Project synopsis

Study title: Preparation **R**egimens to **I**mprove **C**apsule **E**ndoscopy visualization and diagnostic yield: a randomized trial

Study acronym: PrepRICE

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1. ABSTRACT AND AIMS

Small bowel capsule endoscopy (SBCE) has become an important tool in clinical practice since its introduction in 2000[(1)]. This non-invasive method allows the visualization of small bowel mucosa, being essential in the management of many conditions, such as suspected small bowel bleeding, inflammatory bowel diseases and intestinal polyposis syndromes[(2,3)]. Despite recommendations concerning SBCE in different pathologies, there are still some technical concerns to be addressed[(3)]. The optimal preparation for SBCE has been one of these controversial issues.

Currently, the European Society of Gastrointestinal Endoscopy (ESGE) recommends that patients ingest a purgative agent (2L of polyethylene glycol, PEG) and antifoaming agents for SBCE, because it was associated with a better visualization[(3)]. However, it remains unclear which is the optimal timing for purgative use[(3)]. Furthermore, the use of a booster agent after capsule ingestion is already performed in colon capsule endoscopy[(4)], but less is known about its application in SBCE[(5)]. Also, it remains to be clarified whether a better visualization results in higher diagnostic yield and impacts patients' outcomes.

Therefore, the global aim of this prospective, randomized, multi-centric study is to determine the optimal timing and preparation for small-bowel capsule endoscopy

(regardless of the equipment used), comparing four groups of different preparation protocols:

Group 1) 1L of Moviprep® solution the night before the procedure

Group 2) 1L of Moviprep® solution up to 2h before the procedure

Group 3) 0.5L of Moviprep® solution up to 2h before the procedure plus 0.5L of Moviprep® solution after the capsule had reached the duodenum (assessed with real-time viewer)

Group 4) 1L of Moviprep® solution after the capsule had reached the duodenum (assessed using real-time viewer)

<u>Specific aim 1:</u> To evaluate and compare entire and distal third small bowel cleansing between the four different preparation protocols

The administration of PEG solution prior to SBCE has been described to improve mucosal visualization. Split-dose regimens showed good results in large bowel cleansing[6], and considering that the small bowel is located proximally (to the colon, a shorter time period between PEG intake and SBCE ingestion might optimize mucosal visibility. Also, booster application in colon capsule endoscopy showed promising results in terms of small bowel mucosa visualization. *We hypothesize that groups 3 and 4 will present a better mucosal visualization compared to the remaining groups.*

<u>Specific aim 2:</u> To evaluate and compare the diagnostic yield (DY) between the four different preparation protocols

The DY is defined as the likelihood that the findings detected in SBCE will explain patient's complaints or symptoms, and consequently establish a diagnosis or guide patient's management. Until now, it remains unclear which is the real impact of small bowel preparation prior to SBCE in DY. On the other hand, there are already some studies showing that purgative use was associated with better visualization and ability to detect more lesions raising the diagnostic accuracy of this method. *We hypothesize that groups 3 and 4 will present a higher DY in comparison to the remaining groups.*

2. RESEARCH DESIGN AND METHODOLOGY

2.1. Study design

We propose to conduct a multicentric prospective, single-blinded (for investigators) study in patients performing SBCE for obscure gastrointestinal bleeding (overt or occult bleeding of unknown origin that persists or recurs after initial negative bidirectional endoscopic procedures

- OGIB). To ensure blinding, the preparation protocol randomized to each case will be assigned to the nurse responsible for that SBCE in the local participating centre.

2.2. Study population

We plan to include consecutively all outpatients referred to perform SBCE over 20 months, in each participating endoscopy unit. Patients will be enrolled into the study if all inclusion criteria are fulfilled:

I. Be 18 years-old or older
II. Present OGIB (either occult or overt)
III. Agree with study's procedures and have signed the informed consent for the study and SBCE, prior to SBCE procedure

Patients will be excluded if any of the following exclusion criteria is identified:

I. Patients performing capsule endoscopy in urgent setting for overt obscure GI bleeding
II. Inpatients or bedridden
III. History of abdominal surgery
IV. History of abdominal or pelvic radiation therapy
V. Suspected or confirmed stenosis or occlusion
VI. Suspected or confirmed bowel perforation
VII. Severe comorbidities such as cardiopulmonary, renal or liver disease
VIII. Pregnant women
IX. Patients using narcotics or prokinetics in the week before the SBCE

2.3. Data collection at baseline

The following data will be collected at baseline:

- Demographic data (age, gender)
- Current or previous medication (including non-steroid anti-inflammatory, corticosteroids, anticoagulants or angiotensin receptor blockers)
- Previous abdominal surgeries and relevant comorbidities
- Lowest value of haemoglobin in the current "anaemia episode", need for transfusion (yes/no, number of units)

- Previous endoscopic or radiological studies (including upper and lower endoscopies, angiography, tomography or computed tomography: yes/no) and relevant findings in those

2.4. Data collection during procedure and after SBCE analysis

The following variables will be systematically evaluated for each included patient:

1) Preparation completion rate (able to drink 1L of Moviprep)
2) Overall satisfaction with the cleansing regimen (rated on a 5-point scale: 1 - very easy, 2 - easy, 3 - intermediate, 4 - difficult, 5 - very difficult)
3) Symptoms experienced (nausea, vomit, bloating, abdominal pain - yes or no)
4) Small bowel cleansing (entire small bowel and distal tertile - defined by dividing the small bowel transit time by three) scored using the quantitative index (QI) described by Brotz *et al*[21]; this score is less subjective and is associated with a moderate interobserver and intraobserver reliability (k: 0.47 to 0.52 and 0.60 to 0.66, respectively)[22]
5) Adequate cleansing rate, using a cut-off value of QI ≥ 8 points
6) Exam completion rate (proportion of SBCE that visualize the entire small bowel and pass to the colon during the battery life)
7) Time of entry in the stomach, duodenum and cecum
8) SBCE positive findings - findings will be classified based on the Saurin classification; the investigators will consider a positive SBCE when lesions classified as P2 or active bleeding are detected, the remaining cases will be classified as negative SBCE.
9) Diagnostic yield per small bowel tertile
10) Final diagnosis
11) Rate of adverse events

3. AUTHORSHIP CRITERIA

MME, RP, ACG, AP and AR designed the study and will coordinate the project, the randomization process, data collection and analysis and manuscript drafting. The remaining participants will be included as author if the following criteria are met: one author per 30 patients enrolled in each recruiting centre, until the end of the study. All authors will review and approve the final manuscript.

The remaining participants, not eligible for authorship, will be acknowledged in the manuscript.