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Gastric preparation for magnetically controlled capsule endoscopy: A prospective, randomized single-blinded controlled trial

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ABSTRACT

Background and aims: Magnetically controlled capsule endoscopy (MCE) is a novel technique for which there is no agreed gastric preparation. We aimed to determine an optimal standardized gastric preparation regimen.
Methods: 120 patients referred for MCE were randomly assigned to gastric preparation with either water alone (A), water with simethicone (B) or water, simethicone and pronase (C). Image quality was assessed using cleanliness and visualization scores, higher scores equating to better image quality.
Results: The total cleanliness scores were (mean ± SD) 15.83 ± 2.41 (A), 21.35 ± 1.23 (B), and 20.82 ± 1.90 (C). The total visualization scores (mean ± SD) were 10.75 ± 2.02 (A), 15.20 ± 1.32 (B), and 15.08 ± 1.86 (C). While the image quality of the whole stomach in groups B and C were significantly better than group A ($P < 0.0001$), there was no statistical difference between group B and C ($P > 0.05$). MCE detected positive findings in 21 (52.5%), 27 (67.5%) and 21 (53.8%) patients in group A, B and C respectively, with no significant difference between groups ($P > 0.5$).
Conclusions: Simethicone swallowed with water prior to MCE produced the optimal gastric mucosal image quality. The addition of pronase had no demonstrable additional benefit.

1. Introduction

Capsule endoscopy (CE) was first introduced as a non-invasive small bowel imaging modality, better tolerated than conventional endoscopy and therefore possibly improving patients' compliance [1–3]. Given these advantages, CE has been rapidly applied to clinical practice. Whilst capsule endoscopy is now standard practice in small bowel examination, gastric examination remains a challenge because of the capacity and unusual anatomy of the stomach. Recently, several capsules manoeuvred with external magnetic fields, so-called magnetically controlled capsule endoscopy (MCE) or magnetic assisted capsule endoscopy (MACE), have been designed to make non-invasive exploration of the whole stomach possible [4–15]. From 2013 to date, more than 600 MCE have been performed in our center and MCE is widely accepted in China. The feasibility and safety of MCE has already been demonstrated [9,12]. Moreover, the diagnostic accuracy of MCE for gastric focal lesions was reported to be comparable with conventional gastroscopy in a large multi-center study [13].

In clinical practice, diagnostic accuracy may be hampered by the presence of intraluminal air bubbles, mucus, bile and chyme. Many investigators have already used detergents in the preparation of small bowel and colon examination procedures. Simethicone, a defoaming substance and pronase, a mucolytic agent, have been used in gastric preparation for conventional endoscopy with favourable results [16–20]. However, neither of them has been utilized in MCE and there is no agreed standardized regimen for gastric preparation. Therefore, this prospective, randomized, controlled study was performed to determine an optimal standardized gastric preparation regimen for MCE.

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2. Materials and methods

2.1. Study design

This study was a prospective, randomized physician-blinded controlled study. The study protocol was approved by the institutional review board of Shanghai Changhai Hospital and informed consent was obtained from each enrolled patient before the procedure.

2.2. Study patients

Consecutive patients referred for MCE in Changhai Hospital from June to October 2016 were enrolled and analyzed. Adult patients with upper abdominal complaints aged 18–75 years were eligible for this study. Patients with any of the following conditions [13] were excluded: (1) dysphagia or symptoms of gastric outlet obstruction, suspected or known intestinal stenosis, overt gastrointestinal bleeding, history of upper gastrointestinal surgery or abdominal surgery altering gastrointestinal anatomy, or post-abdominal radiation; (2) congestive heart failure, renal insufficiency, use of anticoagulant medication, poor general condition (American Society of Anesthesiologists class III/IV) or claustrophobia; (3) implanted metallic devices such as pacemakers, defibrillators, artificial heart valves or joint prostheses (although the low magnetic field used technically should not interfere with such devices); (4) pregnancy; (5) currently participating in another clinical study.

2.3. Study intervention

2.3.1. Magnetically controlled capsule endoscopy system

The MCE system was provided by Ankon Technologies Co. Ltd (Shanghai, China). The system consists of a guidance magnet robot, an endoscopic capsule, a data recorder, and a computer workstation with software for real-time viewing and controlling. The examiner uses two joysticks which control capsule movement by varying the strength of the magnetic field (by altering the distance of the magnet from the patient) and the polarity of the magnet. Relevant detailed parameters are referred to in previous studies [9,12–13].

2.3.2. Gastric preparation regimen and MCE examination protocol

Based on experience in clinical practice, simethicone (Espumisan; Berlin-Chemie, Germany, containing 40 mg simethicone in 1 mL emulsion) was applied as a defoaming agent to improve gastric mucosal visualization, and pronase granules (Deyou; Beijing Tide Pharmaceutical Co, China, containing 20,000 iu pronase) as a mucolytic [17,21–23]. All patients attended after overnight fasting (>8 h). The patients were equally randomized to one of three study groups according to a computer-generated random number table. Fifty minutes before swallowing the capsule, patients in the water control group (A) ingested 1 l of tap water at near body temperature (35 °C) to provide an air-water interface in the stomach for capsule navigation; patients in the simethicone group (B) ingested 950 ml of water and 400 mg simethicone; patients in the S-P group (C) ingested 900 ml of water, 400 mg simethicone and 20,000 iu pronase granules combined with 1 g $NaHCO_3$ to maintain the intragastric PH at 6–8 [17].

After attaching the data recorder, patients were asked to sit on the examination couch beneath the guidance magnet robot. The capsule was ingested in a left lateral position to facilitate esophageal passage. The examination was conducted with the patient lying in left lateral, supine, and finally right lateral positions. If difficulties in navigation were encountered, further positional change (including the prone position) was tried. If distension was insufficient, the patient was asked to drink more water. When the capsule reached the stomach, the investigator lifted the capsule away from the posterior wall, rotated and advanced the capsule to the fundus and cardiac regions, and then to the gastric body, angulus, antrum, and pylorus. The mean time of MCE examination was 15 min with a maximum of 20 min.

All patients were followed up for up to 2 weeks to confirm capsule excretion and document any adverse events [13].

Conventional gastroscopy to obtain biopsy or for therapeutic intervention was performed according to standard practice if lesions were identified by MCE.

2.4. Randomization

Eligible patients were randomly assigned in a 1:1:1 ratio to one of the three preparation groups, A, B or C, which they drank in the presence of a nurse uninvolved in the treatments or assessments. The randomization was based on a computer-generated list of random numbers using SPSS Statistics software.

2.5. Study outcomes

The primary outcome was the quality of MCE videos. Secondary outcomes included the safety of MCE and pathology detected by MCE including superficial gastritis, chronic erosive gastritis, polyps and ulcers.

To evaluate the quality of MCE videos, scores of gastric cleanliness and mucosal visualization in six primary anatomical landmarks of the stomach (cardia, fundus, body, angulus, antrum, and pylorus) were recorded. A 4-point grading scale (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.dld.2017.09.129) was introduced to define the cleanliness as excellent (no more than small bits of adherent mucus and foam: score 4), good (small amount of mucus and foam, but not enough to interfere with the examination: score 3), fair (considerable amount of mucus or foam present precluding a completely reliable examination: score 2) and poor (large amount of mucus or foam residue: score 1) [13,17,19–20,24]. As for mucosal visualization, a 3-point grading scale was introduced as good (>90% of the mucosa observed: score 3), fair (70–90% of the mucosa observed: score 2) and poor (<70% of the mucosa observed: score 1) as used in our previous study [13]. Scores for total gastric cleanliness and total mucosal visualization were obtained by summating the individual scores of the six anatomical landmarks.

Adverse events, defined as symptoms or signs such as abdominal distension, nausea, or vomiting, were monitored closely during the MCE procedure. Capsule retention (i.e., a capsule endoscope remaining in the gastrointestinal tract for more than two weeks or a capsule endoscope that requires directed intervention or therapy to aid its expulsion) was monitored and followed up for up to two weeks.

In this study, a qualified capsule endoscopist with an experience of more than 500 cases of MCE operation performed the MCE. A second endoscopist with over five years' reading experience, who was blinded to the type of gastric preparation, independently graded the quality of the images captured by MCE.

2.6. Statistical analysis

In the absence of previous studies of MCE preparation regimens, a pilot study was performed to obtain data on which to base a sample size calculation. Total gastric cleanliness scores were assessed for eight patients enrolled into each gastric preparation group, A, B and C. Our study assumed that the preparation regimen of simethicone/simethicone plus pronase granules would be better than clear water. It was calculated that 108 patients (36 per treatment

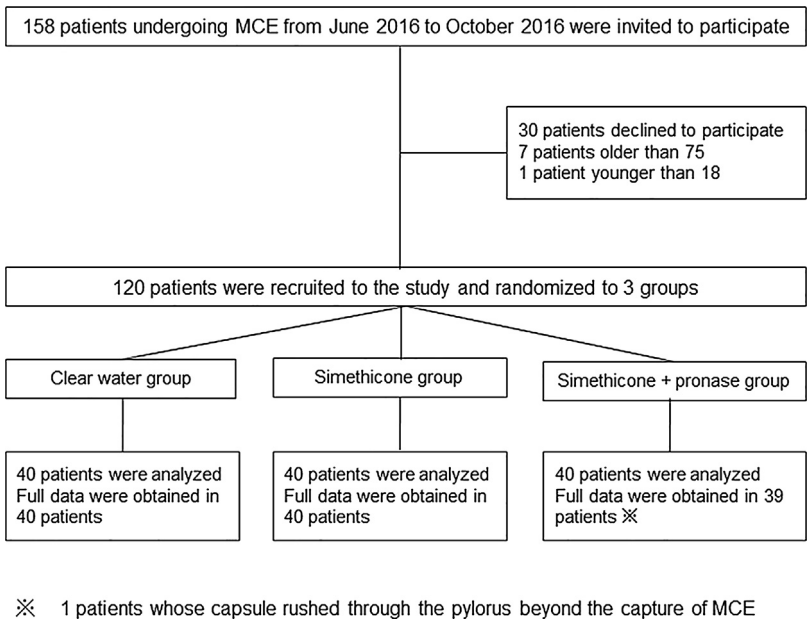

Fig. 1. Schematic flow diagram of the study.

group) would be required to detect a statistical difference with a power of 90% and a two-sided significance level of 0.05. Allowing for a possible withdrawal rate of 10%, 120 patients were enrolled.

Quantitative data were summarized as mean and standard deviation or median and interquartile range. Data with a normal distribution were compared using parametric analysis and non-normally distributed data were compared using nonparametric statistical analyses. Categorical variables were analyzed with the χ^2 exact test and quantitative data were analyzed using the Kruskal–Wallis test with a final two-sided P value of less than 0.05 indicating statistical difference. Semiquantitative ranked data as the scores of the quality (cleanliness and visualization) of the MCE were compared using the Kruskal–Wallis test. All the statistical data were analyzed with SPSS Statistics software (version 19.0).

3. Results

3.1. Patients

From June 2016 to October 2016, 158 patients were referred for MCE. 38 patients were excluded: 30 patients declined to participate in the study and eight patients did not meet the age inclusion criteria (seven patients were over 75 years and one patient less than 18 years of age). A total of 120 patients (40 in each group) were enrolled (72 male, 48 female, mean age 47.05 years (range, 20–74 years), Fig. 1). The characteristics of the study population are shown in Table 1.

3.2. Primary outcome

The results of the image quality of MCE are shown in Tables 2 and 3. The total scores of gastric cleanliness and mucosal visualization are represented in Fig. 2. One patient in group C was excluded from analysis as the capsule passed through the pylorus so quickly that it was not possible to quantify image quality.

3.2.1. Gastric cleanliness

Table 2 depicts the results of gastric cleanliness in the six primary anatomic landmarks. Cleanliness of the distal stomach (angulus, antrum and pylorus) in all three groups was excellent

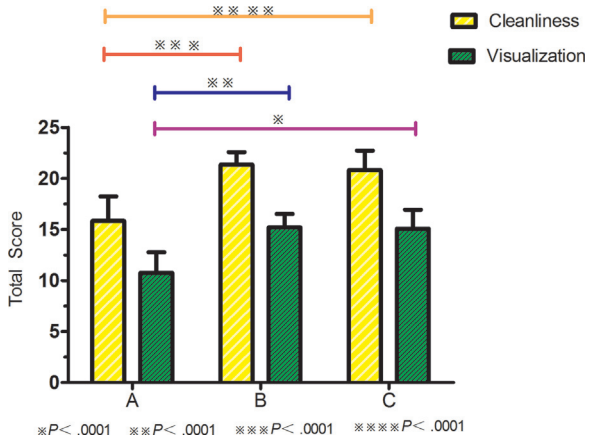

Fig. 2. Histogram showing the total scores of gastric cleanliness and mucosal visualization in different groups.
A. water control group, B. simethicone group, C. simethicone combined with pronase group.
Simethicone group and S-P group presented a better result of gastric mucosal visualization and cleanliness than water control group ($P < 0.001$) while no statistical difference was observed between the group B and group C ($p > 0.05$).

while the preparation of the fundus was good in the presence of simethicone and only fair with water alone. There were significant differences in cleanliness in each of the six primary landmarks among different groups (all $P < 0.0001$). Total gastric cleanliness scores were 15.83 ± 2.41, 21.35 ± 1.23, 20.82 ± 1.90 in the water control group, simethicone group and S-P group, respectively (Fig. 2). Results showed that administration of simethicone with or without pronase before MCE dramatically improves gastric cleanliness ($P < 0.0001$) while pronase did not improve the mucosal image quality ($P = 1.000$). Gender and age did not impact the result.

3.2.2. Mucosal visualization

As shown in Table 3, mucosal visualization was also better in the distal than in the proximal stomach, particularly the fundus. For each of the six primary anatomic landmarks, administration of simethicone with or without pronase significantly improved mucosal visualization (all $P < 0.0001$). As for the total visualization

Table 1
Patients' characteristics and indication for MCE.

	Water control group A (N = 40)	Simethicone group B (N = 40)	S-P group C (N = 40)	Total
Gender (male/female)	26/14	23/17	23/17	72/48
Mean age (range)	47.48 (23–74)	48.58 (20–73)	45.10 (20–69)	47.05 (20–74)
Mean BMI (SD)	23.41 ± 4.09	23.34 ± 3.71	22.36 ± 3.84	23.04 ± 3.88
Mean waist–hip (SD)	82.57 ± 11.64	83.55 ± 11.09	81.00 ± 11.35	82.37 ± 11.31
Indication				
Abdominal pain	22	10	21	53 (44.2%)
Abdominal distension	3	6	5	14 (11.7%)
Acid reflux or nausea or vomit	2	6	4	12 (10.0%)
OGIB or IDA	5	2	2	9 (7.5%)
Health Examination	8	16	8	32 (26.7%)

S-P group, simethicone combined with pronase group; BMI, Boby Mass Index; SD, standard deviation; OGIB, obscure gastrointestinal bleeding; IDA, iron-deficiency anemia.

Table 2
Comparison of gastric cleanliness with different gastric preparation regimen.

Location	Gastric cleanliness scores			P value			
	Group A	Group B	Group C	ABC*	A vs. B**	A vs. C	B vs. C
Cardia	1.95 ± 0.71	3.28 ± 0.68	3.26 ± 0.72	<0.0001	<0.0001	<0.0001	1.000
Fundus	1.78 ± 0.53	3.03 ± 0.62	2.79 ± 0.66	<0.0001	<0.0001	<0.0001	0.660
Body	2.45 ± 0.55	3.23 ± 0.42	3.13 ± 0.52	<0.0001	<0.0001	<0.0001	1.000
Angulus	3.03 ± 0.58	3.90 ± 0.38	3.77 ± 0.43	<0.0001	<0.0001	<0.0001	0.653
Antrum	3.08 ± 0.62	3.95 ± 0.22	3.90 ± 0.38	<0.0001	<0.0001	<0.0001	1.000
Pylorus	3.55 ± 0.55	3.98 ± 0.16	3.97 ± 0.16	<0.0001	<0.0001	<0.0001	1.000

* P value shows the statistical difference among groups A, B and C.
** P value shows the statistical difference between groups A and B.

Table 3
Comparison of mucosal visualization with different gastric preparation regimen.

Location	Mucosal visualization score			P value			
	Group A	Group B	Group C	ABC	A vs. B	A vs. C	B vs. C
Cardia	1.40 ± 0.55	2.25 ± 0.71	2.26 ± 0.72	<0.0001	<0.0001	<0.0001	1.000
Fundus	1.10 ± 0.30	1.95 ± 0.60	1.90 ± 0.60	<0.0001	<0.0001	<0.0001	1.000
Body	1.48 ± 0.51	2.23 ± 0.48	2.28 ± 0.51	<0.0001	<0.0001	<0.0001	1.000
Angulus	2.00 ± 0.56	2.85 ± 0.48	2.77 ± 0.49	<0.0001	<0.0001	<0.0001	1.000
Antrum	2.17 ± 0.68	2.95 ± 0.22	2.92 ± 0.27	<0.0001	<0.0001	<0.0001	1.000
Pylorus	2.60 ± 0.59	2.98 ± 0.16	2.95 ± 0.22	<0.0001	<0.0001	<0.0001	1.000

score, the results were 10.75 ± 2.02, 15.20 ± 1.32, 15.08 ± 1.86 in group A, B and C, respectively (P <0.0001, Fig. 2). Similarly, adding pronase proved no significant difference in total mucosal visualization compared with simethicone alone. Gender and age had no impact on the result.

3.3. Secondary outcomes

As for positive findings in the stomach, 21 (52.5%), 27 (67.5%) and 21 (53.8%) patients were diagnosed with superficial gastritis, chronic erosive gastritis, polyps or gastric ulcer (Supplementary Fig. S2 in the online version at DOI: 10.1016/j.dld.2017.09.129) in the water control group, simethicone group and S-P group, respectively (Table 4). No significant difference existed between the three groups (P > 0.5). One malignant gastric ulcer was detected by MCE and was later confirmed to be an advanced signet-ring cell carcinoma by conventional gastroscopy (Supplementary Fig. S3 in the online version at DOI: 10.1016/j.dld.2017.09.129) and biopsy. The patient died two months later.

3.4. Safety outcomes

All patients swallowed the MCE without difficulty. One capsule retained because of inflammatory pyloric edema required conventional endoscopic removal, giving a complication rate of 0.8%. No other adverse event was reported.

4. Discussion

Gastric mucus, bubbles and other residual debris obscure mucosal visualization [7–9]. Indeed, there is some evidence that a diagnosis of early gastric cancer can be improved with effective premedication through decreasing the amount of mucus and bubbles during conventional upper gastrointestinal endoscopy [18]. Therefore adequate preparation of the mucosal surface is critical for a non-invasive test such as MCE. Poor visualization may necessitate a repeat examination using conventional gastroscopy, which allows inflation and direct mucosal washing, but would add time and cost to the investigative pathway.

This prospective, single-blinded study was the first to investigate the effectiveness of simethicone and pronase on improving gastric image quality by removing bubbles and mucus. Simethicone is an antifoaming substance that disrupts bubbles by reducing surface tension. No known drug interactions and adverse effects have been reported [21]. Chang et al. suggested that the use of a small volume of simethicone suspension required more than 30 min to achieve the optimal visibility before gastroscopy [20]. Recent randomized controlled studies of oral simethicone administered before small bowel capsule endoscopy (SBCE) have shown

Table 4
Positive findings of the stomach for MCE.

Positive findings	Water control group (N = 40)	Simethicone group (N = 40)	S-P group (N = 39)
Superficial gastritis	5	6	6
Chronic erosive gastritis	13	21	12
Gastric polyps	2	0	3
Gastric ulcer[a]	1	0	0
Total	21 (52.5%)	27 (67.5%)	21 (53.8%)[b]

S-P group, simethicone plus pronase group.
[a] Including benign or malignant.
[b] One patient was excluded from the analysis of positive findings because the capsule pass through the pylorus so quickly that was beyond the capture of the whole gastric mucosa.

that it improved the visibility of gastrointestinal mucosa although its effect on diagnostic yield remained controversial [21–22,24–27]. Denzer et al. [10] used simethicone administered an hour before MCE and found the overall visibility and clarity reached 80.3% and 93.1% respectively. Consistent with these data, our study has also demonstrated a significant improvement in gastric cleanliness and visualization by administering simethicone with or without pronase before MCE.

Pronase contains several proteolytic enzymes which degrade gastric mucus and is used with simethicone in some countries prior to gastroscopy. Several studies have shown that pronase [17–19] and other mucolytics, *N*-acetylcysteine [24] and dimethylpolysiloxane [28] improved the visibility of the gastric wall during conventional endoscopy. However, oral pronase administration did not augment the effect compared with simethicone alone in the present study. The result was consistent with the study carried out by Asl and Sivandzadeh [28] who demonstrated that the routine use of 100 mg activated dimethicone alone in water 20 min prior to upper endoscopy led to the best visibility. Based on previous studies, to maximize the function of gastric mucus-removal by pronase, the intragastric pH should be maintained at pH 6–8, thus requiring the addition of sodium bicarbonate. Further study is needed to determine the optimum dose required to maximize the mucolytic action of pronase. Secondly, patients in earlier studies underwent a series of positional changes over a period of 15 min before endoscopy to ensure uniform distribution of the drug suspension throughout the gastric cavity [16–17,29]. In this study it was felt that two series of positional changes (after ingestion of the gastric preparation and again after swallowing the capsule) would make the protocol too cumbersome. But it is possible that adopting this practice might improve the effect of pronase.

Compared with the distal stomach, previous studies have shown that MCE consistently performed less well in visualizing the proximal stomach [12,15]. In our study, preparation of the proximal stomach (cardia, fundus) was poorer than the distal stomach (antrum, pylorus) regardless of the preparation regimen. This difference might be due to the reduced proximal mucosa-detergent contact time because of the effects of gastric peristalsis and gravity. Other approaches to improving visualization have included the addition of air-producing powder, but previous clinical trials have failed to demonstrate obvious benefit [7,9,12]. Although these data suggest that the quality of view is better distally than proximally, a large multicenter trial found diagnostic equivalence between conventional gastroscopy and MCE in detecting focal lesions, perhaps because of the rarity of isolated fundal lesions [13].

Our study has some limitations. As a single-center trial, the result may not be generalizable and further investigation in multicenter studies is desirable. Secondly, better image quality with simethicone did not translate into better diagnostic yield. Although the detection rate was increased in the simethicone group, there was no significant difference and the only malignant ulcer was found in the water control group. This is likely to be attributed to the small sample size and further appropriately powered studies would be needed to determine if better preparation equates to a better yield.

In conclusion, our study suggests that simethicone with water is the optimal gastric preparation regime for MCE examination. No further benefit was demonstrated by the addition of pronase. Further studies are required to determine if pronase at different concentrations, different pH or with positional changes to enhance drug distribution can improve gastric visualization. Given that the proximal stomach is less clean and less well visualized than distally, endoscopists should check these locations more carefully during MCE.

Guarantor of the article

Zhao-Shen Li, MD.

Registration of clinical trials

The project was registered at Clinicaltrials.gov (ID: NCT02846155), approved by Shanghai Changhai Hospital Ethics Committee on June 1th, 2016 (Approval number: CHEC 2016-064) and conformed to the provisions of the Declaration of Helsinki. The full trial protocol can be accessed at Clinicaltrials.gov.

Conflicts of interest

The authors declare no conflict of interest. All the patients were informed and accepted the MCE examination.

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