

Oral purgative and simethicone before small bowel capsule endoscopy

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Abstract

AIM: To evaluate small bowel cleansing quality, diagnostic yield and transit time, comparing three cleansing protocols prior to capsule endoscopy.

METHODS: Sixty patients were prospectively enrolled and randomized to one of the following cleansing protocols: patients in Group A underwent a 24 h liquid diet and overnight fasting; patients in Group B followed protocol A and subsequently were administered 2 L of polyethylene glycol (PEG) the evening before the procedure; patients in Group C followed protocol B and were additionally administered 100 mg of simethicone 30 min prior to capsule ingestion. Small bowel cleansing was independently assessed by two experienced endoscopists and classified as poor, fair, good or excellent according to the proportion of small bowel mucosa under perfect conditions for visualization. When there was no agreement between the two endoscopists, the

images were reviewed and discussed until a consensus was reached. The preparation was considered acceptable if > 50% or adequate if > 75% of the mucosa was in perfect cleansing condition. The amount of bubbles was assessed independently and it was considered significant if it prevented a correct interpretation of the images. Positive endoscopic findings, gastric emptying time (GET) and small bowel transit time (SBTT) were recorded for each examination.

RESULTS: There was a trend favoring Group B in achieving an acceptable (including fair, good or excellent) level of cleansing (Group A: 65%; Group B: 83.3%; Group C: 68.4%) [$P =$ not significant (NS)] and favoring Group C in attaining an excellent level of cleansing (Group A: 10%; Group B: 16.7%; Group C: 21.1%) ($P =$ NS). The number of patients with an adequate cleansing of the small bowel, corresponding to an excellent or good classification, was 5 (25%) in Group A, 5 (27.8%) in Group B and 4 (21.1%) in Group C ($P = 0.892$). Conversely, 7 patients (35%) in Group A, 3 patients (16.7%) in Group B and 6 patients (31.6%) in Group C were considered to have poor small bowel cleansing ($P = 0.417$), with significant fluid or debris such that the examination was unreliable. The proportion of patients with a significant amount of bubbles was 50% in Group A, 27.8% in Group B and 15.8% in Group C ($P = 0.065$). This was significantly lower in Group C when compared to Group A ($P = 0.026$). The mean GET was 27.8 min for Group A, 27.2 min for Group B and 40.7 min for Group C ($P = 0.381$). The mean SBTT was 256.4 min for Group A, 256.1 min for Group B and 258.1 min for Group C ($P = 0.998$). Regarding to the rate of complete examinations, the capsule reached the cecum in 20 patients (100%) in Group A, 16 patients (88.9%) in Group B and 17 patients (89.5%) in Group C ($P = 0.312$). A definite diagnosis based on relevant small bowel endoscopic lesions was established in 60% of the patients in Group A (12 patients), 44.4% in Group B (8 patients) and 57.8% in Group C (11 patients) ($P = 0.587$).

CONCLUSION: Preparation with 2 L of PEG before small bowel capsule endoscopy (SBCE) may improve small bowel cleansing and the quality of visualization. Simethicone may further reduce intraluminal bubbles. No significant differences were found regarding GET, SBTT and the proportion of complete exploration or diagnostic yield among the three different cleansing protocols.

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Key words: Small bowel capsule endoscopy; Bowel preparation; Polyethylene glycol; Simethicone

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INTRODUCTION

The usefulness of bowel preparation prior to small bowel capsule endoscopy (SBCE) remains a controversial issue. It is widely recognized that SBCE may have considerable limitations when the visualization is impaired by bubbles, bile, intraluminal fluid and debris, or when the capsule fails to visualize all of the small bowel due to delayed gastric or small bowel transit times. Since SBCE is a costly, time consuming and not usually a repeated procedure, it is critical to optimize the quality of visualization. The benefits of bowel preparation are, however, still a matter of debate and the best method remains to be determined. Furthermore, no standardized protocol has been widely accepted and overnight fasting remains the standard preparation for SBCE^[1].

The aim of this study was to compare the quality of mucosal visualization, as well as the diagnostic yield, gastric emptying time (GET), small bowel transit time (SBTT) and rate of complete small bowel exploration with cecum visualization within the capsule battery lifespan, using three different small bowel cleansing protocols.

MATERIALS AND METHODS

We conducted a prospective, randomized, single center study, which included 60 consecutive patients undergoing SBCE (PillCam[®] SB2, Given[®] Imaging Ltd. Yoqneam, Israel) for the evaluation of suspected small bowel disease, including overt or occult obscure gastrointestinal bleeding (OGB), suspected or established Crohn's disease (CD), chronic diarrhea or suspected small bowel neoplasia. All evaluations took place between August 2010 and March 2011. At the time SBCE was scheduled, patients were randomly assigned to Group A, B or C. Group A included 20 patients who followed the bowel prepara-

tion currently recommended by the capsule manufacturer, with a 24 h liquid diet and overnight fasting prior to SBCE. Group B included 20 patients who followed the same as protocol A plus 2 L of polyethylene glycol (PEG) solution (Endofalk[®], Dr. Falk Pharma GmbH, Freiburg, Germany), containing macrogol 3350 (105 g/L) + potassium chloride (0.370 g/L) + sodium bicarbonate (1430 g/L) + sodium chloride (2800 g/L), in the evening before the procedure; Group C included 20 patients who followed the same as patients in protocol B plus 100 mg simethicone liquid suspension (Aero-OM[®], OM Pharma SA, Geneva, Switzerland) 30 min prior to capsule ingestion. All patients were allowed to drink clear liquids at 2 h and to have a light snack 4 h after swallowing the capsule. Each examination was reviewed by two endoscopists with experience in SBCE who were unaware of the type of bowel preparation and independently evaluated the endoscopic findings and assessed the quality of mucosal visualization. When there was a disagreement, the images were reviewed and discussed until a consensus was achieved. The GET and the SBTT were automatically calculated by the RAPID Reader[®] software. GET was defined as the time from the first gastric image to the first duodenal image and the SBTT the time from the first duodenal image to the first cecal image. The primary outcome was to evaluate the effects of bowel preparation on the quality of images obtained by capsule endoscopy. The secondary outcome was to evaluate the effect of preparation on other parameters, such as diagnostic yield, GET, SBTT and rate of complete small bowel examination. In order to evaluate the effects of bowel preparation, obstacles such as intestinal contents, intraluminal gas, bile and food residues were evaluated. By using a timer, we recorded the exact time period during which the small intestinal mucosa was not clean. Following a methodology which was similar to that utilized in other publications^[2,3], the quality of small bowel cleansing was assessed according to the proportion of the small bowel mucosa with perfect conditions for visualization, without any liquid, bubbles or debris. We considered it to be excellent if an ideal visualization of the small bowel mucosa was achieved; good if > 75% of the mucosa was in perfect condition, with some fluid or debris which did not seem to interfere with the overall quality of the examination; fair if only 50%-75% of the mucosa was under perfect conditions for observation, with the presence of enough fluid, bubbles or debris to preclude a completely reliable examination; and poor if < 50% of the mucosa could be observed, with the presence of significant amounts of fluid, bubbles or debris such that the examination was unreliable (Figure 1). We considered that the cleansing was adequate if at least 75% of the small bowel mucosa was in perfect condition for visualization (*i.e.*, excellent or good preparation). For study analysis purposes, we further rated small bowel cleansing as acceptable if at least 50% of the mucosa was in perfect condition for visualization (*i.e.*, including excellent, good or fair cleansing).

On the evaluation of the endoscopic findings, those

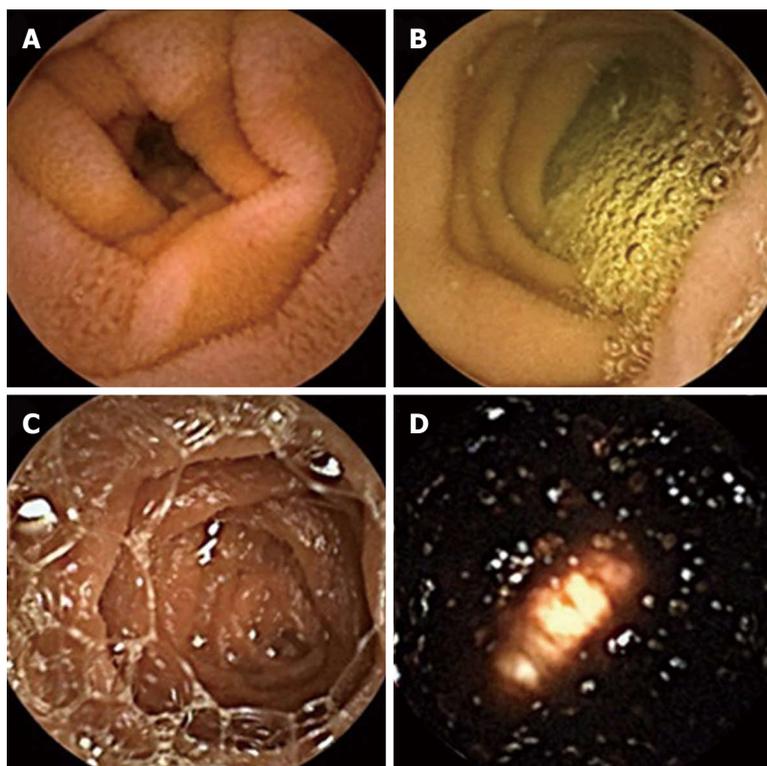


Figure 1 Small bowel cleansing classification. A: Excellent: perfect visualization in every small bowel segments; B: Good: > 75% of the mucosa in perfect condition, with some fluid or debris remaining; C: Fair: 50%-75% of clean mucosa, with the presence of enough fluid, bubbles or debris to preclude a completely reliable examination; D: Poor: < 50% of clean mucosa.

which were considered relevant were hemorrhagic lesions in patients with OGB and/or significant inflammatory activity (Lewis score, $LS \geq 135$) in patients with suspected or established CD.

Ethical considerations

All patients provided written consent to undergo capsule endoscopy and to be randomly assigned to one of the three protocols evaluated in the study. The study was approved by the Ethics Committee of the Alto Ave Hospital Center-Guimarães, Portugal.

Statistical analysis

Quantitative data were summarized as the mean \pm SD. Continuous measures were assessed using analysis of variance (ANOVA). Nonparametric data were analyzed with the Kruskal-Wallis test and categorical measures were compared using the χ^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS® Inc., Chicago, IL, United States).

RESULTS

Patients' characteristics

A total of 60 patients underwent SBCE for the evaluation of suspected small bowel disease, including OGB (occult: 23 patients; overt: 11 patients), CD (suspected CD: 12 patients; established CD: 9 patients), chronic diarrhea (2 patients) or suspected small bowel neoplasia (3 patients). Two patients from Group B were excluded due to technical issues that hampered the recording of several endoscopic images. One patient in Group C was

also excluded from the study because the capsule did not exit the stomach due to a pyloric benign stricture. Consequently, 57 patients (26 men and 31 women) were analyzed. Groups A, B and C included 20, 18 and 19 patients, respectively. Mean ages were 51.8 years for Group A, 50.4 years for Group B and 58.4 years for Group C. No significant differences were observed between the three groups in terms of age, sex or indication for SBCE (Table 1).

Transit time and quality of endoscopic images

The mean GET was 27.8 min for Group A, 27.2 min for Group B and 40.7 min for Group C ($P = 0.381$). The mean SBTT was 256.4 min for Group A, 256.1 min for Group B and 258.1 min for Group C ($P = 0.998$). The capsule reached the cecum in 20 patients (100%) in Group A, 16 patients (88.9%) in Group B and 17 patients (89.5%) in Group C ($P = 0.312$). In every patient with incomplete small bowel enteroscopy, capsule spontaneous exteriorization was confirmed with an abdominal plain radiography performed within two weeks after SBCE.

The number of patients with adequate cleansing of the small intestine, corresponding to excellent or good classification, was 5 (25%) in Group A, 5 (27.8%) in Group B and 4 (21.1%) in Group C ($P = 0.892$). In this subset, the cleansing was considered to be excellent in 2 patients (10%) from Group A, 3 (16.7%) from Group B and 4 (21.1%) from Group C ($P = 0.634$) and good in 3 (15%), 2 (11.1%) and 0 patients, respectively ($P = 0.522$). In a subanalysis also including those patients with fair cleansing, 8 (40%) in Group A, 10 (55.5%) in Group B and 9 (44.7%) in Group C ($P = 0.751$), the overall number of patients with acceptable small bowel cleansing,

Table 1 Patients' characteristics and indications for small bowel capsule endoscopy (%)

	Group A Overnight fast (n = 20)	Group B PEG (n = 18)	Group C PEG + simethicone (n = 19)	P value
Age (yr)	51.8 ± 21.6	50.4 ± 17.5	58.4 ± 18.8	0.437
Sex	11 (55)	11 (61.1)	9 (47.4)	0.702
N female (%)				
Indication				0.403
Occult OGIB	9	7	6	
Overt OGIB	5	0	5	
Suspected CD	3	6	3	
CD	3	2	3	
Chronic diarrhea	0	1	1	
Suspected SB neoplasia	0	2	1	

PEG: Polyethylene glycol; OGIB: Obscure gastrointestinal bleeding; CD: Crohn's Disease; SB: Small bowel.

corresponding to excellent, good or fair classification, was 13 (65%) in Group A, 15 (83.3%) in Group B and 13 (68.4%) in Group C ($P = 0.417$). Conversely, 7 patients (35%) in Group A, 3 patients (16.7%) in Group B and 6 patients (31.6%) in Group C were considered to have poor small bowel cleansing ($P = 0.417$), with significant fluid or debris so that the examination was unreliable (Figure 2). Focusing on the presence of a significant amount of bubbles, it occurred in 10 patients (50%) in Group A, 5 patients (27.8%) in Group B and 3 patients (15.8%) in Group C ($P = 0.065$). In the subanalysis between groups in a head to head comparison, in Group C where simethicone was used, the proportion of patients with a significant amount of bubbles (15.8%) was significantly lower than those in Group A (50%) ($P = 0.026$) (Table 2).

Diagnostic yield of capsule endoscopy

A definite diagnosis based on relevant small bowel endoscopic lesions was established in 60% of the patients in Group A (12 patients), 44.4% in Group B (8 patients) and 57.8% in Group C (11 patients) ($P = 0.587$).

DISCUSSION

Currently, there are no widely accepted guidelines for bowel preparation for SBCE, although inadequate cleansing, especially in the distal part of the small intestine, is considered a limitation^[4,5]. Moreover, only an average of 83.5% of the examinations are completed, with the capsule reaching the cecum during the recording time^[4,6]. The benefits of small bowel preparation prior to SBCE are still an issue of controversy^[7,8]. Currently, no uniform protocol is widely accepted and overnight fasting remains the standard preparation for SBCE. In a recently published prospective, multicenter randomized controlled study that included 291 patients, the authors concluded that a clear liquid diet and overnight fasting is sufficient to achieve an adequate level of cleanliness and is better

tolerated by patients than other forms of preparation^[9]. Another randomized study evaluated 150 patients, concluding that bowel purgatives and prokinetics did not improve completion rates or the quality of visualization and reduce patient acceptability^[10]. Conversely, accumulating evidence from other different studies seems to indicate that bowel preparation with purgative agents increases the diagnostic yield of the procedure by improving small bowel mucosal visualization compared with a clear liquid diet or overnight fast^[11-14]. The 2009 European Society of Gastrointestinal Endoscopy's updated information for SBCE stated that purgative bowel preparation enhances the quality of visualization and the diagnostic yield of SBCE^[1]. A meta-analysis has shown that small bowel purgative preparation, either with PEG solution or sodium phosphate (NaP), may improve the diagnostic yield of the examination^[15]. It also showed better quality of visualization of the mucosa in patients receiving purgatives, although it did not detect any difference between purgative preparation and a clear liquids diet regarding SBCE completion rate, GET and SBT^[15]. Those results are consistent with the conclusions from another meta-analysis that examined the effectiveness of bowel preparation for SBCE, which also included studies using prokinetics and simethicone^[16].

One of the reasons for the controversy surrounding this issue is that the cleansing grading systems have not been standardized, causing difficulties in comparing the results of numerous studies. Most of the reported grading systems are time consuming and difficult to apply routinely in clinical practice. In addition, the reliability and efficacy of these grading systems have rarely been evaluated^[17-19].

With respect to the type of purgative, there is also a lack of standardization in the methodology applied in the different studies, hampering the establishment of widely accepted recommendations. NaP and PEG were prospectively compared, resulting in a similar quality of small bowel preparation and completion rates^[20]. Nonetheless, most of the accumulated evidence in the literature supports the use of PEG. PEG solutions are non-absorbable and osmotically active and have been widely used in capsule endoscopy based on its ability to move through the bowel and potentially distend the lumen, wash out debris and bile, and possibly enhance small bowel transit time. The optimal dose of PEG that needs to be administered before SBCE is not entirely clear but 2 L appears to be sufficient^[21-23]. A recent study concluded that the ingestion of a small amount of PEG after the swallowing of an endoscopy capsule significantly improved CE image quality, but did not enhance the completion rate to the cecum^[24]. Another study has shown that bowel preparation with NaP also improved small bowel mucosal visualization when compared to 12 h overnight fasting^[3,25]. However, an important issue to be considered when using NaP is its potential ability to induce nonspecific aphthoid-like mucosal lesions, which may be endoscopically similar to those seen in CD; because of

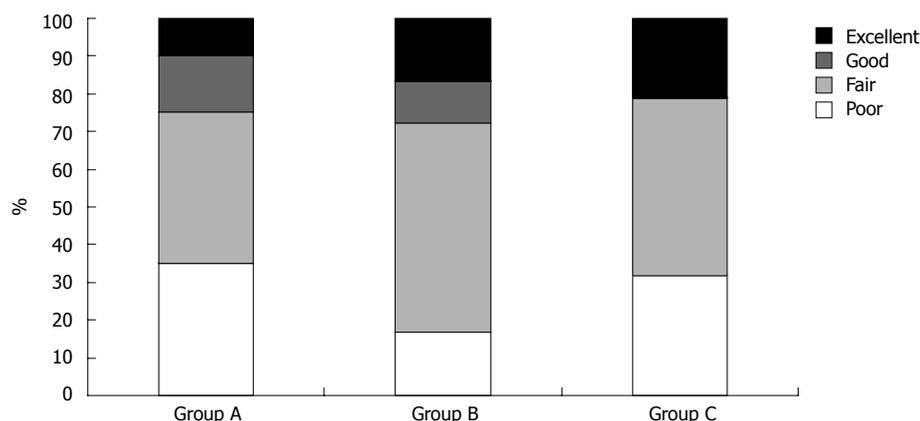


Figure 2 Small bowel cleansing among different groups. The number of patients with adequate cleansing of the small intestine, corresponding to excellent or good classification, was 5 (25%) in Group A, 5 (27.8%) in Group B and 4 (21.1%) in Group C ($P = 0.892$).

Table 2 Transit times, quality of image and relevant endoscopic findings (%)

	Group A overnight fast ($n = 20$)	Group B PEG ($n = 18$)	Group C PEG + simethicone ($n = 19$)	<i>P</i> value
GET (min)	27.8 ± 27.4	27.2 ± 35.2	40.7 ± 32.1	0.381
SBTT (min)	256.4 ± 91	256.1 ± 110	258.1 ± 113	0.998
ICV passing	20 (100)	16 (88.9)	17 (89.5)	0.312
Poor cleansing (< 50%)	7 (35)	3 (16.7)	6 (31.6)	0.417
Fair cleansing (50%-75%)	8 (40)	10 (55.6)	9 (47.4)	0.751
Good cleansing (> 75% although suboptimal)	3 (15)	2 (11.1)	0	0.522
Excellent cleansing	2 (10)	3 (16.7)	4 (21.1)	0.634
"Acceptable" cleansing (includes fair, good or excellent)	13 (65)	15 (83.3)	13 (68.4)	0.417
"Adequate" cleansing (includes good or excellent)	5 (25)	5 (27.8)	4 (21.1)	0.892
Bubbles	10 (50)	5 (27.8)	3 (15.8)	0.065 (A vs C), $P = 0.026$

PEG: Polyethylene glycol; GET: Gastric emptying time; SBTT: Small bowel transit time; ICV: Ileocecal valve.

the potential for misinterpretation of these lesions, some authors have contraindicated the use of NaP as a colonic cleansing preparation for patients with chronic diarrhea or in whom the diagnosis of inflammatory bowel disease is suspected^[26-28]. Moreover, as the oral NaP preparation may induce changes in serum levels of potassium and sodium, it is usually not recommended for patients with chronic renal failure, ischemic heart disease or cirrhosis, who frequently undergo SBCE for investigation of iron deficiency anemia^[25,29,30]. Another recent study evaluated magnesium citrate as preparation for SBCE and did not find differences regarding cleansing efficacy or rate of complete small bowel examinations^[31]. Simethicone is a detergent substance which can reduce the surface tension of air bubbles, thereby leading to their disruption. It is generally used to treat patients with symptoms caused by excess gas in the intestinal tract. Lately, it has also been shown to improve the quality of visualization of SBCE, although its effect on diagnostic yield remains controversial^[32-36]. Conversely, one other study did not support the use of 2 L of PEG and simethicone solution before SBCE^[37]. The recommended regimen for simethicone administration in this context has not been standardized.

In our study, we designed a control arm (Group A) corresponding to the current standard recommendations of liquid diet and overnight fast prior to SBCE and

aimed to compare the outcomes with those obtained when a purgative (PEG) was added to the preparation protocol (Group B). We also aimed to analyze if the addition of simethicone before swallowing the capsule (Group C) would carry any additional benefit. In this study, PEG or simethicone did not interfere with GET, SBTT, proportion of complete small bowel explorations or the diagnostic yield. We looked at the patients with acceptable small bowel cleansing, defining it as at least 50% of the mucosa with perfect condition for visualization, and there was a trend favoring Group B in this setting (Group A: 65%; Group B: 83.3%; Group C: 68.4%), although the differences were not statistically significant. However, if we look for those patients with an adequate small bowel cleansing, we could not find any significant difference between groups (Group A: 25%; Group B: 27.8%; Group C: 21.1%). Nonetheless, there was a trend favoring Group C in terms of attaining excellent cleansing (Group A: 10%; Group B: 16.7%; Group C: 21.1%), although not statistically significant. Our results for adequate cleansing were somewhat lower than those reported in other studies^[3,15,16], which may be due to different methodologies and a subjectivity in the assessment of endoscopic cleansing criteria. Our methodology included the use of a stopwatch to accurately determine the proportion of the mucosa under perfect cleansing conditions. Furthermore,

each exam was assessed by two experienced endoscopists and when there was no agreement, the images were reviewed until a consensus was achieved. Interestingly, when we focus specifically on patients with a significant amount of bubbles, felt by the reader to be sufficient to hamper a reliable interpretation of the endoscopic images, the subanalysis between groups in a head to head comparison showed that the proportion of those patients in Group C, where simethicone was used, was significantly lower than in Group A, where patients underwent standard preparation with liquid diet and overnight fast prior to SBCE (15.8% vs 50% ($P = 0.026$)).

In conclusion, this study shows that the use of simethicone before swallowing the capsule may reduce intraluminal bubbles in patients who were administered a purgative (PEG) the evening before the procedure when compared to standard preparation with clear diet and overnight fast before SBCE. Furthermore, there was a trend favoring the use of PEG to achieve a larger proportion of acceptable small bowel cleansing, and reduce the number of exams with poor cleansing, where the amount of fluid or debris may preclude a reliable interpretation. Moreover, there was also a trend towards obtaining excellent cleansing when protocol C was followed, although it was not statistically significant. This study has the limitation of not being designed to assess the outcomes of simethicone without the administration of concomitant purgative. To conclude, in our opinion, the preparation with 2 L of PEG the evening before SBCE, associated with the administration of 100 mL simethicone before capsule ingestion, seems to provide better conditions for the visualization of the small bowel mucosa when compared to the currently recommended preparation regimen and should be considered in patients who will undergo SBCE.

COMMENTS

Background

It has been over 10 years since small bowel capsule endoscopy (SBCE) was approved for clinical practice; however, the usefulness of routinely performing bowel preparation prior to SBCE still remains a matter of debate. To date, no standardized protocol has been widely accepted and overnight fasting remains the standard preparation for SBCE.

Research frontiers

It remains controversial whether the quality of mucosal visualization, diagnostic yield, gastric emptying time (GET), small bowel transit time (SBTT) and rate of complete small bowel explorations may be optimized with the use of a specific cleansing protocol prior to SBCE, with conflicting results being reported in the literature. This study aimed to evaluate whether the use of polyethylene glycol (PEG), with or without simethicone prior to capsule ingestion, may be useful in this context.

Innovations and breakthroughs

Bowel preparation with 2 L of PEG the evening before the procedure may improve small bowel cleansing and the quality of visualization, when compared to the currently recommended preparation regimen of overnight fasting. The additional use of 100 mg simethicone prior to capsule ingestion may further reduce intraluminal bubbles.

Applications

SBCE may have considerable limitations when the visualization is impaired by bubbles, bile, intraluminal fluid and debris. Since it is a costly and time consuming procedure, the adoption of a standardized regimen that may be able to opti-

mize the quality of visualization is needed. Though the results of these trial are encouraging, the role of PEG and simethicone in this setting should be further investigated in larger controlled studies.

Terminology

PEG (macrogol) is a polymer of ethylene oxide that works as an osmotically acting laxative. Simethicone is a mixture of polydimethylsiloxane and silicon dioxide that decreases the surface tension of gas bubbles and is used as an oral anti-foaming agent.

Peer review

The authors compared the quality of mucosal visualization, diagnostic yield, GET, SBTT and rate of complete explorations using three different cleansing protocols prior to SBCE, with the conclusion that preparation with 2 L of PEG before SBCE may improve small bowel cleansing and the quality of visualization and simethicone may further reduce intraluminal bubbles. This article elucidated the usefulness of bowel preparation prior to SBCE which can be used in clinical practice.

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