



Direct visualization of drug behaviors in the upper GI tract via magnetically controlled capsule endoscopy

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Background and Aims: Actual behaviors of drugs in the upper GI tract are not well elucidated. We assess the feasibility of magnetically controlled capsule endoscopy (MCE) in direct and real-time visualization of oral drug behaviors in the stomach.

Methods: From November 2019 to December 2019, 9 patients with a recent history of upper GI symptoms and 10 healthy volunteers were enrolled in this study. Participants swallowed magnetically controlled capsules to examine the whole stomach. After baseline examination, participants ingested dyed sucralfate gel, and MCE recorded the adhesion time, retention time, and distribution area of sucralfate gel. Outcomes included behaviors of sucralfate gel, safety, and satisfaction assessment of the procedures.

Results: Adhesion time of sucralfate gel in the abdominal symptoms group was significantly shorter than in the healthy control group (23.76 ± 1.37 minutes vs 31.96 ± 3.09 minutes; $P = .032$), whereas retention time was longer (98.85 ± 13.94 minutes vs 63.93 ± 8.57 minutes; $P = .043$). The distribution area of sucralfate gel in the abdominal symptoms group was significantly larger than in healthy control group in cardia (24.29 ± 7.39 vs 9.18 ± 4.06 ; $P < .0001$), fundus (18.90 ± 7.08 vs 8.49 ± 4.10 ; $P = .0015$), and pylorus (4.64 ± 2.72 vs 0.94 ± 0.90 ; $P = .0019$). No adverse events were observed. All participants had a high degree of satisfaction.

Conclusions: MCE is a feasible and noninvasive tool for direct and real-time visualization of drug behaviors (eg, sucralfate gel) in the stomach. ([ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study/NCT04327869). ID: NCT04327869.) (VideoGIE 2021;6:333-8.)

Oral administration is one of the most convenient drug delivery pathways, although the actual behavior of drugs in the upper GI tract is not well elucidated.¹ Bioimaging modalities, such as γ -scintigraphy, radiology, and magnetic resonance imaging, are limited by spatial resolution, long scanning time, and indirect visualization in monitoring the drug-release process.² Upper GI endoscopy, a radiation-free method, provides direct visualization and contributes to a better understanding of drug behaviors in the stomach. Unfortunately, the invasiveness and low patient compliance have limited the usage of upper GI endoscopy.³ Capsule endoscopy was introduced as a noninvasive and well-tolerated technique that minimizes the invasive nature of upper GI endoscopy; however, the passive movement has inhibited complete gastric visualization because of the large size of the gastric cavity.²

The invention of magnetically controlled capsule endoscopy (MCE) has filled this gap. With the use of external magnetic fields, movements of the capsule can be kept under control.^{4,5} Previous research has validated MCE as an important tool for complete gastric visualization and accurate gastric lesion diagnosis.⁴ Sucralfate gel, a new

liquid dosage form of sucralfate, has a stronger adhesion to gastric mucosa compared with the conventional dosage of sucralfate and can be well applied in studies monitoring oral drug behavior in the stomach.⁶ To date, no study has reported direct visualization of the intragastric adhesion and distribution behaviors of sucralfate gel.

Herein, we observed the characteristics of dyed sucralfate gel in the stomach to assess the feasibility of MCE in direct and real-time visualization of drug behaviors.

METHODS

From November 2019 to December 2019, 10 patients with a recent history of upper GI symptoms who met the indication for taking sucralfate gel and 10 healthy volunteers were enrolled in this study and underwent MCE in Changhai Hospital. Patients with any of the following contraindications for MCE were excluded: suspected or known GI stenosis; obstruction or other known risk factors for capsule retention; pregnancy or suspected pregnancy; pacemakers or electromedical devices implanted; use of



Figure 1. Sucralfate gel behavior at 30 minutes.

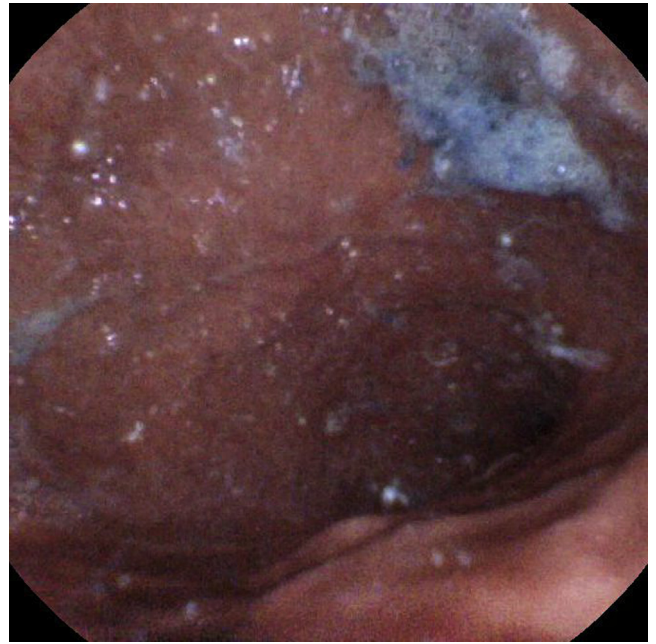


Figure 2. Sucralfate gel behavior at 60 minutes.

medication considered to influence the study outcome; and any other contraindications as determined by endoscopists. Written informed consent was obtained from each enrolled participant.

The NaviCam MCE system (Ankon Technologies Co, Ltd, Wuhan, China) is composed of a capsule endoscopy, a guidance magnet robot, a data recorder, and a computer workstation with software. The capsule (26.8 mm × 11.6 mm, weight of 4.8 g) is controlled by a C-armed guidance magnet robot to capture images of the GI tract at a rate of 2 frames per second, with a resolution of 480 × 480 pixels. The data recorder receives image data from the capsule endoscopy via wireless transmission. The computer workstation with ESNavi software (Ankon Technologies Co, Ltd) is used for real-time viewing and controlling.

Participants fasted from 8 pm the evening before the study. During the procedure, we attached the capsule with a thin hollow string to prevent it from entering the small bowel (Video 1, available online at www.giejournal.org).⁷ To enhance discrimination, sucralfate gel (Kunming Jida Pharmaceutical, Kunming, China) was dyed with 0.3 mL methylene blue (Jumpcan, Taixing, China). Participants swallowed the capsule with water. When the capsule entered the stomach cavity, participants sat up and ingested 4 g of aerogenic powder (Qingdao Redbutterfly Precision Materials, Qingdao, China) with 5 mL of water to distend the stomach. A gastric baseline examination was performed to identify the lesions. After baseline examination, participants ingested dyed sucralfate gel and underwent the examination, which was repeated at 30 minutes (Fig. 1), 60 minutes (Fig. 2), and 90 minutes (Fig. 3) until the sucralfate gel disappeared completely. When the procedure was

completed, the capsule was detached from the string when the operating doctor injected air into the hollow string by using the syringe and continued into the small bowel for further examination (Fig. 4).

Study outcomes

The primary outcome was the sucralfate gel's behavior in the fasted gastric cavity. Four parameters were used to assess sucralfate gel behavior: adhesion time, retention time, empty time, and distribution area. The adhesion time was recorded from when the sucralfate gel entered the stomach until all had adhered to the gastric wall. Retention time was evaluated by calculating the time from adhesion to the time of complete sucralfate gel disappearance. We defined the empty time of sucralfate gel because the empty time adds to the adhesion time.

Images of 6 primary anatomic landmarks (cardia, fundus, body, angulus, antrum, and pylorus) at different times (0, 30, 60, 90, 150, and 180 minutes after dyed sucralfate gel entered the stomach) were imported into MATLAB software (MathWorks, Natick, Mass, USA) to measure the distribution area of sucralfate gel by the following procedures: We used mask to remove the dark or overexposed pixels and converted to hue saturation value space; the thresholds were set to select the pixels containing the appropriate hue value, saturation value, and lightness value; the sucralfate gel distribution area was determined by comparing the number of dyed pixels captured with the number of pixels subtended by a paper square of known dimensions laced at the subsites (Fig. 5).

Secondary outcomes were safety and discomfort during the procedure. Safety was defined as any adverse event



Figure 3. Sucralfate gel behavior at 90 minutes.

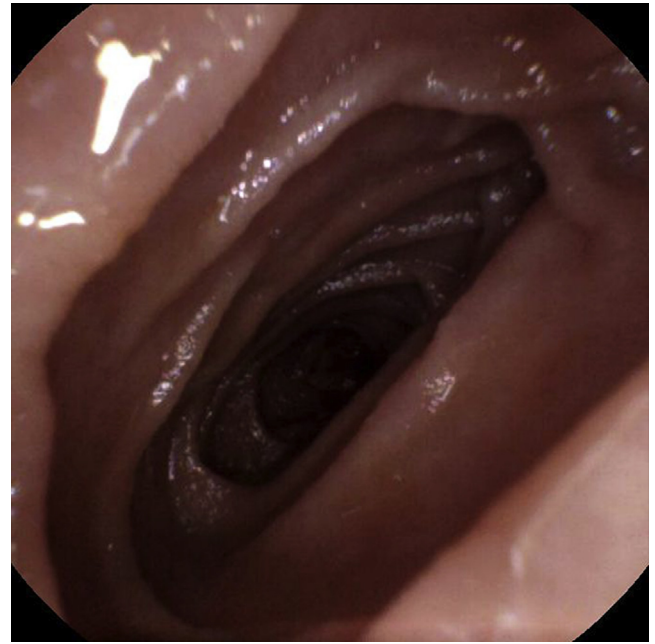


Figure 4. Capsule continued into the small bowel for further examination.

associated with MCE, including capsule retention, swallowing disorder, aspiration, technical failure, and procedural adverse events.⁸ The discomfort associated with the procedures included swallowing difficulty, nausea caused by the string, pulling the capsule up and down, abdominal distension or pain caused by ingesting aerogenic powder, discomfort during MCE examination, and pulling the string out. Participants graded the discomfort of the procedure using the Ramirez system on a scale from 0 to 3 (0 = no discomfort; 1 = mild/minimal discomfort; 2 = moderate discomfort; and 3 = severe discomfort).⁹

Statistical analysis

Descriptive statistics, including the standard error of the mean, median, and range, were provided for each primary outcome parameter (adhesion time, retention time, and empty time). The dynamic changes in the distribution area of the sucralfate gel over time were analyzed with GraphPad Prism 8.0.1 (GraphPad software Inc, La Jolla, Calif, USA). The regions of interest of cardia, fundus, body, angulus, antrum, and pylorus were created, and the area under the time-distribution curve for each primary anatomic landmark was calculated to compare distribution in the whole stomach.¹⁰ The analysis of variance model was used to quantify the difference in means between the healthy group and the abdominal symptom group. All statistical analysis was performed using SPSS statistical software (version 22, IBM, Armonk, NY, USA), and *P* values < .05 were considered statistically significant.

RESULTS

Patient characteristics

All participants swallowed the capsule successfully. Except for 1 patient with incomplete visualization owing to food residue in the stomach, all participants completed the examination: 9 patients (male = 4, mean age 28.1 years, range 21-48 years) with a recent history of upper GI symptoms and 10 healthy volunteers (male = 5, mean age 29.5 years, range 22-49 years) were finally involved in analysis. The main indication in the abdominal symptoms group was upper abdominal pain (*n* = 4, 44.44%), followed by dyspepsia (*n* = 3, 33.33%) and abdominal distension (*n* = 2, 22.22%). After baseline examination, we detected superficial gastritis in 5 cases (4 in the abdominal symptoms group, 1 in the healthy control group), erosive gastritis in 3 cases, and gastric ulcer in 2 cases. Baseline characteristics and lesions are shown in [Table 1](#).

Sucralfate gel behavior

Adhesion time of sucralfate gel in the abdominal symptoms group was significantly shorter than in the healthy control group (23.76 ± 1.37 minutes [range, 18.60-29.07 minutes] vs 31.96 ± 3.09 minutes [range, 17.55-53.37 minutes]; *P* = .032), and the abdominal symptoms group had a longer empty time (122.61 ± 13.34 minutes [range, 73.97-197.67 minutes] vs 108.99 ± 9.68 minutes [range, 58.13-156.07 minutes]; *P* = .126). A significantly longer retention time was found in the abdominal symptoms group (98.85 ± 13.94 minutes [range, 55.37-177.53 minutes] vs 63.93 ± 8.57 minutes [range, 38.13-118.38

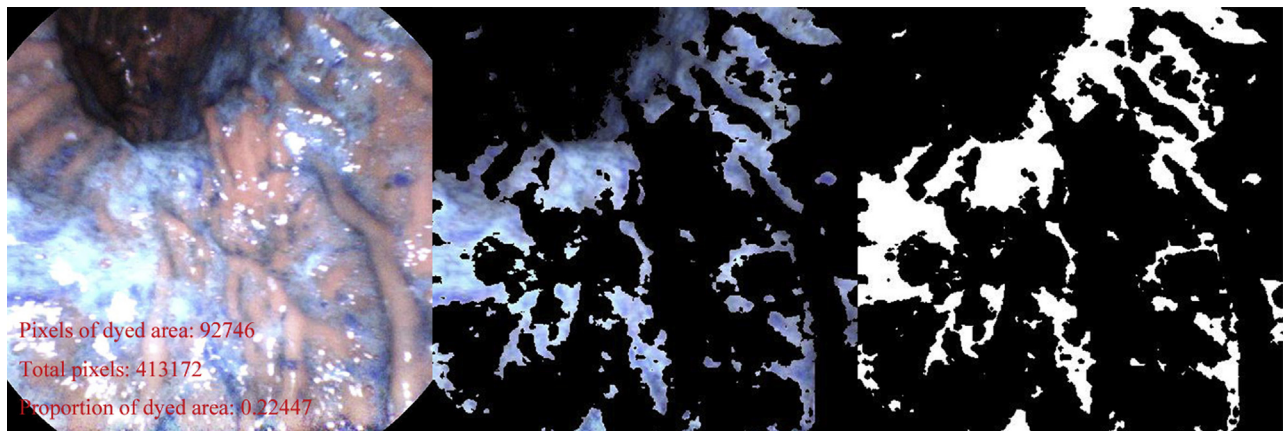


Figure 5. Distribution area of sucralfate gel calculated by MATLAB software.

TABLE 1. Patient characteristics and lesions detected by magnetically controlled capsule endoscopy

Characteristics	Abdominal symptoms group (n = 9)	Healthy control group (n = 10)
Male, n (%)	4 (44.44)	5 (50.00)
Mean age, y (range)	28.78 (21-48)	29.50 (22-49)
Indication, n (%)		
Abdominal pain	4 (44.44)	0 (0.00)
Dyspepsia	3 (33.33)	0 (0.00)
Abdominal distention	2 (22.22)	0 (0.00)
Lesions, n (%)		
Superficial gastritis	4 (44.44)	1 (10.00)
Erosive gastritis	3 (33.33)	0 (0.00)
Gastric ulcer	2 (22.22)	0 (0.00)

minutes]; $P = .043$) (Table 2). The distribution area of sucralfate gel in the abdominal symptoms group was larger than in the healthy control group in cardia (24.29 ± 7.39 vs 9.18 ± 4.06 ; $P < .0001$), fundus (18.90 ± 7.08 vs 8.49 ± 4.10 ; $P = .0015$), and pylorus (4.64 ± 2.72 vs 0.94 ± 0.90 ; $P = .0019$), whereas the distribution areas were similar in the gastric body (11.10 ± 5.08 vs 11.05 ± 6.11 ; $P = .9896$), angulus (4.22 ± 1.59 vs 5.30 ± 3.41 ; $P = .4883$), and antrum (3.70 ± 1.45 vs 4.62 ± 2.19 ; $P = .2709$) (Fig. 6, Table 2).

Safety and satisfaction assessment

There were no adverse events related to MCE. The mean discomfort scores for swallow difficulty, nausea caused by string, pulling capsule up and down, abdominal distention or pain caused by ingesting aerogenic powder, discomfort during MCE examination, and pulling the string out were 0.74 (range, 0-2), 1.11 (range, 0-2), 0.63 (range, 0-2), 0.68 (range, 0-3), 0.11 (range, 0-1), and 1.06 (range, 0-3), respectively.

DISCUSSION

Monitoring the delivery of oral drug substances in vivo is challenging.¹ Radiologic examinations, upper GI endoscopy, and capsule endoscopy are limited by indirect imaging, invasiveness, and lack of control, respectively.^{2,3} As a noninvasive, controllable, and direct imaging technique, MCE is the best choice for imaging the actual fate of oral drug delivery systems in the GI tract, especially in the stomach.^{4,5}

To our knowledge, this is the first study to identify the feasibility of MCE for direct and comprehensive visualization of the behavior of oral formulations (sucralfate gel) in the stomach. Because sucralfate could selectively bind to ulcerated mucosa by the way of strong electrostatic interaction,¹¹ the ability of sucralfate gel to adhere to gastric mucosa was more significant in patients with abdominal symptoms than in healthy volunteers. We found the sucralfate gel more likely adhered to the upper part of the stomach (ie, cardia and fundus) in the abdominal symptoms group, which

TABLE 2. Summary of adhesion, retention, and empty times and distribution area of sucralfate gel in patients with abdominal symptoms and healthy subjects

	Abdominal symptoms group (n = 9)	Healthy control group (n = 10)	P value
Adhesion time, min			.032
Mean (SE)	23.76 (1.37)	31.96 (3.09)	
Median	22.20	32.63	
Range	18.60-29.07	17.55-53.37	
Retention time, min			.043
Mean (SE)	98.85 (13.94)	63.93 (8.57)	
Median	77.47	57.93	
Range	55.37 - 177.53	38.13 - 118.38	
Empty time, min			.126
Mean (SE)	122.61 (13.34)	108.99 (9.68)	
Median	104.83	102.20	
Range	73.97 - 197.67	58.13 - 156.07	
Distribution area of sucralfate gel, mean (SE)			
Cardia	24.29 (7.39)	9.18 (4.06)	< .0001
Fundus	18.90 (7.08)	8.49 (4.10)	.0015
Body	11.10 (5.08)	11.05 (6.11)	.9896
Antrum	4.22 (1.59)	5.30 (3.41)	.4883
Angulus	3.70 (1.45)	4.62 (2.19)	.2709
Pylorus	4.64 (2.72)	0.94 (0.90)	.0019

SE, Standard error.

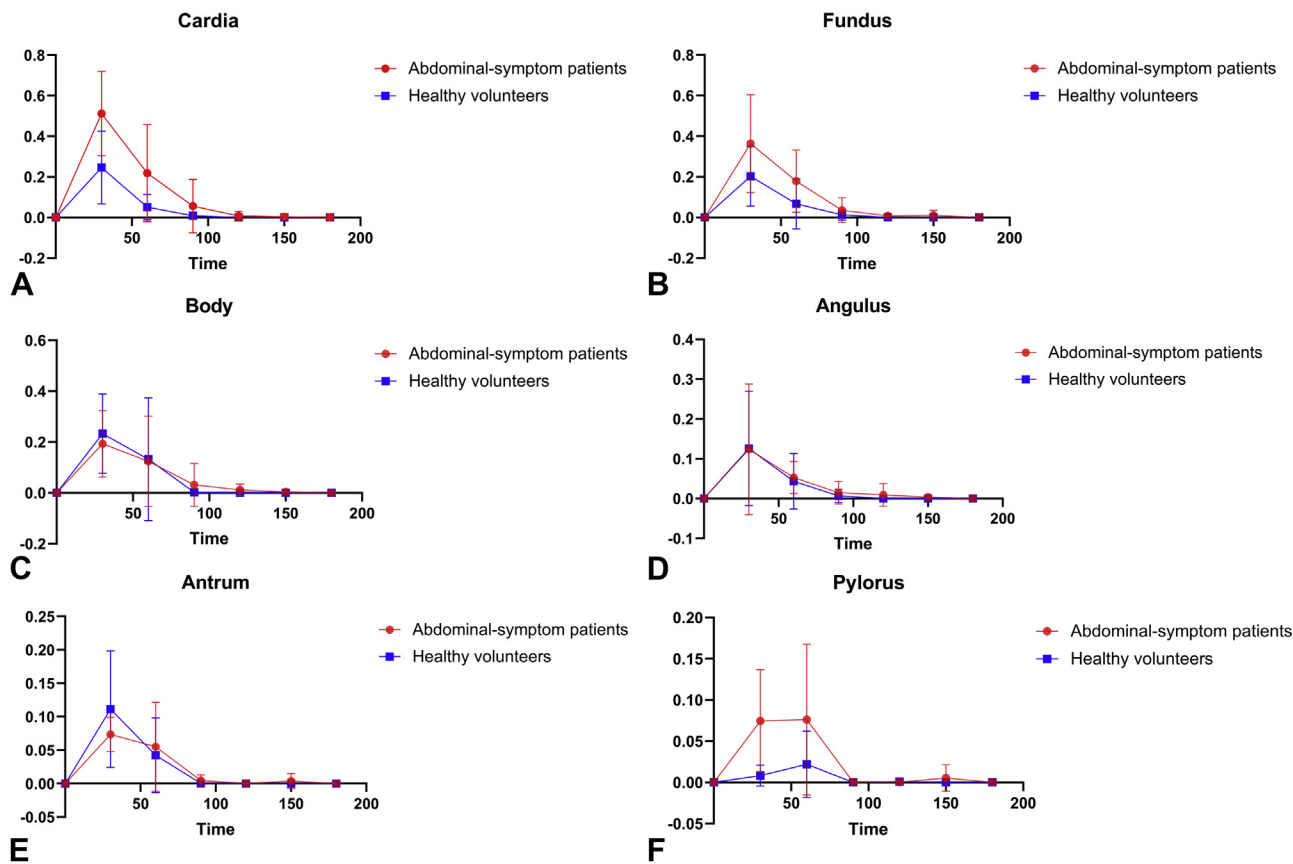


Figure 6. Data analysis of sucralfate gel distribution area at (A) cardia, (B) fundus, (C) body, (D) angulus, (E) antrum, and (F) pylorus.

was probably because most lesions were detected in the fundus and upper gastric body.

All participants had a high degree of satisfaction. The greatest discomfort during the procedure was nausea caused by the string, whereas the discomfort score during MCE examination was only 0.11. Additionally, no adverse events were observed during the procedure. MCE is a useful tool for real-time monitoring of oral dosage forms in the stomach, and MCE can also be used to investigate the performance of targeted drug delivery in specific areas of the GI tract in the future.

Our study has limitations. First, the sample size was limited. Gastric emptying rates varied between individuals, and the retention time of sucralfate gel can be influenced by gastric emptying. Direct visualization of sucralfate gel's protection ability in patients with abdominal symptoms needs further validation. Second, the participants included in our study are relatively young, and studies with larger sample sizes are warranted.

In conclusion, this pilot study demonstrates that MCE is a feasible and safe tool for direct visualization of the intragastric behavior of orally administered drugs (eg, sucralfate gel). With this new method, dynamic changes of other drug delivery systems in the upper GI tract can be further studied.

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DISCLOSURE

All authors disclosed no financial relationships.

Abbreviation: MCE, magnetically controlled capsule endoscopy.

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