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Published in: Endoscopy International Open

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Morpho-functional evaluation of small bowel using wireless motility capsule and video capsule endoscopy in patients with known or suspected Crohn’s disease: pilot study

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Background and study aims: SmartPill® (Given Imaging Corp., Yoqneam, Israel) is an ingestible, non-imaging capsule that records physiological data including contractions and pH throughout the gastrointestinal tract. There are scarce data looking at SmartPill® assessment of patients with known/suspected small-bowel Crohn’s Disease (CD). This pilot study aims to investigate feasibility and safety of SmartPill® to assess gut motility in this group.

Patients and methods: Over 1 year, patients with known/suspected CD, referred for small-bowel capsule endoscopy (SBCE), were invited to participate and 12 were recruited (7 female, 5 male, mean age 44.2 ± 16.6 years). They underwent hydrogen breath test to exclude small-bowel bacterial overgrowth, patency capsule (Agile®), and provided stool samples for fecal calprotectin (FC). Patients ingested PillCam®SB2 and SmartPill® 4 hours apart. Using unpublished data, 33 healthy controls also were identified for the study. P < 0.05 was considered statistically significant.

Results: Of the 12 patients enrolled, 10 underwent complete SmartPill® examination (1 stomach retention, 1 dropout). PillCam® was complete in 10 (1 dropout, 1 stomach retention). Mean fecal calprotectin was 340±307.71 mcg/g. The study group had longer transit times and lower gut motility index than did the controls. The difference in motility appears to be statistically significant (P < 0.05). Longer transit times for SmartPill® (not statistically significant) may have been due to different specifications between the capsules. Limitations included transient Smartpill® signal loss (5/10 studies).

Conclusions: This is the first pilot to attempt combining SBCE and SmartPill® to assess small-bowel CD. Data on motility in CD are scarce. Multimodal information can provide a clearer clinical picture. Despite concerns about capsule retention in CD patients, SmartPill® seems safe for use if a patency capsule is employed beforehand.

Introduction

The wireless motility capsule (WMC) (SmartPill®; Given Imaging Corp., Yoqneam, Israel) is a single-use, ingestible device [1, 2]. With dimensions 26.8 × 11.7 mm, it is slightly bulkier than its imaging counterpart (PillCam®SB Medtronic, Minneapolis, USA). SmartPill® records intraluminal pH, pressure and temperature as it is propelled through the gastrointestinal tract. Hence, the WMC is capable of providing gut motility parameters (i.e. gastric transit time [GTT], small-bowel transit time [SBTT], colonic transit time [CTT] and whole gut transit time [WGTT]) non-invasively. The American and European Neurogastroenterology & Motility Societies recommend the use of WMC to assess suspected gastroparesis, suspected small-bowel (SB) dysmotility and/or CTT in chronic constipation [3].

Data are scarce on the motility patterns in patients with known or suspected Crohn’s disease (CD). Furthermore, the use and clinical validity of the WMC has not been evaluated in this patient group. It is envisaged that future wireless investigation platforms for the digestive tract will be multimodal and versatile, and therefore able to incorporate imaging information with physiological or biochemistry data such as fecal calprotectin (FC), hemoglobin and gas constituents of the gastrointestinal tract. Such combination data could be useful in the investigation and management of patients with CD. For instance, orocecal transit time has been found to be prolonged in CD patients for various reasons including SB bacterial overgrowth (SBBO) whereas SBTT may conversely be shortened in CD patients following ileocolic resection; this would affect absorption of medications and should ideally be taken into
account during drug design [4]. Therefore, we designed a pilot study to investigate whether WMC examination is feasible and safe in the assessment of gut motility in patients with known or suspected CD, and its utility compared to conventional video capsule endoscopy.

**Patients and methods**

**Patient recruitment and study protocol**

Consecutive patients with known or suspected CD (FC > 200 μg/g), referred for SB evaluation with small-bowel capsule endoscopy (SBCE), were invited to participate in this study. The inclusion & exclusion criteria of the study are summarized in **Table 1**. Patients who accepted the invitation and consented to participate were invited for a lactulose hydrogen breath test for exclusion of SB bacterial overgrowth (SBBO) and were provided with a kit for stool sample collection and FC measurement (CALPROLAB™ ELISA (ALP), Calpro AS, Lysaker, Norway; reference range < 50 μg/g). Those with a positive breath test, indicating SBBO, were excluded. Patients with negative SBBO breath test were invited to return a stool specimen and attend for a SB patency check with the AGILE® capsule (Given Imaging Corp., Yqneam, Israel).

The detailed flowchart of the study design is presented in **Fig. 1**. Patients ingested the PillCam®SB, followed 4 hours later, by the SmartPill®. The technical characteristics of the two capsules used (PillCam®SB and SmartPill®) are detailed in **Table 2**.

**Data collection**

Data were downloaded from the recorders to the relevant workstations and analyzed using proprietary software (RAPID® for PillCam®SB and semi-automated pressure analysis software, MotilG® [Given Imaging Corp] for SmartPill®). For the latter, results are presented in both graphical and statistical forms. PillCam® data include gut transit times and SB findings. Inflammation levels were quantified using the Lewis score (LS), which has been devised to objectively report SB inflammation in SBCE. SmartPill® data examined in this study were pH, transit times (GTT, SBTT, CTT and WGTT) and motility index (MI) per segment, where MI = Ln (sum of pressure amplitudes × number of contractions + 1). The data acquired from the study group were compared to historical controls (healthy individuals with no known pathology obtained from unpublished data), used to establish the normal range for segmental and total gut transit times.

**Statistical analysis**

Microsoft Excel (© 2015 Microsoft) and StatsDirect (StatsDirect Ltd, Altrincham, UK) software were used for statistical analysis. A two-tailed Mann-Whitney U test was used for comparison of the study and control groups. Linear regression was used to establish any correlation between motility indices and FC or LS. *P* values < 0.05 were considered statistically significant.

The study was supported by a defined grant by Given Imaging Ltd (ESGE- Given Imaging Research grant 2011) and approved by the local ethics committee (ref. 12/SS/0013).

**Table 1**  Inclusion and Exclusion Criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Age &gt; 18 years</td>
<td>– Pregnancy or lactation</td>
</tr>
<tr>
<td>– Known diagnosis of CD, being referred for (re-)assessment of extent &amp; severity of SB inflammation</td>
<td>– Swallowing difficulties or frailty</td>
</tr>
<tr>
<td>– Suspected CD with FC &gt; 200 μg/g</td>
<td>– Known SB strictures</td>
</tr>
</tbody>
</table>

**Abbreviations**: CD, Crohn’s disease; DM, diabetes mellitus; FC, fecal calprotectin; ICD, implantable cardioverter defibrillator; PC, patency capsule; SB, small-bowel; pts, patients

**Table 2**  Comparison between specifications of PillCam® SB2 and SmartPill®.

<table>
<thead>
<tr>
<th>Specifications</th>
<th>PillCam® SB2</th>
<th>SmartPill®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (mm)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Battery life</td>
<td>8 h</td>
<td>5 days</td>
</tr>
<tr>
<td>Mode of data transmission</td>
<td>Ultra-high frequency band radio telemetry</td>
<td>Radiofrequency-based</td>
</tr>
</tbody>
</table>

**Results**

Over a 12-month period (2012), 19 patients were recruited. Three patients were excluded because their previous history included a known strong functional component to their symptoms that could affect gut motility independently of CD, including irritable bowel syndrome, chronic idiopathic intestinal pseudo-obstruction and cyclic vomiting. Another four patients, referred for SBCE on suspicion of CD, were also excluded because their FC levels were < 200 μg/g. Twelve patients completed the study (7 female/5 male; mean age 44.2 ± 16.6 years). **Fig. 2** shows the number of patients recruited, dropouts, and complete/incomplete data sets obtained. Clinical characteristics and per patient study results are tabulated in detail in **Table 3**. The differences in the motility of the study group vs. the control group are depicted in **Table 4**. Patients in our study had longer transit times and significantly lower gut motility when compared to the control group, **Fig. 3** and **Fig. 4**.

The motility index (MI) in the stomach, SB and colon was significantly lower in patients with CD, as compared with controls, and this was statistically significant (*P* < 0.05) for all motility indices measured throughout the gut. The total transit time for the WMC was longer compared with the SBCE, which could be attributed to the differences in the capsules’ specifications as detailed in **Table 2** [1, 5, 6] and the difference in capsule density, **Fig. 5** [7, 8]. The distribution of WGTT, FC and LS for those study subst-
Table 3  Summary of clinical characteristics and findings of patients in our study.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Indication</th>
<th>MS (if known CD)</th>
<th>FC (μg/g)</th>
<th>SBCE findings</th>
<th>LS</th>
<th>MotiGI® report</th>
<th>TT (min)</th>
<th>pH</th>
<th>MI (segmental)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total time; GTT; SBTT (min)</td>
<td></td>
<td>WBT; GTT; SBTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total time</td>
<td></td>
<td></td>
<td>Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Findings</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>M</td>
<td>Known CD</td>
<td>A2 L1 B1</td>
<td>60</td>
<td>546; 125; 205</td>
<td>135</td>
<td>Signal loss, long GTT of SBCE but not WMCs</td>
<td>1667; 226; 141</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>Known CD</td>
<td>A1/2 L1 B1</td>
<td>–</td>
<td>516; 36; 242</td>
<td>0</td>
<td>Generally prolonged transit times, poor motility</td>
<td>6620; 2577; 288</td>
<td>Gastric 1.4 SB 7.2</td>
<td>Gastric 16.75 Duo 11.60 SB 15.18 Caecum 12.19</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>F</td>
<td>Known CD</td>
<td>A3 L1 B1</td>
<td>590</td>
<td>683; 28; 552</td>
<td>3810</td>
<td>Prolonged transit time</td>
<td>7161; 1096; 638</td>
<td>n/a</td>
<td>Gastric – Duo 12.51 SB – Caecum 14.17</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>F</td>
<td>Known CD</td>
<td>A2 L3 B1 p</td>
<td>Insuff</td>
<td>n/a</td>
<td></td>
<td>High gastric pH, 7pt on PPI</td>
<td>2686; 867; 240</td>
<td>Gastric 5.4 SB 7.1</td>
<td>Gastric 16.3 Duo 9.89 SB 16.24 Caecum 14.72</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>F</td>
<td>Known CD</td>
<td>A7 L1 B1</td>
<td>Insuff</td>
<td>857; 77; 252</td>
<td>5160</td>
<td>Generally low motility</td>
<td>1956; 798; 447</td>
<td>Gastric 1.1 SB 7.2</td>
<td>Gastric 14.65 Duo 9.19 SB 14.16 Caecum 12.00</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>Known CD</td>
<td>A2 L3 B1</td>
<td>80</td>
<td>436; 65; 342</td>
<td>450</td>
<td>Signal loss</td>
<td>1609; n/a; n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>F</td>
<td>Known CD</td>
<td>A2 L3 B1</td>
<td>290</td>
<td>384; 19; n/a</td>
<td>0</td>
<td>WMC not done – dropout</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>F</td>
<td>Known CD</td>
<td>A2 L3 B1</td>
<td>–</td>
<td>410; 10; 254</td>
<td>0</td>
<td>Signal loss, rapid transit time</td>
<td>808*; 233; n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>F</td>
<td>?CD</td>
<td>NA</td>
<td>970</td>
<td>369; n/a; n/a</td>
<td>n/a</td>
<td>Data loss, CR</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>M</td>
<td>?CD</td>
<td>–</td>
<td>320</td>
<td>517; 31; 169</td>
<td>280</td>
<td>Low motility, acidic SB</td>
<td>1312; 167; 192</td>
<td>Gastric 1.2 SB 6.4</td>
<td>Gastric 11.58 Duo 11.41 SB 15.98 Caecum 14.61</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>M</td>
<td>?CD</td>
<td>–</td>
<td>110</td>
<td>234; 33; 188</td>
<td>450</td>
<td>Signal loss but normal transit of WMC</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>F</td>
<td>?CD</td>
<td>–</td>
<td>300</td>
<td>439; 14; 327</td>
<td>450</td>
<td>High gastric pH, very long colon transit</td>
<td>6650; 142; 252</td>
<td>Gastric 3.7 SB 6.6</td>
<td>Gastric 10.26 Duo 11.31 SB 15.77 Caecum 11.97</td>
</tr>
</tbody>
</table>

Abbreviations: CD, Crohn’s Disease; CR, capsule retention; Duo, duodenum; FC, fecal calprotectin; GTT, gastric transit time; LS, Lewis score; MI, motility index; MS, Montreal score; PPI, proton pump inhibitor; SB, small bowel; SBCE, small-bowel capsule endoscopy; SBTT, small-bowel transit time; TT, transit times; WBT, whole-bowel transit time; WMC, wireless motility capsule

* In the case of patient 8, WBT was taken as time to excretion of capsule in ileostomy.
Table 4 Comparison of results from our patients vs controls. For our patients, some results were not available for all patients, therefore N is given where n = number of patients for whom results were available.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>7F, 5M</td>
<td>15F, 18M</td>
<td></td>
</tr>
<tr>
<td>Average Age ±SD</td>
<td>44.25 ±16.66 years</td>
<td>40.85 ±16.28 years</td>
<td></td>
</tr>
<tr>
<td>FC (μg/g)</td>
<td>340 ±107.71 (n = 8)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>1073.5 ±1835.5 (n = 10)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>GTT (min)</td>
<td>763.25 ±821.47 (n = 8)</td>
<td>249.61 ±167.47</td>
<td>0.09</td>
</tr>
<tr>
<td>SBTT (min)</td>
<td>314 ±171.99 (n = 7)</td>
<td>288.81 ±107.74</td>
<td>0.89</td>
</tr>
<tr>
<td>WBTT (min)</td>
<td>3385.44 ±2621.03 (n = 9)</td>
<td>1988.67 ±972.99</td>
<td>0.82</td>
</tr>
<tr>
<td>Gastric pH</td>
<td>2.56 ±1.92 (n = 5)</td>
<td>1.64 ±0.89</td>
<td>0.35</td>
</tr>
<tr>
<td>SB pH</td>
<td>6.9 ±0.37 (n = 5)</td>
<td>7.16 ±0.45</td>
<td>0.17</td>
</tr>
<tr>
<td>Gastric MI</td>
<td>13.91 ±2.88 (n = 5)</td>
<td>52.00 ±32.68</td>
<td>0.002</td>
</tr>
<tr>
<td>Duodenal MI</td>
<td>10.99 ±1.22 (n = 6)</td>
<td>90.27 ±76.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>SB MI</td>
<td>14.55 ±1.92 (n = 5)</td>
<td>122.48 ±65.90</td>
<td>0.0004</td>
</tr>
<tr>
<td>Cecal MI</td>
<td>13.28 ±1.35 (n = 6)</td>
<td>108.58 ±121.10</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Abbreviations: FC, fecal calprotectin; GTT, gastric transit time; LS, Lewis score; MI, motility index; SB, small bowel; SBTT, small-bowel transit time; WBTT, whole-bowel transit time

Fig. 1 Summary of study protocol.

Patency test: PillCam® patency capsule (Given Imaging Corp) ingested with 10mg liquid domperidone

30 h

Patency check with proprietary handheld scanner

Capsule present

Outpatient abdo plain film to confirm excretion or retention

Capsule absent

5–7 days before test: Discontinue the following

(a) medications that alter gastric pH
(b) medications that alter GI motility

Proton pump inhibitors, H2 antagonists, antacids
Prokinetics, antiemetics, anticholinergics, laxatives

Day before test: Strict liquid diet, no bowelprep

Day of test

Pillcam® ingested

4 h

SmartBar®* ingested followed by SmartPill®

* standardised cereal bar of known caloric and nutritional content

Communication established between receiver and SmartPill®:

pH < 4 indicating capsule in stomach

Patients left unit with instructions to:

- Fast for 6h before resuming normal food and drink intake
- Record events including meals, sleep and bowel movements

After each bowel movement

Wait for 1 min before flushing the toilet, then check data receiver

Loss of signal connection between capsule and data receiver

Data receiver returned
19 patients recruited over 1 year: Consecutive patients referred for SBCE with the indications of CD or ?CD

- Excluded: 3 patients: strong functional history
- Excluded: 4 patients: FC < 200 μg/g in suspected CD

12 included in final study

- 2 incomplete studies:
  - 1 patient did not undergo Smartpill®
  - 1 patient had capsule retention in stomach

10 completed studies as per protocol

- 5 incomplete data sets due to data loss

5 complete studies with full data sets

Fig. 2 Recruitment process for this study.

Discussion

This pilot study is the first to attempt dual use of SBCE and WMC in assessment of patients with known or suspected CD. Currently, diagnosing CD requires a clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations [9]. To date, the value of SBCE in the investigation of CD has already been established [10]. A previous study [11], in which cine magnetic resonance enterography (MRE) was employed in addition to the regular MRI protocol, found that imaging areas of altered gut motility helped to detect more CD-specific findings. Other studies have shown that CD is associated with delayed gastric emptying, possibly due to inflammation [12]. Therefore, addition of motility data in this setting could be of use.

Fig. 3 Comparison of transit times between study group and controls.

Abbreviations: Ctrl, controls; GTT, gastric transit time; SBTT, small-bowel transit time; WBTT, whole bowel transit time

Fig. 4 Comparison of motility index between study group and controls.

Abbreviations: Ctrl, controls; duo, duodenum; MI, motility index; SB, small bowel
**Fig. 5** Floating characteristics of Pillcam SB2 (left) and Smartpill (right) submerged in 400 mL sterile water for irrigation.

**Fig. 6a** (see above) Distribution of WBTT, FC and LS for patients in our study for whom the relevant data sets were available. Each plot point represents a patient in our study with the numbers corresponding to patient numbers in Table 3. **Abbreviations:** FC, fecal calprotectin; LS, Lewis score; WBTT, whole bowel transit time

**b** Linear regression of FC against motility indices for patients in our study for whom the relevant data sets were available.

**c** Linear regression of LS against motility indices for patients in our study for whom the relevant data sets were available.
[2,13], especially when first-line investigations are inconclusive. Compared to the traditional method of assessing gastrointestinal motility with scintigraphy/radio-opaque markers, WMC is not associated with any radiation exposure. Concurrent use of SBCE and WMC shows how multimodal information can provide information not only on the mucosal appearances of patients with CD but also physiological motility data. However, that needs to be balanced against the risk of capsule retention, a feared complication in patients with CD. In our study, there was one case of stomach retention of the capsule, which occurred despite patency check with follow-up plain abdominal x-ray where the patency capsule had been reported to be in the large bowel. Limited CT scanning post-patency may be more useful in these patients [14]. Our patients had significantly longer transit times compared to the controls (P<0.05 for all parameters measured) (Table 4). However, statistical significance should be interpreted with caution given the small sample size. Other limitations of this pilot study include potential selection bias, as patients with significant inflammation given the small sample size. Other limitations of this pilot study include potential selection bias, as patients with significant inflammation given the small sample size. However, statistical significance should be interpreted with caution given the small sample size. Our patients had significantly longer transit times compared to the controls (P<0.05 for all parameters measured). This can be seen in other studies that have tried to understand and maximize use of the motility information, the development of a simplified interpretation system is necessary. Despite concerns about capsule retention in patients with CD, our study suggests that the SmartPill® seems generally safe for use in these patients, although use of a patency capsule is recommended beforehand.

Competing interests: Dr. Koulaouzidis has received a research grant from ESGE Given Imaging.

Acknowledgements

The study was supported by a defined grant by Given Imaging Ltd (ESGE- Given Imaging Research grant 2011).

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