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DOI: 10.17235/reed.2020.7196/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:

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Pan-enteric capsule for bleeding high-risk patients. Can we limit endoscopies?

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Received: 30/04/2020
Accepted: 22/9/2020
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Conflict of interest: Cristina Carretero has received consultant and speaker’s fees from Medtronic.

ABSTRACT

Introduction: obscure gastrointestinal bleeding is defined as bleeding from a source that cannot be identified on upper or lower gastrointestinal endoscopy and capsule endoscopy is the next step in these patients. Some patients may be unsuitable for conventional endoscopy and performing a capsule panendoscopic test as a first line procedure might potentially reduce the number of endoscopies and their subsequent risk.

Aim: to analyze our experience with capsule endoscopy in the bleeding setting.

Methods: the first 100 panendoscopic capsule procedures performed in our center from August 2011 until December 2016 were retrospectively reviewed.
**Results:** positive findings were observed in 61.2% of patients; 46.26% had a previous negative gastroscopy and the capsule detected small bowel lesions in 67.7% and colonic findings in 80.64%. Taking into consideration that our population were high-risk patients (mainly because of comorbidities) and that we used up to 45 ml of sodium phosphate, sodium, potassium and creatinine changes were analyzed before and after procedure. The mean “before” values were 140.68, 4.04 and 1.36, respectively. The mean “after” values were 140.28, 3.9 and 1.35 (p = n.s.). According to our findings, no other endoscopic studies would be needed in 64.5% of patients with negative gastroscopy. According to capsule results, conventional endoscopy could have been avoided in 68.6% of cases.

**Conclusion:** panendoscopy with a capsule may be useful and safe in bleeding high-risk patients, by selecting those who need therapeutic endoscopy, avoiding up to 68.6% of diagnostic endoscopies in our series.

**Keywords:** Gastrointestinal bleeding. Capsule endoscopy. Colon capsule. Obscure gastrointestinal bleeding.

**INTRODUCTION**
Obscure gastrointestinal bleeding (OGIB) represents more or less 100 episodes per 100,000 persons per year (1) and it can be defined as any bleeding from the gastrointestinal tract that persists or recurs after a negative esophagogastroduodenoscopy (EGD) and colonoscopy. In this setting, small bowel (SB) capsule endoscopy is considered to be the next step and has proven its efficacy and diagnostic yield, especially when performed as soon as possible (2). Thus, in our center we usually perform EGD and colonoscopy on the same day when facing gastrointestinal bleeding (occult or overt). If these procedures are negative, then a small bowel capsule endoscopy is performed in less than 14 days, although we generally do it in the next three days.

Furthermore, since 2006 we were able to explore the colon with the PillCam® COLON platform (PillCam® COLON was launched in 2006 and PillCam® COLON2 in 2011) and this platform not only allows the visualization of colonic images but also SB images.
Thus, a complete pan-enteric visualization can be achieved. This may be useful to assess inflammatory bowel disease (IBD) activity and extent, for obscure gastrointestinal bleeding with a previous incomplete colonoscopy and for patients with anemia undergoing colon capsule endoscopy (CCE) to screen for a colonic pathology (3).

Since 2011, we offer pan-enteric capsule endoscopy in our service portfolio and is more frequently requested for patients with suspected/known gastrointestinal bleeding, especially those who are unsuitable or at high risk for conventional endoscopy. After almost ten years of experience, we wondered if performing a pan-enteric capsule test in this population might potentially reduce the number of endoscopies and their subsequent risk.

**Aim**

The purpose of this observational study was to assess the feasibility of a capsule pan-enteric test as a first line procedure and to determine whether it may change patient management, especially regarding conventional endoscopy.

**PATIENTS AND METHODS**

**Patients**

Ethical approval was obtained from the Medical Ethical Committee to retrospectively review our first 100 panendoscopic capsule procedures performed (August 2011-December 2016).

The inclusion criteria were all patients that underwent a pan-enteric capsule endoscopy. All were 18 years old or more and gave their consent to the procedure. Exclusion criteria were patients with occlusive symptoms or patients who were unable to complete the bowel prep required for the procedure. Figure 1 shows the patient inclusion flowchart:

demographical data, previous endoscopic procedures, hospitalization, previous transfusion needs, blood tests before/after bowel preparation, capsule transit times (gastric, SB and colon), SB findings, colon findings and other findings (esophagus or stomach) and complications were collected.
The main outcome was finding a bleeding source in the capsule study that may potentially decrease the number of endoscopic procedures to those that might be therapeutic.

**Capsule**

All capsule procedures were performed with the PillCam® COLON2 (C2) system. The C2 has two optical domes, each one with an angle view of 172°. It has an adaptive frame rate (AFR) that becomes active once the capsule automatically detects its location in the SB. The AFR ranges from four frames per second (when the capsule is stationary or circulates at a very low speed) to 35 frames per second when the capsule is in motion. Once the capsule is activated, it starts blinking at four frames/second and three minutes later, the frame rate decreases to 14 frames/minute to save battery life. However due to technical issues, SB recognition (and AFR activation) may be delayed up to 30 minutes from the real SB entrance (4). For panendoscopic purposes, the AFR can be manually activated. Therefore, the whole gut can be explored at 4-35 frames/second, offering the reader images from mouth to the anus. In our center, we manually activate the AFR before capsule ingestion.

**Bowel preparation**

The cleansing protocol used was the one recommended by the European Society of Gastrointestinal Endoscopy (ESGE) guidelines for the colon capsule (5), four liters of polyethylene glycol (PEG) in a split dose. The day before examination, all patients had two liters of PEG from 7 p.m. to 9 p.m.; then, the day of examination the patient took two additional liters of PEG before capsule ingestion. Additional laxatives (boosters) are required to let the capsule reach the anus and keep the colon clean throughout the exploration. We used 30 ml of sodium phosphate for the first boost and 15 ml of sodium phosphate for the second boost. The first boost was given once the capsule had entered the small bowel; the second boost was given three hours later, if the capsule had not yet been excreted.

**Statistical analysis**
The IBM SPSS 20.0 version was used for analysis. For description, the mean values and standard deviation were used, and the two-tailed Student’s t-test was used for comparative measurements. Any result with a p value < 0.05 was considered as statistically significant.

RESULTS
One hundred panendoscopies were performed from August 2011 to December 2016. Thirty-three were discarded for the analysis as they were not bleeding patients. Patient characteristics are described in table 1.

Indication for panendoscopy
As described in figure 1, 67 patients underwent panendoscopy because of suspected/known gastrointestinal bleeding; 46/67 had occult bleeding and 21/67 overt bleeding.

Transit time and completion rate
The mean transit times are described in table 2. In 69% (46/67) of cases, a panendoscopic test was achieved, meaning that we were able to explore from the mouth to the anus. In one patient, the enteroscopy was not complete due to capsule retention in an unsuspected stricture located in the small bowel, which was finally resolved surgically. The remaining 20 cases had a complete small bowel visualization, but an incomplete colonic exploration. In 6/20 patients (30 %), it was not considered to be a problem as five of them had a previous optical colonoscopy; the other patient had an incomplete previous optical colonoscopy and the capsule was able to explore the part of the colon previously unseen. Furthermore, the capsule was able to detect the bleeding source in 14 of these incomplete panendoscopies (70 %).

Esophageal and gastric findings
The following esophageal lesions were found: Barrett’s esophagus in 1/67 patients, erosive esophagitis in 1/67 (1.5 %) patients and esophageal varices in 1/67 (1.5 %) patients. Gastric findings were arteriovenous malformations (AVM) in 1/67 (1.5 %)
patients, gastric portal hypertension in 1/67 (1.5%), gastric ulcer with fibrin in 1/67 (1.5%), gastric polyps in 1/67 (1.5%) and gastric peptic ulcer in 1/67 (1.5%) patients.

Patients with positive small bowel and colonic findings
In our series, there were 41/67 capsules with abnormal findings (61.2%). The most common small bowel findings were multiple AVM difficult to manage with device assisted enteroscopy (21/67, 31.3%), polyps (7/67, 10.4%), ulcers (6/67, 9%) and blood (without seeing the bleeding source) (8/67, 12%). In 28/67 (42%) patients, SB findings were considered as the bleeding source. Regarding colonic findings, four patients were excluded from the analysis due to poor colonic preparation. The most frequent findings were polyps (32/63, 50% of cases), diverticula (29/63, 46.8%), AVM (17/63, 27%) and colon cancer (2/63, 3.2%). In 21/67 (31%), colonic findings were considered as the bleeding source. Indeed, in 14 of these patients, optical colonoscopy was recommended as we recognized the bleeding stigmata (13 related to AVM and one related to colonic diverticula).

Patients with previous negative EGD
With regard to patients with a previous negative EGD, 31/67 (46.26%) underwent panendoscopic capsule and the capsule was able to find the bleeding source in 18 of them (58%). In 1/31 cases (3%), it was due to an overlooked gastric vascular lesion, SB lesions in 4/31 (13%) cases, colonic lesions in 10/31 (32%) and both SB and colonic bleeding lesions with high bleeding potential in 3/31 (10%) patients. The SB lesions found included several SB ulcers in 1/7 patient, AVM in 3/7 cases, an ulcerated and obstructive stricture in 1/7 case, one ulcerated submucosal mass and one active bleeding where we were not able to see the lesion underneath. Regarding colonic lesions, all but one were AVM. The remaining case was a colonic ulcer. As previously stated, we found colonic lesions in 13/31 (42%) patients, meaning that if colonoscopy had been performed in these patients, we would not have found any bleeding source in 58% so they potentially may have been avoided. There were no statistically significant differences regarding the need for a colonoscopy or the suggested treatment between patients with iron deficiency anemia (IDA), occult and overt OGIB.
Therapeutic impact of panendoscopic capsule

According to capsule results, different strategies were suggested. These strategies are summarized in figure 2. Thus, the panendoscopy capsule results led to a therapeutic EGD or therapeutic colonoscopy in only 21/67 patients (31.3%). There were no statistically significant differences regarding the need for colonoscopy or the suggested treatment between patients with IDA, occult and overt OGIB.

Renal function

Panendoscopy was performed instead of conventional endoscopy because patients were considered as high-risk patients (mainly because of comorbidities) and sodium phosphate was used as a booster. Thus, we analyzed sodium, potassium and creatinine changes before and after the procedure. The mean values of sodium, potassium and creatinine before preparation with four liters of PEG and up to 45 ml of sodium phosphate were 140.68, 4.04 and 1.36. The mean values after the preparation and boosters were 140.28, 3.9 and 1.35. The differences between the before and after the prep were not statistically significant (Fig. 3).

DISCUSSION

Patients with a suspicion of a gastrointestinal bleeding source may be a challenge, requiring at least upper endoscopy, colonoscopy and sometimes small bowel capsule endoscopy. From the beginning of colon capsule endoscopy, it was considered as a potential tool to perform a pan-enteric endoscopy exploration (3,6) and our results show that a capsule panendoscopic test is feasible. However, there were 21/67 (31%) incomplete procedures. In our series, the impact of these incomplete procedures was low, as the bleeding source could be detected in 15/21 cases (71.4%).

The use of the capsule as a pan-enteric test, even before EGD and colonoscopy, has shown that the bleeding source was located in the SB in 42% of cases and the colon in 31% of cases. This suggests that performing a panendoscopy before colonoscopy would potentially avoid 69% of colonoscopies. We are aware that the main drawback of our study is its design as a retrospective observational study, as well as the
heterogeneous population included. However, in the light of what we have found, we believe further prospective controlled studies are needed to rule out the role of panendoscopy in patients with gastrointestinal bleeding.

The rate of complete procedures in our study was 69 %, which is lower than previously reported (either for colonic studies with CCE2 or panendoscopies with the same device [3,7]). In our opinion, this may be related to the high rate of inpatients (70 %) and the characteristics of our study population, mainly elderly patients with other comorbidities. Nevertheless, the capsule was able to detect the bleeding source in 70 % of these incomplete procedures. Transit times were significantly higher in incomplete procedures, both for small bowel and colon, but not for the stomach. However, if we compare inpatient transit times with outpatient transit times, the gastric transit time was higher in the inpatient group, which was statistically significant. Hence, the use of gastric prokinetics may be useful, particularly in this group.

One of the main concerns about colon capsule use is the need for a more intensive preparation, especially considering that the best booster results are achieved using sodium phosphate (5,7,8). As a great part of our study population was considered as high risk population due to cardiac conditions, the use of this booster may rise some concerns. However, our results show that around 30 % of patients may only need the first booster (30 ml) and this did not have a negative impact on kidney function.

In conclusion, we believe that a pan-enteric capsule exploration may have an interesting role in bleeding patients, as it is able to select those patients who may potentially need a therapeutic endoscopy.

References
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n (%) or mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>42 (62.7 %)</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.13 (13,15)</td>
</tr>
<tr>
<td>Inpatients</td>
<td>65 (67.2 %)</td>
</tr>
<tr>
<td>Cardiac conditions</td>
<td>49 (73 %)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>19 (28 %)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>24 (26 %)</td>
</tr>
<tr>
<td>Both</td>
<td>6 (9 %)</td>
</tr>
<tr>
<td>Respiratory conditions</td>
<td>14 (20.9 %)</td>
</tr>
<tr>
<td>Kidney injury</td>
<td>13 (19.6 %)</td>
</tr>
<tr>
<td>Transfusions</td>
<td>22 (32.8 %)</td>
</tr>
<tr>
<td>Units of RBC</td>
<td>1.94 (3.3)</td>
</tr>
<tr>
<td>Previous endoscopy</td>
<td>34 (50.74 %)</td>
</tr>
<tr>
<td>Only gastroscopy</td>
<td>13 (19.4 %)</td>
</tr>
<tr>
<td>Only colonoscopy</td>
<td>3 (4.5 %)</td>
</tr>
<tr>
<td>Gastroscopy + colonoscopy</td>
<td>18 (26.9 %)</td>
</tr>
<tr>
<td>Need of the second booster</td>
<td>48 (71.6 %)</td>
</tr>
</tbody>
</table>

SD: standard deviation; RBC: red blood cells.
Table 2. Mean transit times in patients with complete vs incomplete procedures and inpatients vs outpatients

<table>
<thead>
<tr>
<th>Mean transit times (SD)</th>
<th>All patients</th>
<th>Patients with complete panendoscopies</th>
<th>Patients with incomplete panendoscopies</th>
<th>p</th>
<th>Inpatients</th>
<th>Outpatients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>0:27:12 (0:27:35)</td>
<td>0:26:05 (0:22:49)</td>
<td>0:30:00 (0:37:30)</td>
<td>0.606</td>
<td>0:30:24</td>
<td>0:20:22</td>
<td>0.091</td>
</tr>
<tr>
<td>Colon</td>
<td>3:19:59 (2:34:56)</td>
<td>2:34:57 (2:14:14)</td>
<td>5:11:21 (2:29:10)</td>
<td>0.000</td>
<td>3:32:36</td>
<td>2:54:43</td>
<td>0.353</td>
</tr>
</tbody>
</table>
Fig. 1. One hundred patients considered at high-risk for endoscopy were included. These patients were either on anticoagulant or antiplatelet treatment (which could not be stopped), patients with chronic liver disease (with prolonged prothrombin time) or patients with pneumonia.
Fig. 2. Number of patients and different strategies suggested according to their capsule findings.
Fig. 3. Changes in sodium, potassium and creatinine before and after capsule procedure.