), multiple ulcers with bleeding (n=1). The rate of detection of upper SB lesions was significantly higher in CD (26/40; 65%) than in non-IBD C patients (8/40; 20%; p<0.0001).

Small bowel transit times in CD *vs.* non-IBD controls: Among the 40 CD patients, SBCE showed marked inter individual variations in terms of both gastric and of SB transit times (29 [3-182] and 281 [77-480] mins, respectively). When the SB transit times were considered in CD patients with or without previous intestinal resections, a significant difference was observed between the two groups in terms of gastric transit times (resected *vs.* not resected: 13 [2-80] *vs.* 20 [3-182] minutes; p=0.025;), but not in terms of SB transit times (285.5 [77-480] *vs.* 258 [236-443 minutes]; p=0.18).

Non-IBD C patients showed marked inter individual variations in terms of both gastric and SB median transit times (19.5 [1-435] and 268 [84-404] minutes, respectively). When comparing the median transit times between the whole group of 40 CD and non-IBD C patients, no significant differences were observed in terms of both gastric (p=0.08) and SB transit times (p=0.7). Differently, in the 28 CD patients with previous intestinal resection, the median gastric transit times was significantly lower than in non-IBD C (p=0.04), while no differences were observed between the two groups in terms of SB transit times (p=0.77). No significant differences were also observed when comparing the transit times between non-IBD C *vs.* CD patients with previous surgery (gastric transit times p=0.74; SB transit times p=0.33).

In CD, diffuse jejuno-ileitis is currently considered among risk factors for severe and aggressive course of the disease, requiring immune modulatory treatments [15, 16]. Superficial mucosal lesions of the SB, related to CD may not be detected by standard imaging techniques, while SBCE may visualize minor lesions in this setting [1,6]. The role of SBCE in clinical management of patients with CD is under investigation, and guidelines indicate its usefulness in patients with symptoms highly compatible with CD [1,6,16,17]. Whether the radiation-free SBCE may be useful for detecting minor upper SB lesions and whether this technique may be useful for assessing the SB transit times in not defined. In order to address this issue, in a monocentric prospective study, findings using SBCE in all patients with a diagnosis of CD made according to conventional techniques and in non-IBD C were reviewed.

The first message arising from the present study is that in our CD population, SBCE visualized upper SB lesions in a very high proportion of patients (65%), not visualized by conventional imaging techniques in almost two/third of patients. The rate of detection of upper SB lesions was indeed significantly higher using SBCE than conventional techniques. This observation from a cohort of 40 CD patients further supports the few findings at this regard [1,5,16,17]. Moreover, in the present study, upper SB lesions detected by SBCE included not only superficial lesions (i.e. erosions, aphthous ulcers), but also few established lesions (2 deep ulcers, 1 stricture). The retrospective analysis of the data represents a major limit of our study. Nevertheless, both SBCE findings (including transit times) and clinical characteristics of patients were prospectively recorded, thus allowing an appropriate analysis of the data. The use of SBCE lead to changes of clinical management in a low proportion of patients (2/40, 5%). Nevertheless, in our CD population, SBCE allowed in one patient the detection of a symptomatic jejunal stricture, not detected by conventional techniques, successfully treated with surgical resection.

Whether the finding of previously undetected upper SB lesions using SBCE implies the need to modify clinical management of CD patients needs to be determined on a case by case analysis. However, growing evidences support the need to consider not only clinical activity, but also the extent and severity of CD lesions as a target of medical treatments in these patients [16,18-21]. This issue assume particular relevance in the era of biologics, as mucosal healing is currently considered one of the targets of medical treatments [16,18-21]. These observations suggest that using SBCE may help to properly assess the extent of CD lesions, particularly in the subgroup of patients with signs and/or symptoms compatible with upper SB lesions not detected by conventional techniques. The use of SBCE has also indeed been reported to determine management changes in the majority of patients with established CD [20,22]. SBCE may also be useful to further define the natural history of CD lesions and the cause of recurrent anaemia in subgroups of patients.

In our series, asymptomatic SBCE retention was occasionally observed in one patient with side-to-side ileo-ileal anastomosis. At surgery, SBCE was localized in the ileal "cul de sac" of the anastomosis, thus supporting that in CD patients; this type of anastomosis may lead to SBCE retention even in the absence of overt strictures or stenosis. This finding also further supports the need to carefully assess indication for SBCE in CD patients, even in the absence of sub/obstructive symptoms, particularly in patients with previous intestinal resections with side-to-side anastomoses. The rate of detection of upper SB lesions in our non-IBD control population was quite high (20%), when compared to previous studies (up to 13%), However, in our control population, indication for SBCE was mostly represented by anaemia of unknown origin.

In our study, when comparing CD patients *vs.* non-IBD controls matched for age and gender, upper SB lesions were detected in a

higher proportion of CD patients, as expected (p<0.0001). The type of SB lesions detected by using SBCE appeared also quite different between the two groups, as polyps and angiodysplasia were detected only in non-IBD C s and not in CD patients. This observation, although expected, requires further investigations in larger studies.

Additional aim of the present study was to evaluate the gastric transit times and SB transit times between CD and non-IBD patients. SBCE indeed allows a quite accurate evaluation of this parameter and, by our knowledge; data at this regard are quite few, particularly for patients with CD. In our series, this analysis showed no differences between CD and non-IBD C patients, although a faster gastric transit times was observed in CD patients with *vs.* without previous intestinal resections. As expected, a marked inter individual variation was observed in terms of bot gastric and SB transit times, both in CD and in non-IBD C patients. However, possible intra-individual variations when considering these parameters were not assessed, due to the need of repeated SBCE examinations to address this issue.

Overall, the reported findings from a cohort of patients with a defined diagnosis of CD under regular follow up, adds support to the concept that SBCE is able to visualize upper SB lesions missed by conventional techniques. The clinical relevance of these findings in patients with an established diagnosis of CD needs to be determined on a patients' basis. Nevertheless, SBCE may be helpful to identify the subgroup of patients with extensive jeuno-ileiitis requiring immune modulators and also to better define the natural history of the lesions in CD.

Conclusion

The gastric transit times and SB transit times showed a marked inter individual variation, being comparable between CD and non-IBD patients. However, a faster gastric transit times was observed in CD patients with *vs.* without previous intestinal surgery for the disease. Present observations support that this additional parameter provided by SBCE may be useful for investigative purposes, including patients with previous intestinal resections for CD.

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