EXCELLENT LONG-TERM NEGATIVE PREDICTIVE VALUE OF CAPSULE ENDOSCOPY IN SUSPECTED ISOLATED SMALL BOWEL CROHN’S DISEASE

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EXCELLENT LONG-TERM NEGATIVE PREDICTIVE VALUE OF CAPSULE ENDOSCOPY IN SUSPECTED ISOLATED SMALL BOWEL CROHN’S DISEASE (Abstract): There is no unique diagnostic test for Crohn’s disease (CD), and the diagnosis of isolated small bowel Crohn’s disease (SBCD) is even more challenging, due to non-pathognomonic clinical picture and low availability of accurate exploration methods. Small bowel capsule endoscopy (SBCE) revolutionized the approach of middle gastrointestinal tract, becoming the first investigation tool when small bowel pathology is suspected. The aim of our study was to assess the value and safety of SBCE in diagnosing isolated SBCD. Materials and methods: We retrospectively studied the patients undergoing SBCE for suspected isolated SBCD, in a six-year period, including in our analysis only the patients with a minimum of 18-month follow-up period. We assessed the global diagnostic yield (DY) of SBCE, as well as its yearly variation in time over the six-year period, and the complication rate. Subsequently, analyzing follow-up data, positive and negative predictive values were assessed. Results: 78 patients were investigated by SBCE for suspected isolated SBCD, mostly men (60.3%), with age ranging from 20 to 69 years old. SBCE showed lesions compatible with the diagnosis of SBCD in 49 patients, corresponding to a specific diagnostic yield of 62.8%, while for the remaining 29 patients (37.2%), no suggestive lesions were found. Following additional investigations, three of the 49 patients initially thought as having isolated SBCD were reclassified as intestinal lymphoma, eosinophilic gastroenteritis and intestinal tuberculosis, respectively, corresponding to a positive predictive value of 93.8%. During follow-up, none of the 29 patients with negative SBCE was diagnosed with CD, corresponding to a negative predictive value of 100%. We found a progressively increase of the diagnostic yield over time (from 42.6% in the first year to 70.2% in the last year of the analyzed period), corresponding the most probably to the refinement of the indication. Conclusions: SBCE has good DY and a high positive predictive value for isolated SBCD. However, it remains a purely visual technique with no capability of taking biopsies, so final diagnosis needs confirmation by additional investigations. Nevertheless, SBCE has a 100% long-term negative predictive value, being an excellent tool for ruling out isolated SBCD. Keywords: CAPSULE ENDOSCOPY, SMALL BOWEL, CROHN’S DISEASE.
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Crohn’s disease is a chronic inflammatory bowel disease, with various phenotypes and different particularities in each individual’s clinical picture. Crohn’s disease may affect any part of the gastrointestinal tract, the most frequent being the ileocecal localization - when both terminal ileum and part of colon are involved, while in approximately one third of cases, patients have only small bowel involvement (1). As there is no unique gold standard diagnostic test for Crohn’s disease, the positive diagnosis is based on a combination of clinical evaluation, together with biological, imaging, endoscopic and histologic data (2). Moreover, due to the fact that clinical manifestations are not always pathognomonic, and that accurate exploration methods for the small bowel are not universally available, the diagnostic of isolated SBCD is even more challenging.

However, the introduction into the clinical practice of the capsule endoscopy, which has become the first investigation tool when small bowel pathology is suspected, has revolutionized the approach of the middle gastrointestinal tract (3). SBCE is nowadays consensually indicated in several IBD situations, as suspected Crohn’s disease, evaluation of extension and activity of known CD, assessing the response to therapy, identifying the postoperative CD recurrence, and evaluation of unclassified colitis (4). The use of SBCE is justified by its advantages compared to other investigation methods; firstly, the safety and the non-invasiveness versus enteroscopy, and the superior diagnostic yield compared to imaging methods as enteroclysis, computed tomography-enterography, and magnetic resonance-enterography for incipient lesions (5-7). Nevertheless, SBCE has its limits, the main one being the inability of taking biopsies. Thus, SBCE remains a visual technique, and in some cases, for arriving at the final diagnosis, supplementary investigations might be necessary. Consequently, the discriminative power of SBCE as a single technique for exploring the small bowel is a question of debate. In this context, we aimed to assess the value of SBCE in diagnosing isolated SBCD. In the same time, considering that CD is one of the conditions predisposing patients to the retention risk, we also aimed to evaluate the safety of SBCE in investigating patients with suspected isolated SBCD.

MATERIAL AND METHODS

Patients

We retrospectively studied the patients undergoing SBCE for suspected isolated SBCD, in a six-year period (January 1st 2016 – December 31st 2021), in the Institute of Gastroenterology and Hepatology. We included in our analysis patients with clinical, biologic and/or imaging suspicion of CD, with no diagnostic findings at conventional ileocolonoscopy, who were followed after SBCE exploration for at least 18 months period.

Methods

We assessed the performance parameters of SBCE, as well as the complication rate.

The performance parameters were the diagnostic yield (DY), defined as number of capsule endoscopy exams with positive findings from the total number of investigations, the positive prediction value (PPV), defined as ratio of patients truly diagnosed as positive to all those who had positive results, and the negative predictive value (NPV), defined as the ratio of subjects without disease to all those who had
negative test results. Both PPV and NPV were retrospectively assessed, by analyzing follow-up data.

All patients were investigated after contraindications were excluded, and every patient signed the informed consent for SBCE prior to the investigation. The diagnostic work-up was conducted following the actual guidelines for the use of SBCE. Before SBCE, all patients underwent colonoscopy, which did not CD lesions.

The preparation was made with two liters of polyethylene-glycol the evening before the procedure, and the patients fastened overnight. The third-generation endoscopic capsule for small bowel examination (PillCam SB3) manufactured by Given Imaging, Yoqneam, Israel, was used. Interpretation of data was made with RAPID™ reader software.

The diagnostic of Crohn’s disease was sustained according to Mow’s criteria – more than three ulcerations, in the absence of nonsteroidal anti-inflammatory drugs (NSAIDs) administration (8). Anyway, patients with recent (four weeks or less) history of NSAIDs use were excluded from the analysis. For all the patients with Mow’s criteria fulfilled, the Lewis score (LS) were afterwards assessed. The Lewis score is an incorporated software algorithm which sums up the points assigned to three characteristic findings – strictures, ulcers, fistula in the three segments of the small bowel, and classify the severity of inflammation into three categories: insignificant, mild or moderate-to-severe (9).

Complications of CE were noted. Incomplete examinations were not included in the study.

Statistical analysis was conducted using the SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients’ characteristics

In the analyzed six-year period, 78 patients underwent SBCE for suspected isolated CD. Their characteristics are presented in the first table.

| TABLE I. Clinical characteristics of patients, findings at SBCE and follow-up data |
|---------------------------------|---------------------------------|
| Total number of patients = 78   |                                 |
| Age, years, mean + SD           | 43 ± 12.5                       |
| Range, years                    | 20-69                           |
| Gender ratio                    | 31/47                           |
| Women/Men, n (%)                | (39.7%/60.3%)                   |
| SBCE exam results               |                                 |
| Positive for CD, n (%)          | 49 (62.8%)                      |
| Negative for CD, n (%)          | 29 (37.2%)                      |
| Follow-up data                  |                                 |
| CD confirmed                    | 46/49 (93.8%)                   |
| CD ruled out                    | 29/29 (100%)                    |

Diagnostic yield

SBCE showed lesions compatible with the diagnosis of CD in 49 patients, corresponding to a diagnostic yield of 62.8%. For the remaining 29 patients (37.2%), no suggestive lesions were found, and consequently CD was ruled out.

We found a progressively increase of the diagnostic yield over time (from 42.6% in the first year to 70.2% in the last year of the analyzed period), corresponding the most probably to the refinement of the indication.

Lewis score

For the inflammation quantification, the Lewis score was used; 22 patients presented a score between 135 and 790, being classified as having mild inflammation, while the remaining 27 patients had a score > 790 points, corresponding to moderate-to-severe inflammation.
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Positive predictive value
Analyzing follow-up data, we found that three of the 49 patients initially considered as having isolated SBCD were consequently further explored, and eventually a different diagnosis was made, corresponding to a positive predictive value of 93.8%. Out of the three patients, one patient was diagnosed with eosinophilic enteritis, one patient was confirmed as having intestinal T-cell lymphoma, and one patient had intestinal tuberculosis. All the three patients had a baseline moderate-to-severe inflammation, according to the LS.

Negative predictive value
During the follow-up period, none of the 29 patients with negative SBCE exam was diagnosed with CD, corresponding to a negative predictive value of 100%.

Complications
One case of capsule retention was noted (retention rate 1.28%), due to an ileal stricture in a patient with small bowel CD. Medical treatment was not successful, so the patient underwent surgery; stricturoplasty, as well as removal of retained capsule, were performed.

DISCUSSION
SBCE has emerged as a valuable tool for the diagnosis of CD. The ability to directly visualize the intestinal mucosa allows a comprehensive evaluation of the small bowel. Because CD may involve only small bowel segments, SBCE is a particularly valuable method in cases where other diagnostic methods, such as conventional endoscopy, are not contributive.

Studies have reported diagnostic yields of SBCE ranging from 50% to 80%, generally superior compared to other diagnostic modalities (5, 7, 10, 11). Ileocolonoscopy with biopsy remains the gold standard for the diagnosis of CD (4), but if it is normal, it must be followed by the SBCE in the absence of obstruction. A large meta-analysis showed superiority of SBCE compared to small bowel follow-through (52% vs. 16%), computed tomography-enterography (68% vs. 21%), and ileocolonoscopy (47% vs. 25%) (7). SBCE also proved its significantly higher sensitivity for incipient lesions, especially in the jejunum and ileum, compared to magnetic resonance-enterography, as a recent Spanish study showed (77% vs. 48%) (12).

Our study showed a global diagnostic yield for isolated CD of 62.8%, proving the value of SBCE in this particular type of CD patients, with exclusive small bowel involvement, where conventional endoscopy has limited role. The yearly analysis of the DY showed a higher DY over time (up to 70.2%), which we interpret as refinement of the indication.

Even if SBCE is a sensitive tool for mucosal abnormalities, one important limitation consists in the lack of definitive diagnostic criteria for CD. Mow’s criteria are generally used for diagnosis, while other scoring systems, as Lewis score and, more recently, the Capsule Endoscopy Crohn’s Disease Activity Index, are useful especially for disease monitoring and treatment guidance (13). Moreover, for suspected SBCD, it has as drawback a relative lack of specificity. In our analysis, three patients initially considered as having isolated SBCD were further explored and reclassified. They underwent SBCE for suspected CD based on their clinical picture; abdominal pain, chronic diarrhea, weight loss and anemia are overlapping symptoms for CD, eosinophilic enteritis, intestinal tuberculosis and intestinal lymphoma. SBCE findings consisted in oedema, hyperemia, erosions and superficial and deep ulcerations, which may appear
both in CD and in other inflammatory or non-inflammatory conditions. All the three patients had a baseline moderate-to-severe inflammation, according to the LS. Notably, all the three patients had a baseline moderate-to-severe inflammation, according to the Lewis score; however, the most appropriate role of the Lewis score is monitoring established CD. Additionally, imaging data may be similar; for both eosinophilic gastroenteritis and lymphoma, entero-CT showed similar SB wall modifications. Following the final diagnosis, made by device-assisted enteroscopy with biopsy, different therapeutic strategies were applied.

Indeed, a main limitation of SBCE is its inability of taking biopsies, while a definite diagnostic of CD would require, in order to be considered beyond any doubt, histologic confirmation. Small bowel ulcerations are not pathognomonic for CD; even they are a common finding in CD and the diagnostic criteria rely on their presence, they however may appear in a variety of other small intestine disorders, such as: infectious enteritis - like intestinal tuberculosis or cytomegalovirus infection, NSAID enteropathy, eosinophilic enteritis, ischemic enteritis, or intestinal lymphoma (14). Moreover, mucosal erosions may be found even in approximately 10% of healthy subjects (15). Precautions must be taken before SBCE, such as stopping NSAIDs at least four weeks before the investigation. Also, sometimes, further evaluation modalities must be considered. Enteroscopy with biopsy is a complementary investigation, which could ensure a final diagnosis. SBCE acts as a non-invasive evaluation tool, guiding the decision and the access way for a further enteroscopy. Current guidelines recommend upper or lower device-assisted enteroscopy after SBCE, allowing targeted biopsies.

In our study, follow-up data showed that none of the patients with negative SBCE exam was diagnosed afterwards with CD. Basically, normal SBCE can rule out CD with maximum confidence. As SBCE is recommended as a first line test for SB pathology suspicion, its capability to exclude CD makes it a very reliable tool in CD work-up.

SBCE is generally considered a safe technique; however, retention can occur, if narrowing, stricture, or obstruction of a certain intestinal segment exists. Other complications are extremely rare. The retention rate varies according to the indication, from 1%-2% in patients with suspected CD, up to 10-13% in patients with known CD (16). In our study, the retention rate was 1.28%, similar to other reports. Nevertheless, concerning capsule retention in suspected CD, several comments should be made. Apart known strictures, all other contraindications may be considered relative, and even in the event of retention with no response to conservative management, surgery will solve both the capsule impaction and the obstructive lesion, allowing also a definite histologic diagnosis. Patency capsule is indicated in order to confirm the permeability of gastrointestinal tract only when there is a clinical suspicion of small bowel obstruction, otherwise it is not routinely advised (4). Showing a retention rate close to that reported for obscure gastrointestinal bleeding, which remains the most common indication - pooled retention rate 1.2%, as reported by a systematic review by Liao et al (17), SBCE in suspected CD appears to be a safe technique.

**CONCLUSIONS**

SBCE has a good diagnostic yield and a good positive predictive value for isolated
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SBCD. It is a safe first line tool in suspected CD, with low retention rate. However, it is a purely visual technique with no capability of taking biopsies. Hence, its results should be interpreted in conjunction with other relevant clinical data, and the final diagnosis needs confirmation by additional investigations. Definitive diagnostic criteria for CD are still lacking. Nevertheless, SBCE showed a very high clinical accuracy for excluding CD. With a 100% long-term negative predictive value, SBCE emerges as an excellent tool for ruling out isolated SBCD.

CONFLICT OF INTEREST AND FUNDING

All the authors declare no conflict of interest. No funding was received for this study.

REFERENCES