

## Randomized Controlled Trial

**Effects of premedication with Pronase for endoscopic ultrasound of the stomach: A randomized controlled trial**

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**Abstract****AIM**

To analyze the effects of premedication with Pronase for endoscopic ultrasound (EUS) examination of the stomach.

**METHODS**

This was a prospective, randomized and controlled clinical study. All patients were randomly assigned to either the Pronase group or placebo group. The pretreatment solution was a mixed solution of 20000 U of Pronase and 60 mL sodium bicarbonate solution in the Pronase group, while an equal amount of sodium bicarbonate solution was administered to the placebo group. All operators, image evaluators and experimental recorders in EUS did not participate in the preparation and allocation of pretreatment solution. Two blinded investigators assessed the obscuration scores for the EUS images according to the size of artifacts (including ultrasound images of the gastric cavity and the gastric wall). Differences in imaging quality, the duration of examination and the usage of physiological saline during the examination process between the Pronase group and the control group were compared.

## RESULTS

No differences existed in patient demographics between the two groups. For the gastric cavity, the Pronase group had significantly lower mean obscuration scores than the placebo group ( $1.0476 \pm 0.77$  vs  $1.6129 \pm 0.96$ , respectively,  $P = 0.000$ ). The mean obscuration scores for the gastric mucosal surface were significantly lower in the Pronase group than the placebo group ( $1.2063 \pm 0.90$  vs  $1.7581 \pm 0.84$ , respectively,  $P = 0.001$ ). The average EUS procedure duration for the Pronase group was  $11.60 \pm 3.32$  min, which was significantly shorter than that of the placebo group ( $13.13 \pm 3.81$  min,  $P = 0.007$ ). Less saline was used in the Pronase group than the placebo group, and the difference was significant ( $417.94 \pm 121.38$  mL vs  $467.42 \pm 104.52$  mL, respectively,  $P = 0.016$ ).

## CONCLUSION

The group that had Pronase premedication prior to the EUS examination had clearer images than the placebo group. With Pronase premedication, the examination time was shorter, and the amount of saline used during the EUS examination was less.

**Key words:** Artifacts; Randomized controlled trial; Endosonography; Pronase; Stomach

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**Core tip:** Previous studies have confirmed that Pronase can improve the quality of endoscopic ultrasound (EUS) images. Based on previous findings, this study hypothesized that Pronase could further shorten the duration of examination and reduce the usage of physiological saline during EUS examination through improving the quality of EUS images. Moreover, this study verified this hypothesis. This study found that for EUS examination, preoperative application of Pronase could provide clearer ultrasound images, shorten the duration of EUS examination, and reduce the intraoperative usage of physiological saline.

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## INTRODUCTION

Endoscopic ultrasound (EUS) is an important tool to diagnosis benign and malignant diseases of the gastrointestinal tract and pancreaticobiliary system<sup>[1-4]</sup>. Previous studies demonstrated its superiority in evaluating the staging of early gastric carcinoma and gastric submucosal tumors, as compared with

standard diagnostic modalities such as computed tomography, conventional ultrasonography, and magnetic resonance imaging<sup>[5-14]</sup>. Gastric mucus is one of the most frequent sources of artifacts during an EUS<sup>[15,16]</sup>. The vague image will influence the EUS procedure and increase the inspection time. Low-quality EUS images could lead to the misdiagnosis of small lesions and misinterpretation of the invasion depth in early gastric cancer<sup>[17,18]</sup>. To flush the mucosa and eliminate artifacts, more saline would need to be injected into the stomach, which is associated with a more uncomfortable examination and an increased risk of aspiration.

Pronase, separated and extracted from the culture filtrate of *Streptomyces griseus*<sup>[19-21]</sup>, is a kind of proteolytic enzyme that can disrupt the mucous gel layer on the surface of the stomach<sup>[22]</sup>, and it has been used to prepare digestive and anti-inflammatory enzymes. Fujii *et al*<sup>[23]</sup> first found that during chromoendoscopy and conventional endoscopy procedures, premedication with Pronase could improve endoscopic visualization. Over the last 10 years, it has become common practice to provide patients a pretreatment solution containing dimethylpolysiloxane and Pronase before endoscopy. Sakai *et al*<sup>[15]</sup> found that pretreatment with Pronase could reduce artifacts during an EUS examination. Han *et al*<sup>[24]</sup> also found that premedication with a mixture containing bicarbonate and Pronase seemed to reduce hyperechoic artifacts secondary to the gastric wall and lumen.

Herein, we presumed that decreasing the number of artifacts would shorten the EUS examination, leading to a decrease in the amount of saline solution irrigated during the procedure. To further address this hypothesis, we conducted this study to analyze the effects of Pronase on EUS imaging and EUS duration time, as well as the saline volume irrigated during EUS.

## MATERIALS AND METHODS

### Patients

This prospective, randomized and controlled single-center study was conducted at the Endoscopic Center of Shengjing Hospital of China Medical University. The eligibility and exclusion criteria are listed in Table 1. At least 102 patients were needed to acquire 90% statistical power based on a previous study performed by Han *et al*<sup>[24]</sup> in 2011. All patients provided written informed consent before the procedure. The Institutional Review Board of China Medical University approved this study based on the Helsinki Declaration. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR-DPD-15006240).

### Randomization and endoscopic procedures

The local clinical trials unit performed computerized individual randomization. Included patients were

**Table 1** Eligibility and exclusion criteria for this study

Eligibility criteria	
1	Patients who required an EUS examination because of gastric diseases
2	Patients aged 18-70 yr
Exclusion criteria	
1	Patients with contraindications to endoscopy
2	Patients allergic to the pharmaceutical ingredients
3	Patients with gastric bleeding or suspected gastric bleeding
4	Patients with blood coagulation dysfunction
5	Patients with severe psychological diseases such as depression, anxiety, hypochondria and hysteria
6	Patients with severe cardiac dysfunction (NYHA cardiac function classification $\geq$ class III)
7	Patients with abnormal hepatic function (serum ALT and AST levels of $\geq$ 4 times the upper normal limit)
8	Patients with renal dysfunction (serum Cr level of $\geq$ 2 times the upper normal limit)
9	Patients with moderate to severe ventilatory dysfunction
10	Diabetic patients with unsatisfactory glycemic control
11	Hypertensive patients with unsatisfactory blood pressure control
12	Pregnant women or women who are breastfeeding

ALT: Alanine aminotransferase; AST: Aspartate transaminase; Cr: Creatinine; EUS: Endoscopic ultrasonography; NYHA: New York Heart Association.

**Table 2** Scoring of the gastric cavity obscurity grade

Score	Number of high-echo spots
0	No or few
1	Low
2	Moderate
3	High

**Table 3** Scoring of the gastric wall surface in endoscopic ultrasonography imaging

Score	Artifacts
0	Notable, affecting the diagnosis
1	Moderate
2	Negligible
3	None, clear wall interface

randomly assigned to either the Pronase or placebo group with a computer-generated random allocation sequence. In the placebo group, the premedication solution contained a 1 g sodium bicarbonate solution; in the Pronase group, the premedication solution contained a 1 g sodium bicarbonate solution and 20000 U of Pronase. All the solutions were placed in a paper cup of the same color. In both groups, 60 mL of the premedication solution was administered about 10-30 min before the EUS examination, as a previous report recommended<sup>[25]</sup>. The study investigators were not involved in the preparation of the premedication solution. All patients underwent EUS examinations using both radial and linear-array systems. All procedures were carried out by one endosonography.

### Measurements

As previously reported<sup>[15,24]</sup>, for EUS imaging, the gastric cavity obscurity grade is scored from 0 to 3 (Figure 1), according to the number of high-echo spots, as shown in Table 2. EUS imaging of the gastric wall surface was similarly scored (Figure 2), as shown in Table 3. All EUS images were assigned to two experienced endoscopists, who scored the images and were blind to the procedure at the time of scoring. We recorded the duration of the EUS procedure for all patients. EUS duration was measured from the time the endoscope was inserted into the mouth to the time the endoscope was withdrawn from the mouth. One investigator recorded the volume of saline solution irrigated during the EUS procedure to determine

whether premedication with Pronase decreased the amount of saline used.

### Statistical analysis

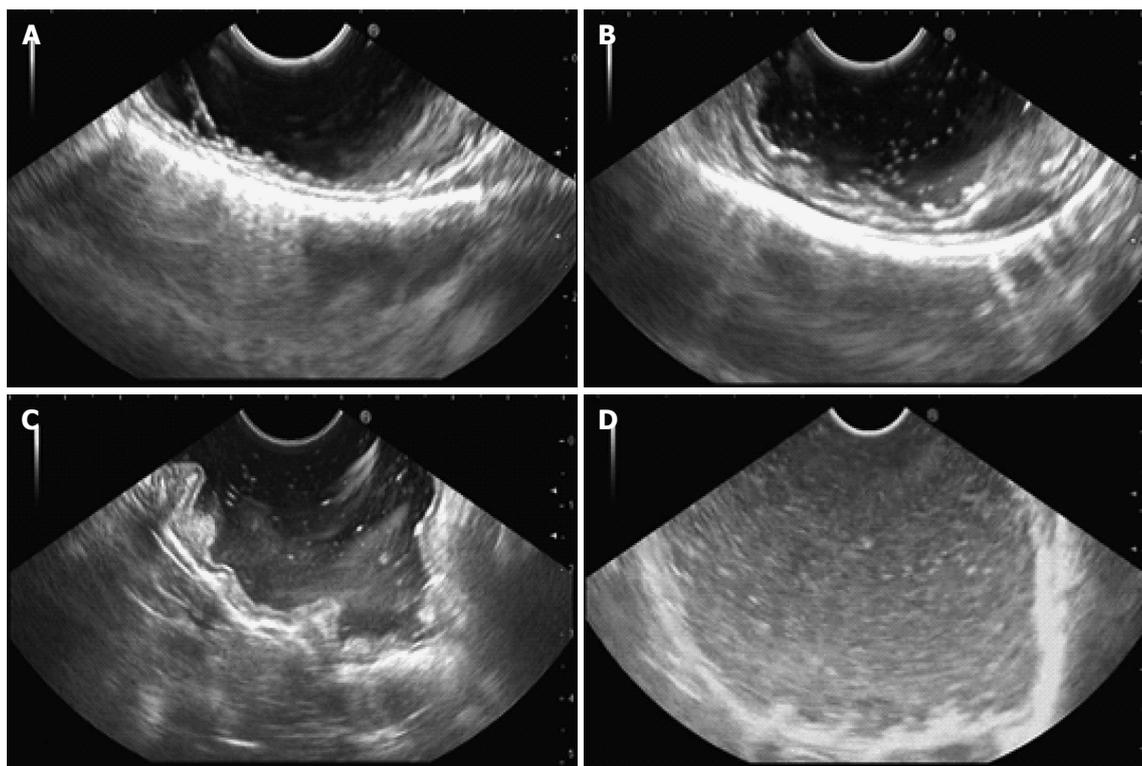
The demographic characteristics were assessed using a Pearson  $\chi^2$  test or one-way analysis of variance. The obscurity scores for the two groups were assessed using a rank sum test with Mann-Whitney *U* comparisons and the Student's *t*-test. The mean obscurity scores for the gastric cavity and gastric mucosal surface, the EUS procedure duration and the volume of saline were expressed as mean  $\pm$  SD and compared using the Student's *t*-test. A *P* value of  $< 0.05$  was considered significant.

## RESULTS

From May 2015 to July 2015, 125 patients were enrolled in the study and allocated equally to either the Pronase group (63 patients) or placebo group (62 patients). There were no differences in age ( $P = 0.319$ ), sex ( $P = 0.611$ ), location ( $P = 0.532$ ), or EUS methods ( $P = 0.391$ ) between groups, as shown in Table 4.

The obscurity scores for the gastric cavity and gastric mucosal surface were compared between the two groups (Table 5). The Pronase group had significantly lower obscurity scores for the gastric cavity and gastric mucosal surface than the placebo group ( $P < 0.05$ ).

Table 6 compares the mean obscurity scores for the gastric cavity and gastric mucosal surface, and



**Figure 1** Scoring of the gastric cavity obscurity grade depending on the numbers of high-echo spots. A: Score 0, few or no high-echo spots in the gastric cavity; B: Score 1, low number of high-echo spots; C: Score 2, moderate number of high-echo spots; and D: Score 3, high number of high-echo spots.

**Table 4** Demographic characteristics of enrolled patients

	Pronase group	Placebo group	Value	P value
Number of patients	63	62		
Age, mean $\pm$ SD	55.78 $\pm$ 12.37	53.47 $\pm$ 13.41	$t = 1.001$	0.319
Sex				
Male	22	19	$\chi^2 = 0.259$	0.611
Female	41	43		
Location				
Fundus	14	9	$\chi^2 = 1.264$	0.532
Corpus	26	29		
Antrum	23	24		
Methods				
Radial EUS	48	43	$\chi^2 = 0.737$	0.391
Linear-array EUS	15	19		

EUS: Endoscopic ultrasonography

EUS procedure means, as well as the mean volume of saline irrigated during the EUS procedure. As for the gastric cavity, the mean obscurity scores in the Pronase and placebo groups were  $1.0476 \pm 0.77$  and  $1.6129 \pm 0.96$ , respectively. Additionally, for the gastric cavity, the Pronase group had significantly lower mean obscurity scores than the placebo group ( $P = 0.000$ ). As for the gastric mucosal surface, the mean obscurity scores in the Pronase and placebo groups were  $1.2063 \pm 0.90$  and  $1.7581 \pm 0.84$ , respectively. Further, for the gastric cavity, the Pronase group had significantly higher mean obscurity scores than the placebo group ( $P = 0.001$ ).

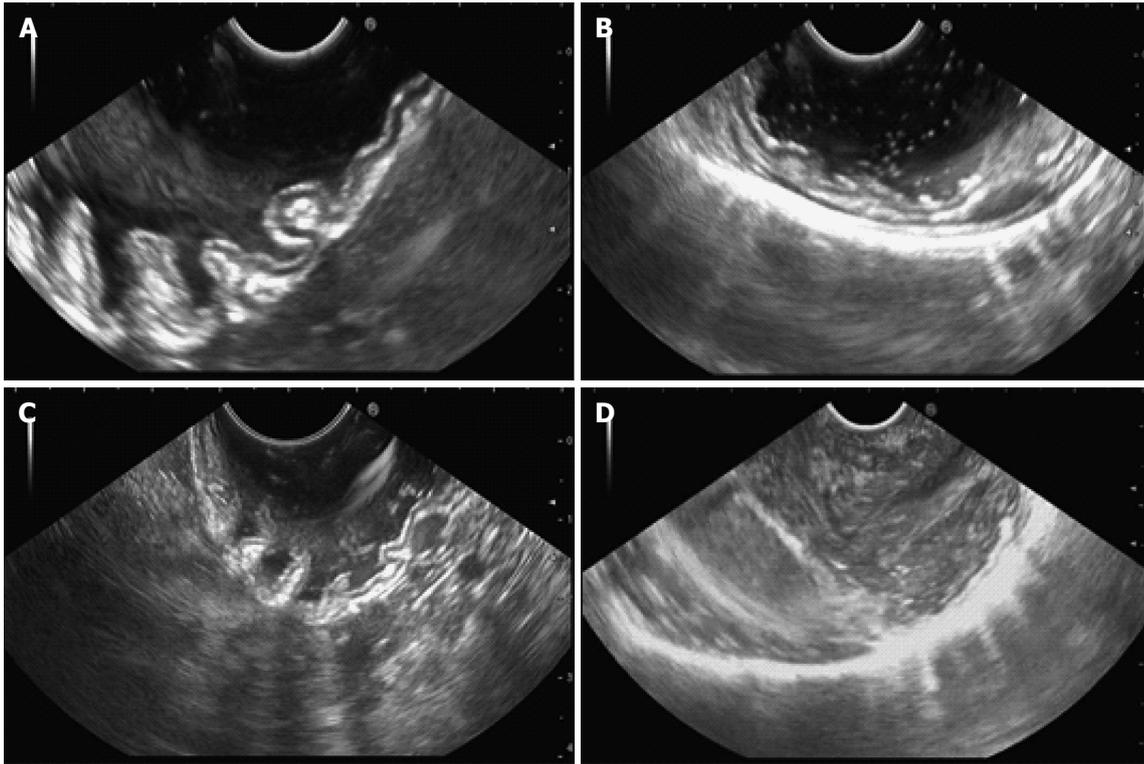
The average EUS procedure time for the Pronase

group was  $11.60 \pm 3.32$  min, which was significantly shorter than the placebo group ( $13.13 \pm 3.81$  min,  $P = 0.007$ ). The mean saline volumes were  $417.94 \pm 121.38$  mL and  $467.42 \pm 104.52$  mL in the Pronase group and placebo group, respectively. The amount of saline used for the Pronase group was less than that of the placebo group, and the difference was significant ( $P = 0.016$ ).

## DISCUSSION

EUS is now increasingly available and plays a significant role in the diagnosis and intervention of gastrointestinal and pancreaticobiliary diseases<sup>[1,26-29]</sup>. Artifacts secondary to gastric mucus can potentially interfere with visibility during EUS scanning of the stomach. Bubbles and foams may lead to blurred layers and borders and the possible diagnosis of a lesion that does not exist<sup>[16,30-32]</sup>. Before EUS, premedication played a major role in ensuring satisfactory visualization of the gastric cavity and wall<sup>[22,23,33]</sup>.

Pronase, which can eliminate gastric mucus as a mucolytic enzyme, can further improve diagnosis of gastric diseases using radiographic imaging techniques<sup>[34]</sup>. A randomized study conducted by Fujii *et al*<sup>[23]</sup> demonstrated that premedication with Pronase not only substantially enhanced visibility before and after methylene blue spraying, but also reduced the duration of chromoendoscopy examination. In 2002, Kuo *et al*<sup>[22]</sup> also found that premedication with Pronase provided



**Figure 2** Scoring of the gastric wall surface depending on the amount of adherent mucus. A: Score 0, no artifacts, clear wall interface; B: Score 1, minimal artifacts, negligible; C: Score 2, moderate artifacts; and D: Score 3, significant artifacts affecting diagnostic judgment.

**Table 5** Endoscopic ultrasonography obscurity scores for the gastric cavity and mucosal surface

	Pronase group	Placebo group	Value	P value
Gastric cavity obscurity scores during EUS				
3	14	8	Z = -3.428	0.001
2	35	21		
1	11	20		
0	3	13		
Gastric mucosal surface obscurity scores during EUS				
3	11	7	Z = -3.861	0.000
2	37	10		
1	6	36		
0	9	9		

EUS: Endoscopic ultrasonography.

**Table 6** Mean endoscopic ultrasonography obscurity scores for the gastric cavity and mucosal surface

	Pronase group	Placebo group	Value	P value
Mean gastric cavity obscurity scores	1.0476 ± 0.77	1.6129 ± 0.96	t = -3.617	0.000
Mean gastric mucosal surface obscurity scores	1.2063 ± 0.90	1.7581 ± 0.84	t = -3.534	0.001
Duration of EUS, mean ± SD	11.60 ± 3.32	13.13 ± 3.81	t = -2.387	0.018
Volume of saline, mean ± SD	417.94 ± 121.38	467.42 ± 104.52	t = -2.441	0.016

the clearest endoscopic visibility. In 2003, Sakai *et al.*<sup>[15]</sup> reported the first Pronase trial and suggested that premedication with Pronase reduced artifacts during endoscopic ultrasonography. In 2011, Han *et al.*<sup>[24]</sup> found that premedication with bicarbonate mixed with Pronase decreased the number of hyperechoic artifacts secondary to the stomach wall and lumen during EUS.

As for the gastric mucosal surface and gastric cavity, we found that the Pronase group had significantly lower obscurity scores than the placebo group. The average time for the EUS examination was significantly shorter for the Pronase group than the placebo group. The amount of saline irrigated was significantly less for the Pronase group than the placebo group. The Pronase

premedication solution provided clearer images of the patients according to the endosonographer, which may facilitate EUS examination and shorten the procedure duration. Meanwhile, a clearer image may lead to less saline usage during the EUS examination.

Woo *et al.*<sup>[25]</sup> found that the administration of Pronase, sodium bicarbonate, and dimethylpolysiloxane 30 min before gastroduodenoscopy helped improve endoscopic visualization remarkably, and the best visibility was achieved with the Pronase administration 10 min to 30 min before the gastrointestinal endoscopic procedure. In this study, we recommended that patients take the premedication solution 10 min to 30 min before the EUS procedure.

In conclusion, for EUS, the group that was administered Pronase premedication had clearer images than the placebo group. With Pronase premedication, the examination time was shorter, and the amount of saline used during the EUS procedure was less.

## COMMENTS

### Background

Previous studies have confirmed that Pronase can improve the quality of endoscopic ultrasonography (EUS) images. Based on previous findings, this study hypothesized that Pronase could further shorten the duration of examination and reduce the usage of physiological saline during EUS examination through improving the quality of EUS images.

### Research frontiers

A few human studies have suggested that premedication with Pronase could improve endoscopic visualization. This study found that for EUS examination, preoperative application of Pronase could provide clearer ultrasound images, shorten the duration of EUS examination, and reduce the intraoperative usage of physiological saline.

### Innovations and breakthrough

This study aimed to analyze and evaluate the effect of pretreatment with Pronase on imaging quality, the duration of examination and the usage of physiological saline during the examination process in gastric endoscopic ultrasound.

### Applications

With Pronase premedication, the EUS examination time was shorter and the amount of saline used during the EUS procedure was less.

### Peer-review

This is an interesting study on the use of Pronase premedication during EUS examination. The authors analyzed the effects of premedication with Pronase for EUS examination of the stomach. Two blinded investigators assessed the obscurity scores for the EUS images.

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