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### Digestive Endoscopy

## Bowel preparation for small bowel capsule endoscopy – The later, the better!

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### ABSTRACT

**Background:** In small bowel capsule endoscopy (SBCE), the presence of residue may compromise diagnostic accuracy.

**Aims:** To assess differences in quality of visualisation and diagnostic yield of SBCE using 3 different preparation protocols.

**Methods:** Prospective, randomized, blind, pilot study. Protocol A: Clear liquids diet the day before the examination with fasting from 8 p.m.; Protocol B: Protocol A + 2 pouches of Moviprep<sup>®</sup> (polyethylene glycol electrolyte solution + sodium ascorbate) in 1 L of water from 8 p.m. of the day before the examination; Protocol C: Protocol A + 2 pouches of Moviprep<sup>®</sup> in 1 L of water consumed after real-time confirmation of capsule arrival at small bowel.

Small bowel preparation was classified by two experienced physicians, considering the percentage of the examination during which mucosal observation was adequate: Excellent (>90%); Good (90–75%); Fair (75–50%); Poor (<50%).

**Results:** 101 patients randomized to the 3 protocols (A 37, B 31, C 33 patients). Protocol C had an excellent/good small bowel preparation in a higher percentage of examinations for both readers (Reader 1: A: 37.8% vs B: 45.2% vs C: 78.8%,  $p = 0.002$  and Reader 2: A: 37.8% vs B: 41.9% vs C: 75.8%,  $p = 0.003$ ). Also, protocol C had a higher detection of angiodysplasia (A: 5.4% vs B: 9.7% vs C: 27.3%,  $p = 0.022$ ).

**Conclusions:** The administration of Moviprep<sup>®</sup> after the capsule had reached the small bowel was associated with a better small bowel preparation and a higher detection of angiodysplasia.

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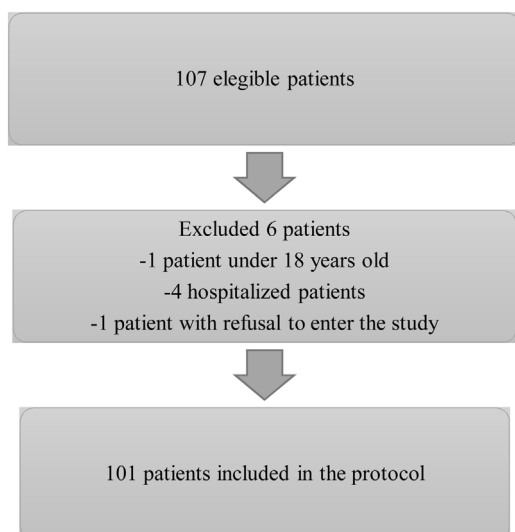
### 1. Introduction

Small bowel capsule endoscopy (SBCE) is now widely available in clinical practice and provides an intraluminal assessment of the small bowel, being particularly useful in the study of obscure gastrointestinal bleeding and in patients with suspected or known Crohn's disease [1].

Since the development of this diagnostic tool, the need for small bowel preparation for SBCE was one of the most controversial topics in the capsule endoscopy scientific community. The first manufacturer of the small bowel capsule endoscopes (Given Imaging<sup>®</sup>) recommended a low-fiber diet on the day before the

procedure with only clear liquids in the evening, followed by a 12-hour fast, and did not recommend the use of purgative solutions before the procedure. However, several authors assessed the effect of purgative solutions in small bowel cleansing and diagnostic yield, and, even though the results are less clear regarding its benefits in diagnostic yield and rate of complete examinations [2–6], so far four meta-analysis concluded that the ingestion of 2 L of polyethylene glycol (PEG) prior to SBCE leads to improvement in small bowel cleansing. Considering this evidence, the European Society of Gastrointestinal Endoscopy (ESGE) issued a technical review in 2018 recommending the use of purgative solutions prior to SBCE [7]. Nevertheless, no consensus has been reached regarding the optimal timing for the ingestion of purgative solutions until the moment. With this in mind, we aimed to assess differences in the quality of small bowel visualization, in the diagnostic yield, in the rate of

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Graph 1. Enrolment Flow Chart.

complete examinations and small bowel transit time (SBTT) using three different preparation protocols.

## 2. Methods

A prospective, randomized, blind pilot preliminary study including 101 patients consecutively performing SBCE between February and May 2018 was performed at a highly experienced (>2000 examinations) University affiliated Hospital Gastroenterology Department. We excluded patients who were under 18, hospitalized patients, those with contraindication to ingest polyethylene glycol electrolyte solution and those who refused to participate in the study (Graph 1). SBCE was performed using PillCam® SB3 (Medtronic, Minneapolis, MN, USA) and patients were randomized to one of three protocols: Protocol A (standard protocol): clear liquid diet the day before the procedure and a 12 h night-fast; Protocol B: Protocol A + 2 pouches of Moviprep® (polyethylene glycol electrolyte solution) in 1 L of water from 8 p.m. of the day before the examination. Protocol C: Protocol A + 2 pouches of Moviprep® in 1 L of water to be consumed after real-time confirmation of SBCE arrival at small bowel. For all SBCE, regardless of the preparation protocol, patients were given 100 mg of Simethicone 30 min before capsule ingestion and 1 h after ingestion they returned to our unit for real time visualization using the data recorder DR3; at this point, if the capsule remained in the stomach, the patient was given 10 mg of oral Domperidone. Thirty minutes after pro-kinetic administration, if the capsule remained in the stomach, it was placed into the duodenum by upper gastrointestinal endoscopy [8].

The complete video obtained in each SBCE was reviewed independently by two gastroenterologists with vast experience in capsule endoscopy (over 500 examinations), blinded to the preparation protocol assigned for each patient and to each other's assessment, using Rapid® Reader Software v9.0, at 8–12 frames per second rate. Each physician recorded with the time counter of the Rapid Reader® software the exact time period during which the mucosa was not clean, due to contamination with obstacles such as intestinal contents, intraluminal gas, bile and food residues. After the examination, the authors classified the preparation according to the following criteria: Excellent, if an ideal visualization of the small bowel mucosa was achieved in over 90% of the recording time; good, if the mucosa was in perfect condition in 90–75% of the recording time, containing some fluid or debris which did not

seem to interfere with the overall quality of the examination; fair, if mucosa was under perfect conditions for observation in only 50%–75% of the recording time, with the presence of enough fluid, bubbles or debris to preclude a completely reliable examination; and poor, if the mucosa could be observed in < 50% of the recording time, with the presence of significant amounts of fluid, bubbles or debris such that the examination interpretation was compromised [9].

We collected data on age, gender, SBCE indication, quality of bowel preparation, completion of the exam and small bowel transit time (SBTT). Regarding small bowel findings, we assessed the detection of relevant findings throughout the small bowel (diagnostic yield, DY) and the presence of specific findings (active bleeding/hematic residue, angioectasia, villous edema, villous atrophy, erosions, ulcers, stenosis, polyps/tumours), presence/absence of findings in each tertile and in extra-small bowel segments was also reported. The relevance of the findings in the clinical setting was at the physician's discretion: for patients performing SBCE for suspicion/staging of inflammatory bowel disease, erosions, ulcers, stenosis and villous edema were considered relevant; for patients performing SBCE for obscure gastrointestinal bleeding, active bleeding, angioectasia, varices, erosions, ulcers, polyps/masses were considered relevant [10]; for patients performing SBCE for unresponsive celiac disease, villous atrophy, ulcers and polyps/masses were considered relevant; for patients performing SBCE for polyposis syndrome polyps/masses were considered relevant). It was also assessed if specific landmarks, as Z line and the papilla, were identified during the examination.

Since studies performed with the new administration schedule (i.e. Moviprep® one liter at time of capsule passage in the small bowel) are lacking, a formal sample size calculation was not performed. We therefore arbitrarily planned to enrol at least 30 patients in each arm.

Statistical analysis was performed using SPSS v.23.0.0.0 and MedCalc v12.5.0.0 and a two-tailed p value <0.05 was defined as indicating statistical significance. Categorical variables were presented as frequencies and percentages, and analyzed with the use of Fisher's exact test, chi-square test or chi-squared test for trend (Cochran-Armitage test), as appropriate. Continuous variables were presented as means and standard deviations or medians and interquartile range and analyzed with the use of ANOVA test. Interobserver agreement regarding quality of preparation was assessed with calculation of Intraclass Correlation Coefficient with a 95% confidence interval.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (Ethical Committee of Hospital Senhora da Oliveira, Guimarães; approved February 23th, 2018). All patients signed an informed consent form and consensual contraindications for SBCE procedure were respected as described elsewhere [1].

## 3. Results

Overall 101 patients were included; 37 of them were randomized to protocol A, 31 to protocol B and 33 to protocol C. Patients had a mean age of  $46.6 \pm 19.3$  years and 64.4% were females.

SBCE was more frequently performed in the investigation of obscure gastrointestinal bleeding (40.6%) and for suspected inflammatory bowel disease (37.7%) (Table 1).

SBCE had a good or excellent preparation in 53.5% of the examinations according to Reader 1 and in 51.5% according to Reader 2 and the two readers showed an excellent interclass correlation coefficient for the evaluation of the quality of mucosal visualization (ICC = 0.968, 95% CI 0.952–0.978,  $p < 0.001$ ).

**Table 1**  
SBCE indications and findings.

	Global	Protocol A	Protocol B	Protocol C	p value
SBCE Indication (%)					
Obscure Gastrointestinal Bleeding	40.6	43.2	32.3	45.5	0.516
Suspected Inflammatory Bowel Disease	37.6	37.8	45.2	30.3	0.471
Crohn's Disease –treatment assessment	14.9	13.5	12.9	18.2	0.805
Unclassified Inflammatory Bowel Disease	3	2.7	6.5	0.0	0.313
Non-responsive Celiac Disease	1	0.0	0.0	3.0	0.353
Other	3	2.7	3.2	3.0	0.992
SBCE Findings (%)					
Ulcers	23.8	24.3	19.4	27.3	0.755
Villous Edema	23.8	35.1	16.1	18.2	0.122
Erosions	14.9	21.6	9.7	12.1	0.334
Angioectasia	13.9	5.4	9.7	27.3	<b>0.022</b>
Bleeding	4.0	2.7	6.5	3.0	0.693
Polyp/tumour	4.0	2.7	0.0	9.1	0.156

**Table 2**  
Reader 1 and 2 assessments on preparation quality.

	Excellent	Good	Fair	Poor
Reader 1 – preparation quality				
Protocol A	5/37	9/37	20/37	3/37
Protocol B	4/31	10/31	15/31	2/31
Protocol C	14/33	12/33	4/33	3/33
Reader 2 – preparation quality				
Protocol A	4/37	10/37	19/37	4/37
Protocol B	4/31	9/31	14/31	4/31
Protocol C	15/33	10/33	5/33	3/33

Overall, the study was complete in 94.1% of patients, with a mean SBTT of  $250 \pm 113$  min and a diagnostic yield of 57.4%, with ulcers and villous edema (found in association with either ulcer or erosions) being the most frequently identified findings (23.8% of examinations each) (Table 1). First tertile had findings in 25.7%, second tertile in 12.9% and third tertile in 25.7% of the examinations and extra-small intestinal findings were present in 11.9% of patients (9.9% in the stomach and 2.0% in the colon). The papilla and Z-line were identified in 16.8% and 42.6% of the examinations, respectively.

When comparing the three groups no statistical differences were found regarding age (A:  $48.7 \pm 20.5$  years vs B:  $42.7 \pm 19.4$  years vs C:  $48.7 \pm 17.5$  years,  $p=0.361$ ), gender (females in group A: 59.5% vs B: 70.9% vs C: 63.6%,  $p=0.611$ ) or SBCE indication (Table 1).

Protocol C patients exhibited an excellent or good preparation in a higher percentage of examinations for both readers (Reader 1 – A: 14/37 vs B: 14/31 vs C: 26/33,  $p=0.001$  and Reader 2 – A: 14/37 vs B: 13/31 vs C: 25/33,  $p=0.002$ ) (Table 2) with no differences regarding neither SBTT (A:  $278 \pm 123$  min vs B:  $275 \pm 107$  min vs C:  $245 \pm 149$  min,  $p=0.504$ ) nor the rate of complete examinations (A: 89.2% vs B: 100% vs C: 93.9%,  $p=0.171$ ). Even though no differences were found regarding diagnostic yield between the three protocols (A: 59.5% vs B: 48.4% vs C: 63.6%,  $p=0.445$ ), patients on protocol C had a significantly higher detection of angioectasia (A: 5.4% vs B: 9.7% vs C: 27.3%,  $p=0.022$ ). Apart from that, no differences were found between the three protocols regarding other findings (Table 1). Moreover, no differences were found regarding papilla identification (A: 10.8% vs B: 22.6% vs C: 18.2%,  $p=0.914$ ) nor regarding the presence of findings in the first, second or third tertile (A: 24.3% vs B: 16.1% vs C: 36.4%,  $p=0.175$ ; A: 16.2% vs B: 6.5% vs C: 15.2%,  $p=0.0436$  and A: 27.0% vs B: 29.0% vs C: 21.2%,  $p=0.755$ , respectively).

#### 4. Discussion

The presence of residue in the small bowel lumen, in small bowel capsule endoscopy (SBCE), limits the observation, hampers the

interpretation and may compromise diagnostic accuracy. Several meta-analyses have confirmed that the use of purgative solutions prior to SBCE improves small bowel cleansing, however, so far, no consensus has been reached regarding the ideal timing for purgative ingestion [7].

In our clinical practice, reading colon capsule endoscopies or capsule pan-endoscopies we verified that these examinations usually have an appropriate small bowel cleansing. Based on the fact that the most frequently used preparation protocols include not only the ingestion of a purgative solution prior to capsule ingestion but also of a purgative boost after confirmation of capsule arrival at the small bowel, we tried to compare the standard protocol for SBCE (12 h fast only) with 2 other protocols in which a PEG solution was ingested either the night before SBCE or after confirmation of capsule arrival at the small bowel.

In fact, we verified that the administration of purgative solutions after confirmation of capsule arrival at the small bowel was associated with a higher percentage of examinations with good or excellent preparation. To the best of our knowledge, this is the first study assessing small bowel quality preparation and diagnostic yield with PEG administration after confirmation of capsule arrival at the small bowel. Some other authors have also tried to assess the impact of different timings for purgative ingestion. Song et al. compared the ingestion of 2 L of PEG 14 h before SBCE with the ingestion of PEG 4 h before the procedure and found no differences in the diagnostic yield, completion rate or SBTT [11]. Adler et al. tried a different protocol in which 45 patients were either randomized to a 2 L PEG solution 12 h prior to SBCE or to one sachet of Picolax® dissolved in 250 ml of water one hour after swallowing the capsule with 500 ml of water [12]. In this study, patients in the post-ingestion group had a better visibility in the distal third of the small bowel, however they also had a shorter SBTT and no differences were found regarding diagnostic yield. These results suggested that ingestion of preparation after capsule ingestion is associated with better small bowel cleansing. On the other side, patients' adherence to endoscopic studies is usually compromised by the discomfort associated not only with the procedure itself but, most frequently, due to the purgative preparation. This discomfort is usually related to the volume of purgative solutions, and in fact, a work by van Tuly et al. in which patients performing SBCE were randomized to three preparation regimens (clear liquid diet or 1 L of PEG the night before the procedure or 2 L of PEG the night before the procedure) found that the diagnostic yield did not change significantly between protocols – however, the use of 2 L of PEG was considered more uncomfortable than no PEG solution or 1 L PEG [13]. In our study, patients only ingested 1 L of PEG solution and were able to obtain better preparation results and a higher detection of angioectasia when this ingestion was performed after the capsule reached the duodenum, suggesting that perhaps the most

relevant factor for attaining an adequate small bowel preparation is the timing and not the volume of the purgative solution.

Several authors reported that SBCE diagnostic yield is related with SBTT, with positive correlation between the diagnostic yield and SBTT, indicating that the longer the SBTT, the higher the diagnostic yield [14,15]. In contrast with Adler et al. findings [12], in our study, the delayed ingestion of PEG solution did not associate with a shortened SBTT.

Proximal small bowel has a faster transit time and therefore, SBCE has a higher rate of missed lesions in this segment [16,17]. Since major duodenal papilla is present in all individuals who have not undergone surgery, and is in the proximal small bowel, its detection may be used as an indirect marker of a possible missed lesion in proximal small bowel in capsule endoscopy studies. Therefore, we assessed papilla detection rate and each tertile findings to evaluate whether a delayed purgative ingestion could interfere with SBCE diagnostic yield. We found that papilla detection rate and each tertile findings were not significantly different between protocols, suggesting that a delayed purgative ingestion does not compromise lesion detection, even in the most proximal segments.

As a further matter, in our study, angioectasia detection was significantly higher in Protocol C and, even though it did not reach statistical significance, ulcers and polyps/tumour detection was also attained in a higher percentage of patients. Considering that our sample was homogenous for the different SBCE indications, these findings suggest that an improved small bowel cleansing might potentially translate into a higher diagnostic yield. A meta-analysis by Wu et al. including 9 randomized controlled trials also found that PEG 2L was especially useful in improving small bowel visualization quality-related diagnosis of angiodysplasias and polyps [5] and another recent metanalysis by Kotwal et al. found that both PEG and sodium phosphate preparation significantly improved the diagnostic yield [4].

Regarding study limitations, we must highlight the fact that no sample size estimation was performed and therefore, this study could be underpowered to find out relevant differences regarding diagnostic yield. In addition, we did not record the amount of patients who needed prokinetic administration during the procedure and, therefore, cannot state if this was different between protocols.

In conclusion, the administration of Moviprep® after the confirmation of capsule arrival at the small bowel was, in our series, associated with a better small bowel preparation and a higher detection of angioectasia, without interfering with SBTT. Even though these results require further validation, this innovative protocol may become the standard used to improve procedure results.

## Fundings

None declared.

## Conflict of interest

Sofia Xavier, Bruno Rosa, Sara Monteiro, Cátia Arieira, Rui Magalhães, Tiago Cúrdia Gonçalves, Pedro Boal de Carvalho, Joana Magalhães, Maria João Moreira and José Cotter hereby declare that they do not have any conflict-of-interest (including but not limited to commercial, personal, political, intellectual, or religious interests) to the work submitted herein.

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Sofia Xavier designed the study, performed the literature search, collected and analyzed clinical data, designed the text structure and

wrote the text. Bruno Rosa designed the study, contributed to analysis and interpretation of data and made several critical corrections and revisions; Sara Monteiro, Cátia Arieira, Rui Magalhães, Tiago Cúrdia Gonçalves, Pedro Boal Carvalho and Joana Magalhães contributed to the analysis and interpretation of data and made several critical corrections and revisions; Maria João Moreira and José Cotter suggested the theme to be reviewed, designed the study and made several critical corrections and revisions, including English editing, until the submitted version was achieved. Hugo Sousa performed English review and editing. All authors approved the final version of the article.

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