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

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ABSTRACT

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

Aim
To analyse our experience with capsule endoscopy in the bleeding patient setting.

Methods
We retrospectively reviewed the first 100 pan-endoscopic capsule procedures performed in our centre from August 2011 until December 2016.

Results
61.2% of our patients had positive findings; 46.26% had a previous negative gastroscopy and in 67.7% of them the capsule detected small bowel lesions and in 80.64%, colonic findings. Taking into consideration that our population were high-risk patients (mainly because of comorbidities), and that we use up to 45 ml of sodium phosphate, we analysed sodium, potassium and creatinine changes before and after procedure. The mean “before” values were respectively 140.68, 4.04 and 1.36. The mean “after” values were 140.28, 3.9 and 1.35 (p=n.s) According to our findings in 64.5% of patients with negative gastroscopy no other endoscopic studies would be needed. According to capsule results, in all our study sample, in 68.6% of cases conventional endoscopy could have been avoided.

Conclusion
Panendoscopy with capsule may be useful and safe in bleeding high-risk patients, by selecting the patients 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.

Abbreviations
Esophagogastrroduodenoscopy (EGD); Inflammatory Bowel Disease (IBD); PillCam COLON2 (C2); Adaptive frame rate (AFR); Small bowel (SB); Arteriovenous malformations (AVM); Iron defiency anemia (IDA).

INTRODUCTION
Obscure gastrointestinal bleeding 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 esophagogastrroduodenoscopy (EGD) and colonoscopy. In this setting, small bowel capsule endoscopy is considered the next
step and it has proven its efficacy and diagnostic yield, especially when performed as soon as possible(2). So, in our center, what we usually do when facing gastrointestinal bleeding (occult or overt), is to perform EGD and colonoscopy on the same day. If these procedures are negative, then we do a small bowel capsule endoscopy in less than 14 days, though we generally do it in the next three days.

Further, since 2006 we are able to explore the colon with the PillCam COLON® platform (PillCamCOLON® was launched in 2006 and PillCam COLON2® in 2011) but this platform allows not only visualization of colonic images but small bowel images as well, being possible to achieve a complete pan-enteric visualization. This possibility has been suggested to be useful for assessing inflammatory bowel disease (IBD) activity and extent, for obscure gastrointestinal bleeding with previous incomplete colonoscopy and for patients with anemia undergoing CCE to screen for colonic pathology(3).

Since 2011 we offer pan-enteric capsule endoscopy in our service portfolio, being requested more frequently for patients with suspected/known gastrointestinal bleeding, especially for those who are unsuitable or at high risk for conventional endoscopy. After almost 10 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 panenteric 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 pan-endoscopic capsule procedures performed (August 2011-December 2016).

The inclusion criteria were all patients submitted for a pan-enteric capsule endoscopy. All of them 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. The following figure 1 shows patient’s inclusion flowchart:

We collected demographical data, previous endoscopic procedures, hospitalization, previous transfusion needs, blood tests before/after bowel preparation, capsule transit times (gastric, small bowel and colon), small bowel findings, colon findings and other findings (esophagus or stomach) and complications.

The main outcome was considered 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 172º. It has an adaptive frame rate (AFR) that becomes active once the capsule detects automatically its location in the small bowel (SB). The AFR ranges from 4 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 4 frames/second, and 3 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 up to 30 min delayed from the real SB entrance(4). For pan-endoscopic purposes, the AFR can be manually activated, therefore the whole gut can be explored at 4 to 35 frames/second, offering to the reader images from mouth to annus. In our center, we manually activate the AFR before capsule ingestion.

**Bowel preparation**

The cleansing protocol used was the one recommended by the ESGE guidelines for colon capsule (5), 4 liters of PEG in split dose. The day before examination, all patients had 2 liters of PEG from 7 pm to 9 pm, then the day of examination the patient took 2 additional liters of PEG before capsule ingestion. To let the capsule reach the annus and keep the colon clean throughout the exploration, additional laxatives (boosters)
are required. We used 30 ml of sodium phosphate for the first boost and 15 ml of sodium phosphate for the second boost. The first boost is given once the capsule has entered the small bowel, the second boost is given 3 hours later, if the capsule has not been excreted yet.

**Statistical analysis**
We have used the IBM SPSS 20.0 version. For description we have used the mean values and standard deviation, for comparative measurements, we have used the 2 tailed t-Student test. Any result with a p value < 0.05 was considered significant.

**RESULTS**
We have performed 100 panendoscopies from August 2011 to December 2016. 33 were discarded for analysis as they were not bleeding patients. Patient characteristics are described in table 1.

**Indication for panendoscopy**
As described in fig 1, 67 patients were submitted to 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, we achieved a panendoscopic test, meaning that we were able to explore from mouth to anus. In one patient, the enteroscopy was not complete due to capsule retention in an unsuspected stricture located in the small bowel, finally solved 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 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. Even more, in 14 of these incomplete panendoscopies (70 %) the capsule was able to detect the bleeding source.
Esophageal and gastric findings
We have found the following esophageal lesions: 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 have been AVM 1/67 (1.5 %) patients, gastric portal hypertension in 1/67 (1.5 %) patients, gastric ulcer with fibrin in 1/67 (1.5 %) patients, gastric polyps in 1/67 (1.5 %) patients and gastric peptic ulcer in 1/67 (1.5 %) patients.

Patients with positive small bowel and colonic findings
In our series, we had 41/67 capsules with abnormal findings (61.2 %).
Most common small bowel findings were multiple arteriovenous malformations difficult to manage with device assisted enteroscopy (AVM) (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 the bleeding source.
Regarding colonic findings, we have excluded 4 patients 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 the bleeding source. Indeed, in 14 of these patients, we recommended optical colonoscopy as we recognized bleeding stigmata (13 related to AVM and 1 related to colonic diverticula).

Patients with previous negative EGD
31/67 (46.26 %) patients were submitted to panendoscopic capsule after a previous negative EGD and in 18 of these patients (58 %), the capsule was able to find the bleeding source. In 1/31 case (3 %) it was due to an overlooked gastric vascular lesion, in 4/31 (13 %) cases it was due to SB lesions, in 10/31 (32 %) cases it was due to colonic lesions and finally, 3/31 (10 %) patients had both SB and colonic bleeding lesions with high bleeding potential.
The SB lesions that we found were: several SB ulcers in 1/7 patient, AVM in 3/7 cases, an ulcerated and obstructive stricture in 1/7 case, 1 ulcerated submucosal mass and 1 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 stated before, we found colonic lesions in 13/31 (42 %) patients, meaning that if we had performed colonoscopy in these patients, in 58 % we would not have found any bleeding source so they potentially may be avoided.

There were no statistically significant differences regarding neither the need of colonoscopy nor the suggested treatment between patients with IDA, occult and overt OGIB.

**Therapeutic impact of panendoscopic capsule**

According to capsule results, different strategies were suggested. Those strategies are summarized in Fig. 2. Thus, only in 21/67 patients (31,3 %) panendoscopy capsule results led to a therapeutic EGD or therapeutic colonoscopy.

There were no statistically significant differences regarding neither the need of colonoscopy nor the suggested treatment between patients with IDA, occult and overt OGIB.

**Renal function**

Taking into consideration that panendoscopy was performed instead of conventional endoscopy because patients were considered high-risk patients (mainly because of comorbidities), and that we use sodium phosphate as a booster, we analyzed sodium, potassium and creatinine changes before and after procedure. The mean values of sodium, potassium and creatinine before preparation with 4 liter 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 before and after the prep were not statistically significant. (fig. 3)

**DISCUSSION**

Patients with 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 for performing a pan-enteric endoscopy exploration\(^{(3,6)}\). And our results show that a capsule panendoscopic test is feasible, although we have had 21/67 (31\%) of incomplete procedures. In our series, the impact of these incomplete procedures has been low, as in 15/21 cases (71.4\%) the bleeding source could be detected. The use of the capsule as a panenteric 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, and that the heterogeneous population that we included, but 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 in 70\% of these incomplete procedures, the capsule was able to detect the bleeding source. Transit times were significantly higher in incomplete procedures both for small bowel and colon, but not for the stomach. Yet, if we compare inpatient transit times with outpatient transit times, we observe that gastric transit time is higher in the inpatient group, being this difference 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 of 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 is considered a high risk population due to cardiac conditions, the use of this booster may rise some concerns, but our results show that around 30\% of patients may only need the first booster (30 ml) and we didn’t have a negative impact on our patient’s kidney function.
In conclusion, we believe that a panenteric 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.

CONFLICT OF INTEREST
Cristina Carretero has received consultant and speaker’s fees from Medtronic.

REFERENCES

Table 1.

<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></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>49 (73%)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>19 (28%)</td>
</tr>
<tr>
<td>Both</td>
<td>24 (26%)</td>
</tr>
<tr>
<td></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 Units of RBC</td>
<td>22 (32.8%)</td>
</tr>
<tr>
<td></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>

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>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>
</tr>
</tbody>
</table>
Figure 1: 100 patients considered at high-risk for endoscopy were included. Those patients were either on anticoagulant or antiplatelet treatment (which couldn’t be stopped), patients with chronic liver disease (with prolonged prothrombine time) or patients with pneumonia.
Figure 2. Number of patients and different strategies suggested according to their capsule findings.

Figure 3. Changes in sodium, potassium and creatinine before and after capsule procedure.