Randomized controlled trial of 3 days fasting and oral senna, combined with mannitol and simethicone, before capsule endoscopy

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Abstract

Background and Study Aims: The approach to small bowel preparation before capsule endoscopy (CE) is still suboptimal.

Patients and Methods: One hundred eighty patients were randomly allocated to 3 groups. Patients in Group A took 250 mL 20% mannitol and 1 L 0.9% saline orally at 05:00 hours on the day of the procedure. In Group B the same preparation was taken at 20:00 on the day before, and at 05:00 on the day of CE: in addition, 20 mL oral simethicone was taken 30 minutes before CE. Group C was treated identically to Group B, except that the patients fasted for 3 days and took 3 g senna orally 3 times daily before CE. The length of bowel containing green luminal contents was assessed by ImageJ software and bowel cleanliness was evaluated by computed assessment of the cleansing score.

Results: Cleansing of the whole small bowel and the distal small bowel were significantly different between the 3 groups ($\chi^2 = 22.470, P = .000; \chi^2 = 17.029, P = .000$, respectively). There were also significant differences between the 3 groups in the length of small bowel and specifically the length of the distal small bowel containing green luminal contents ($\chi^2 = 12.390, P = .000, \chi^2 = 15.141, P = .000$, respectively), but not with regard to the proximal small bowel ($\chi^2 = 0.678, P = .509$).

Conclusions: Three days fasting and oral senna, combined with 20% mannitol and simethicone, before CE, can reduce the effects of bile on the small bowel and improve small bowel cleansing, especially in the distal small intestine.

Abbreviations: AAC = visualized area percentage assessment of cleansing scores, AVM = arteriovenous malformation, CAC = computed assessment of cleansing score, CE = capsule endoscopy, ChiCTR = Chinese Clinical Trial Register, GET = gastric emptying time, PGE = polyethylene glycol, SBT = small bowel transit time.

Keywords: bowel preparation, capsule endoscopy, mannitol, senna, simethicone

1. Introduction

It is well known that intestinal cleanliness affects the quality of mucosal visualization and the diagnostic utility of capsule endoscopy (CE), especially with regard to positive findings in the distal small intestine. Many studies have been conducted on the effectiveness of preparations for the improvement of intestinal cleanliness, but no preparation is universally regarded as the most effective. This is because the following issues remain unresolved: the optimal choice of laxative, its dosage and time of administration, the best method of eliminating bile in the small intestine, the best method of reducing gas bubbles, and the most effective method for evaluating intestinal cleanliness.

The purpose of this study was to investigate the efficacy of senna, 20% mannitol, simethicone, and 3 days’ fasting in the elimination of bile, chyme, fecal residue, bubbles, and opaque intraluminal mucus in the preparation of the bowel.

2. Materials and methods

2.1. Patients

This randomized controlled trial enrolled patients who were undergoing CE examination for suspected small bowel disease at Sanming First Affiliated Hospital of Fujian Medical University during the period March 2014 to March 2017. It conformed to the 1995 Declaration of Helsinki and was approved by the Ethics Committee of Sanming First Hospital. This study was registered on March 9, 2014, in the Chinese Clinical Trial Register (ChiCTR) (number ChiCTR-DYT-1400440).

One hundred eighty inpatients were eligible and were randomly allocated into 3 groups using a computer-generated random number. This part of the study was conducted by a gastroenterology assistant, who also administered the study
medications. Exclusion criteria were: known or suspected obstruction, constipation or perforation of the gastrointestinal tract, chronic renal or cardiac failure, pregnancy, difficulty swallowing, history of gastrointestinal or abdominal surgery, use of antispasmodic, analgesic or prokinetic drugs, thyroid disease, diabetes mellitus and an inability to obtain informed consent. Patients with impaired intestinal motility were also excluded, because this can affect enteric cleansing. Before the procedure, all patients were given an explanation of what was to follow and informed consent was obtained.

2.2. Bowel preparation

Patients randomized to Group A took 250 mL 20% mannitol and 1 L 0.9% saline orally at 05:00 hours on the day of the procedure. Patients randomized to Group B took the same medication at 20:00 on the day before and at 05:00 on the day of CE, and 20 mL oral simethicone (Simethicone Emulsion (Espumisan) Berlin-Chemie AG Glienicker, Berlin, Germany, 40 mg/mL) was taken 30 minutes before CE. Patients randomized to Group C were treated identically to Group B, except that they fasted for 3 days and took 3 g oral senna 3 times daily before CE. During the 3 days of fasting, Group C patients were infused intravenously with 2.5 to 3.0 L glucose-containing fluid to provide the daily caloric requirement. Adverse events were recorded by a gastroenterology assistant.

2.3. Capsule endoscopy procedure

The OMOM CE system (Chongqing Jinshan Science and Technology Group, China) is composed of a smart capsule, image recorder, and image workstation. After ingesting a capsule, it is moved through the gut by gastrointestinal peristalsis and transmits a video signal to an image recorder carried on the body of the patient. It captures an image every 2 seconds, has a field of view of 140°, and has a capsule battery life of about 10 to 12 hours. Therefore, a total of about 20,000 images are captured per patient, using a charge-coupled device. Patients were permitted to move during the procedure. The recorder was disconnected after approximately 11 hours, and data were downloaded to a workstation and Chongqing Jinshan Image Processing Software, version 6.05, was used to evaluate the CE images.

2.4. Interpretation of capsule endoscopy

Two blinded, experienced investigators, who had reviewed images from over 300 patients, independently evaluated small bowel cleansing and the CE images. The gastric emptying time (GET) and small bowel transit time (SBTT) were recorded for all patients. The GET was defined as the time from the first gastric image to the time of the first duodenal image. The SBTT was defined as the time from the first duodenal image to the time of the first cecal image, for patients in whom the capsule reached the cecum, and the time from the first duodenal image to the time of the last small intestinal image, for patients in whom the capsule did not reach the cecum. SBTT was divided into 2 equal intervals describing the proximal and distal small bowel transit times.[6]

2.5. Evaluation of bowel cleansing

Small bowel cleansing was evaluated using the previously described computed assessment of cleansing score (CAC) grading system.[7,8]

2.6. Evaluation of bile contents

The Rapid reading station software (Given Imaging, Yoqneam, Israel)[7] and the Jinshan OMOM Imaging Station 6.05 use a tissue color bar for the identification of anatomic landmarks and for the maintenance of an appropriate perspective on the images, and generates a summary of the color representations of individual CE images. It often demonstrates greenish segments of gut, corresponding to individual CE images of luminal contents, consisting mostly of bile. To measure the amount of green luminal contents, an electronic high-resolution image of the Rapid user interface was captured using commercially available software (Screen Print and Capture 32 3.5, Provtech Ltd, West Kilb ridge, UK). The color bars for the entire region, the stomach, the small bowel, and the proximal and distal segments of the small bowel, were captured individually. The lengths of gut containing green luminal contents in the latter 4 segments were calculated using ImageJ 1.45 (National Institutes of Health).

2.7. Analysis of endoscopy findings

Endoscopy findings were described by our previously published article.[9]

2.8. Statistical analysis

Quantitative data are summarized using the mean (standard deviation (SD)). Differences between groups in categorical variables were assessed using the Chi-square test or Fisher exact test (when the expected count was <5). Normally distributed variables were compared using one-way ANOVA, and non-normally distributed variables using the Kruskal–Wallis test. Differences in constituent proportions were evaluated by the one sample goodness-of-fit test. P < .05 was considered to be statistically significant using 2-tailed tests. SPSS (version 19.0 Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Gender, age, and indications for CE

One hundred eighty patients (96 men and 84 women, aged 10–85 years, mean age 53.8 ± 16.3 years) were enrolled in the study. The indications for CE were obscure gastrointestinal bleeding (83 patients), abdominal pain (44 patients), chronic diarrhea (37 patients), and others (comprising 16 patients, including 8 patients with abdominal, 3 patients with suspected small bowel Crohn disease, and 5 patients who did not want to undergo gastrointestinal endoscopic examination and asked to check the CE by themselves).

All patients swallowed the CE spontaneously. In total, 7 patients (2 patients in Group A, 3 patients in Group B, and 2 patients in Group C) were not included in the analysis because the capsule had not reached the cecum before the end of the examination. Two patients in Group A were excluded owing to capsule retention by a stromal tumor in the jejunum and delayed gastric emptying (the capsule stayed in the stomach for 128 minutes). Three patients withdrew from Group B: 1 refused the procedure, 1 withdrew because the capsule was trapped in the cecum because of Crohn disease, and 1 because the capsule was trapped in the ileum due to the presence of a large adenomatous polyp. Two patients in Group C were excluded because of capsule retention at a region of ileal stenosis, caused by a lymphadenoma and a malignant tumor, respectively. Thus, 173
patients were included in the final analysis. The characteristics of the study population are shown in Table 1. There were no statistically significant differences among the 3 groups.

### 3.2. Gastric emptying time and small bowel transit time

GET was 53.1 ± 11.0 minutes in Group A, 51.3 ± 10.4 minutes in Group B, and 52.8 ± 9.8 minutes in Group C, which did not differ significantly between the 3 groups (F = 1.129, P = .326). Similarly, SBTT did not differ significantly between the groups: it was 365.5 ± 49.6 minutes in Group A, 363.7 ± 48.9 minutes in Group B, and 362.5 ± 50.8 minutes in Group C (F = 0.691, P = .532) (Table 2).

### 3.3. Tissue color bar segments

The total length of the captured tissue color bar segment in the 3 groups was the same (30.5 cm). The lengths of the stomach (3.8 ± 1.1 cm, 3.8 ± 1.3 cm, 3.6 ± 1.2 cm, F = 0.064, P = .938) and small bowel (23.2 ± 4.4 cm, 24.0 ± 4.5 cm, 23.2 ± 5.0 cm, F = 0.191, P = .826) segments were also not different among the 3 groups. In addition, there were no differences among the greenish luminal content lengths of the captured proximal small bowel segments (1.5 ± 0.8 cm, 1.5 ± 1.0 cm, 1.5 ± 0.8 cm, F = 0.084, P = .919), and there were no statistically significant differences between Groups A and B (P = .933), A and C (P = .757), or B and C (P = .697). However, the greenish luminal content lengths of the captured tissue color bars of the whole small bowel (6.7 ± 3.1 cm, 5.7 ± 2.9 cm, 4.2 ± 2.3 cm, F = 12.390, P = .000) and the distal small bowel (5.5 ± 2.3 cm, 4.2 ± 2.2, 3.3 ± 2.1, F = 15.141, P = .000) segments did show significant differences between the 3 groups. Specifically, among the whole small bowel segments: Group A versus Group B (P = .044), Group A versus Group C (P = .000), Group B versus Group C (P = .040), and among the distal small bowel segments: Group A versus Group B (P = .020), Group A versus Group C (P = .000), Group B versus Group C (P = .022), were significantly different (Table 2).

### 3.4. Assessment of small bowel cleanliness

When using CAC to evaluate small bowel cleanliness, a red-green ratio of >1.5 was considered adequate and a ratio of ≤1.5 was considered inadequate. In proximal small bowel, of 58 patients in Group A, 53 (91.4%) were rated as adequate and 5 (8.6%) as inadequate, of 57 patients in Group B, 55 (96.5%) were rated as adequate and 2 (3.5%) as inadequate, and of 58 patients in Group C, 57 (98.3%) were rated as adequate and 1 (1.7%) as inadequate. In the assessment of cleansing of the distal small bowel, 58.6% (34/58) in Group A were rated as adequate and 44.4% (24/58) as inadequate, 77.2% (44/57) in Group B were rated as adequate and 22.8% (13/57) as inadequate, and 91.4% (53/58) in Group C were rated as adequate and 8.6% (5/58) as inadequate. There was a statistically significant difference among the 3 groups (χ² = 17.029, P = .000), and there were also significant differences between Groups A and B (χ² = 4.544, P = .033), A and C (χ² = 16.598, P = .000), and B and C (χ² = 7.328, P = .007).
There were also significant differences between the 3 groups with regard to cleansing of the whole small bowel: 50.0% (29/58) in Group A were rated as adequate and 50.0% (29/58) as inadequate, 73.7% (42/57) in Group B were rated as adequate and 26.3% (15/57) as inadequate, and 89.7% (52/58) in Group C were rated as adequate and 10.3% (6/58) as inadequate ($\chi^2 = 22.470, P = .000$). There were also significant differences between the Groups A and B ($\chi^2 = 6.827, P = .009$), A and C ($\chi^2 = 21.645, P = .000$), and B and C ($\chi^2 = 4.913, P = .027$) (Table 3).

### 3.5. Positive rate analysis

A definite or probable diagnosis was achieved in 173 patients. The red spot (43 of 162, 26.5%) was the most common mucosal lesion, followed by mucosal erosion (29 of 162, 17.9%), arteriovenous malformation (AVM) (24 of 162, 14.8%), ulcer (18 of 162, 11.1%), polyph (12 of 162, 7.4%), intestinal varix (8 of 162, 4.9%), venous ectasia (6 of 162, 3.7%), diverticulum (4 of 162, 2.5%), and ascaris lumbricoides (3 of 162, 1.9%). Fifteen patients (9.3%) with recent or ongoing intestinal bleeding did not show any obvious lesion by CE (Table 4).

Eighty-five pathological lesions were found in the proximal small bowel, of which the constituent proportions in Groups A, B, C, and D were 30.6% (26 of 85), 34.1% (29 of 85), and 35.3% (30 of 85), respectively. The proportion in 3 groups were similar. Seventy-seven pathological lesions were detected in the distal small bowel: Group A, 16.9% (13 of 77); Group B, 33.8% (26 of 77); and Group C, 49.3% (38 of 77); respectively. Group C showed higher proportions (Table 5).

### 4. Discussion

CE has been used in clinical practice for 17 years, but the optimal method for bowel preparation before CE has not yet been established. The present study suggests that the use of laxatives can improve the cleanliness of the small intestine, but the form of the laxative used, its dose and the time of administration are not standardized. Previous studies have shown that increasing the dose of laxative does not improve intestinal cleanliness, but just prolongs the period over which its effects are inexperience.

The current European guide clearly states that preparation of the colon should be undertaken 3 to 8 hours ahead of the examination, and the last dose of bowel preparation should be no longer than 4 hours. Thus, if a laxative is taken the night before the procedure, the bowel preparation is poor. This is because the contents of the small intestine (food residues, fecal residue, and opaque secretions) continue to empty into the colon.

In this study we used 3 full days of intestinal preparation, which is 3 times the length of the normal bowel clearance regimen, during which the patient also fasts. Bowel clearance was aided by the administration of 20% mannitol at 20:00 the day before and at 05:00 on the day of the examination. This protocol aimed to ensure that the distal content of the small intestine was...
clearly demonstrated that the use of CAC to assess small bowel cleanliness is rapid, simple, and practical. This method is increasingly being adopted by gastroenterologists for decades. At present, evaluation of small bowel cleanliness is usually undertaken using the visualized area of the image will be smaller if bile secretion is lower, thereby improving the quality of bowel preparation in advance of CE. Although polyethylene glycol (PGE) is usually the first choice laxative used before CE in the recommended scheme for bowel preparation, we used 20% mannitol for this study, and these preparations are reported to be equally effective (European Association, 2013[18]). In the same year, the J. Curr. Med. Res. Opin. published consensus guidelines that also recommended 20% mannitol as the effective drug for bowel preparation before CE. Mannitol is an osmotic laxative that softens stools, stimulates gastrointestinal peristalsis, accelerates fecal expulsion, and washes out intraluminal contents. When cost effectiveness is taken into consideration, 20% mannitol is superior to PGE. However, oral administration of mannitol can cause the production of hydrogen gas, which is added to the gas produced by bacteria and intestinal gas exchange, and the gas (oxygen, nitrogen, and carbon dioxide) that is swallowed. All of these gases generate bubbles that adhere to the surface of the intestinal mucosa and which seriously detract from intestinal cleanliness. Simethicone is an antifoaming agent that decreases the surface tension of such bubbles, thereby reducing foaming and enhancing visualization of the mucosa.

Assessment of small bowel cleanliness has been difficult for gastroenterologists for decades. At present, evaluation of small bowel cleanliness is usually undertaken using the visualized area percentage assessment of cleansing scores (AAC) or the CAC[9]. The disadvantages of using the AAC are that the data generated vary significantly between clinicians, and that the calculation of the visualized area is complex and time-consuming. The advantages of using the CAC are that it can be used to evaluate a single image or a number of images of any part of the small intestine, that it is relatively quick and simple, and is less time-consuming, and that the results are not influenced by variation between clinicians. This method is increasingly being adopted by gastroenterologists.[18,16,19] Furthermore, the incorporation of these scores into the CE reading software would permit the generation of a fully automated score. Our study has demonstrated that the use of CAC to assess small bowel cleanliness is rapid, simple, and practical.

This study had several limitations. First, 3 days of bowel preparation is a long period of time and this is less convenient for patients, and left some patients feeling hungry. Second, a disadvantage of the use of CAC to assess small bowel cleanliness and the extent of green luminal contents is that it uses a visual analog scale (color intensity ratio of red to green) to evaluate the images. Although the green segments of the tissue color bar mainly represent bile, chyme, fecal residue, bubbles, and opaque secretions may also influence appear this color, and the visual analog scale cannot differentiate among these.

CE cannot deliver water or air into the intestine, and cannot suction, inflate or wash the intestinal lumen like a gastrointestinal endoscope. Moreover, it is a disposable product that cannot be reused, while the diagnostic yield of CE and quality of mucosal visualization may be impaired by the presence of bile, chyme, fecal residue, bubbles, intraluminal opaque mucus, or brightness. We have shown that bile in the intestine was the most important factor influencing small bowel cleanliness, with the second most important being chyme and fecal residue, followed by bubbles, intraluminal opaque mucus, and brightness. However, the brightness can be adjusted using the imaging software to ameliorate this particular problem.

In conclusion, our prospective study suggests that 3 days’ fasting and oral senna, combined with 20% mannitol and simethicone, before CE can reduce the effects of the aforementioned factors and improve image quality in the entire small bowel. In particular, this protocol can improve visualization of the distal small intestinal mucosa, facilitating more accurate capture of lesions during an hour-long video observation, thereby increasing the diagnostic yield of the procedure.

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