Use of pronase in screening for early cancers of the upper gastrointestinal tract

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A B S T R A C T

Introduction: This study aimed to investigate the effectiveness of pronase in improving the detection rate of early cancer and enhancing visual field clarity during gastroscopy in China.

Methods: In total, 1450 patients who participated in an early diagnosis and treatment programme of upper gastrointestinal cancer in Wuwei, Gansu Province between 2020 and 2021 were enrolled. Cluster randomisation was utilised at the community level. All patients underwent endoscopy and biopsy. The experimental group (n=725) received pronase granules and dimethicone prior to gastroscopy; the control group (n=725) received dimethicone alone. Endoscopic visibility scores, examination durations, and lesion detection rates were recorded for both groups.

Results: Visibility scores for all regions of the stomach were significantly lower in the experimental group than in the control group (P<0.001). This finding remained consistent after adjustment for confounding factors in multiple linear regression analysis. The detection rate of precancerous lesions and early cancer was significantly higher in the experimental group than in the control group (77.5% vs 62.5%; P<0.001). Binary logistic regression analysis indicated that the likelihood of detecting early cancer was greater in the experimental group, with an odds ratio of 3.840 (95% confidence interval=1.204-12.241; P=0.023). Also, average gastroscopy time was significantly shorter in the experimental group than in the control group (6.52±2.51 min vs 10.03±1.23 min, *t*=33.81; P=0.001).

Conclusion: The administration of pronase prior to gastroscopy enhances visual field clarity, reduces examination time, and increases the detection rates of precancerous lesions and early cancer.

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New knowledge added by this study

- Pronase enhances visual field clarity during gastroscopy and reduces examination time.
- Pronase can enhance diagnostic precision by minimising misdiagnoses and missed lesions.

Implications for clinical practice or policy

- Pronase improves the detection rates of precancerous lesions and early cancer. The results provide a strong scientific foundation for using pronase in endoscopic screening during clinical diagnostic examinations.
- The findings support adoption of pronase as a standard adjunct in gastroscopy to improve diagnostic accuracy and procedural efficiency.

Introduction

The implementation of early gastric cancer screening in community populations and performance of endoscopic examinations in high-risk groups represents a feasible, cost-effective, and efficient strategy to address the challenges of gastric cancer diagnosis and treatment in China.[1] More than 80% of early-stage gastric cancer cases are identified in asymptomatic community populations aged ≥40 years. Thus, community-based screening programmes are important for increased detection of early-stage cancer. Gastroscopy remains the gold standard for diagnosing upper gastrointestinal diseases. High-quality intragastric visibility is essential for ensuring diagnostic accuracy, minimising the risks of misdiagnosis and missed diagnosis, and improving the detection of minimal-change gastric lesions. However, air bubbles and

鏈黴蛋白酶在上消化道早期癌症篩查中的應用

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引言：本研究旨在了解鏈黴蛋白酶在中國胃鏡檢查過程中的安全有效性及在提高視野清晰度方面的應用價值。

方法：在2020年至2021年期間，共有1450名患者參加了甘肅省武威市的上消化道癌症早期診斷和治療計劃。本研究在社區層面採用集群隨機化抽樣。所有患者均進行內窺鏡檢查和活檢。我們將患者隨機分為兩組，試驗組（n=725）在內窺鏡檢查時服用鏈黴蛋白酶顆粒劑和胃鏡膠，對照組（n=725）則只給予胃鏡膠。我們記錄了兩組的內窺鏡可視性評分、檢查時間和病變檢出率。

結果：實驗組的胃各區域可見性評分顯著低於對照組（P<0.001）。在多元線性迴歸分析中調整混雜因素後，這發現保持一致。實驗組的癌前病變及早期癌症檢出率明顯高於對照組（77.5%與62.5%；P<0.001）。二元邏輯迴歸分析顯示，實驗組早期癌症檢出率較高，比值比為3.840（95%置信區間=1.204-12.241；P=0.023）。而且，實驗組胃鏡檢查平均時間明顯短於對照組（6.52±2.51分鐘與10.03±1.23分鐘，*t*=33.81；P=0.001）。

結論：胃鏡檢查前給予鏈黴蛋白酶可提高視野清晰度，縮短檢查時間，提高癌前病變和早期癌症的檢出率。

mucus in the stomach often reduce gastroscopic field visibility, leading to missed diagnoses and prolonged examination times. Pretreatment with defoaming agents and mucolytic agents enhances gastroscopic field visibility.[2] Pronase, a proteolytic enzyme isolated from the culture filtrate of *Streptomyces griseus*, effectively cleaves the peptide bonds of glycoproteins, thereby dissolving and eliminating gastric mucus.[3] This study aimed to evaluate the impact of pronase on the detection rate of precancerous lesions and early cancer, clarifying its utility in early gastric cancer screening. The findings will provide foundational evidence for the incorporation of pronase in endoscopic screening for upper gastrointestinal tract cancers and clinical diagnostic examinations.

Methods

Participants

This study enrolled 1450 individuals aged 40 to 70 years from a community population who participated in the 2020-2021 Upper Gastrointestinal Cancer Screening Programme in Wuwei, Gansu Province, China. The inclusion criteria were: (1) ability to cooperate with the gastroscopic procedure; (2) ability to discontinue anticoagulant medications 1 week prior to endoscopy; and (3) voluntary participation and provision of written informed consent. The exclusion criteria were: (1) contraindications to gastroscopy; (2) severe heart disease or heart failure; (3) severe respiratory disease; (4) posterior pharyngeal abscess or severe spinal deformity; (5) other serious illnesses or physical conditions that precluded tolerance of endoscopy; and (6) bleeding tendency.

Gastroscopy examinations

Using a random number table, all 1450 participants from the community population were randomly assigned to either an experimental group (n=725) or a control group (n=725). All participants underwent gastroscopy and tissue biopsy. In the experimental group, 1 sachet (20 000 U) of pronase (Beijing Tide Pharmaceutical, Beijing, China) and 1 g of sodium bicarbonate were dissolved in 50 to 80 mL of drinking water (20-40°C) by shaking. The solution was orally administered 15 to 30 minutes before gastroscopy (GIF-H290; Olympus, Tokyo, Japan). Dimethicone was also given orally to lubricate the cavity and remove gastric bubbles. To ensure that pronase reached all areas of the stomach, participants laid flat on a bed under a nurse's guidance, then turned sideways three to five times. Subsequently, routine gastroscopy was performed. In the control group, participants received oral dimethicone 15 to 30 minutes before routine gastroscopy (GIF-H290).

The gastroscopy examinations were performed by two physicians holding the title of associate chief physician or higher, each having >10 years of experience in gastroscopy. The visibility of each part of the visual field was evaluated during the procedure; pathological examinations were conducted on tissue biopsies collected from minimal-change lesions.

Observation indicators

Endoscopic visibility scores were compared between the two groups. Scoring criteria were as follows[4]: 1 point, no mucus; 2 points, a small amount of mucus but no blurring of the visual field; 3 points, a large amount of mucus with a blurred visual field, requiring <30 mL of water for rinsing; and 4 points, very thick mucus with a blurred visual field, requiring ≥30 mL of water for rinsing. Lower scores indicated better endoscopic visibility. To minimise errors during the scoring process, each visibility score was recorded as the average of scores assigned by the two physicians who performed gastroscopy. The lesion detection rate was defined as the percentage of subjects within a group in whom lesions were identified. Gastroscopy time was measured from entry of the gastroscope into the oesophagus until its removal. Adverse reactions included nausea, vomiting, difficulty breathing, facial flushing, and other symptoms.

Statistical analyses

R software (version 4.0.5) was used for statistical analysis. Quantitative data were expressed as

mean±standard deviation; intergroup differences were analysed using independent sample *t* tests. Qualitative data were expressed as frequency and percentage; intergroup differences were assessed using the Chi squared test or Fisher's exact test. Multivariable linear regression analysis was performed to evaluate the effect of group assignment on visibility scores after adjustment for confounding factors. Differences in early cancer detection rates between the two groups were analysed using multivariable binary logistic regression analysis. All statistical tests were two-sided, and P values <0.05 were considered statistically significant.

Results

A summary of the baseline characteristics of the experimental and control groups is provided in Table 1. Among the 1450 patients in the cohort, 416 (28.7%) had a family history of gastrointestinal disease, 172 (11.9%) had a history of smoking, 91 (6.3%) had a history of alcohol consumption, and 335 (23.1%) had a history of gastrointestinal disease. Significant differences between the two groups were observed in the proportions of patients with a history of smoking, alcohol consumption, and gastrointestinal disease.

Average visibility scores for the oesophagus, cardia, gastric fundus, gastric body, gastric antrum, gastric angle, and duodenum were significantly lower in the experimental group than in the control group (P<0.001 for all comparisons) [Table 2]. The visibility of different regions of the stomach under gastroscopy substantially differed between the two groups (Fig).

Effect of pronase on visibility score

Multiple linear regression analysis was performed with the visibility score for each site as the dependent

TABLE 1. Baseline characteristics of the study groups*

	Overall (n=1450)	Experimental group (n=725)	Control group (n=725)	t/χ^2	P value
Age, y (mean±SD)	60.74±7.90	54.62±6.40	66.86±2.98	-46.710	<0.001
Sex				5.379	0.020
Male	664 (45.8%)	354 (48.8%)	310 (42.8%)		
Female	786 (54.2%)	371 (51.2%)	415 (57.2%)		
Marital status				N/A	0.073
Unmarried	8 (0.6%)	5 (0.7%)	3 (0.4%)		
Married	1379 (95.1%)	694 (95.7%)	685 (94.5%)		
Widowed	60 (4.1%)	23 (3.2%)	37 (5.1%)		
Divorced	3 (0.2%)	3 (0.4%)	0		
Education level				N/A	<0.001
Elementary school and below	1410 (97.2%)	718 (99.0%)	692 (95.4%)		
Junior high school	23 (1.6%)	1 (0.1%)	22 (3.0%)		
High school	14 (1.0%)	3 (0.4%)	11 (1.5%)		
Bachelor's degree and above	3 (0.2%)	3 (0.4%)	0		
Smoking status				8.549	0.003
No	1278 (88.1%)	621 (85.7%)	657 (90.6%)		
Yes	172 (11.9%)	104 (14.3%)	68 (9.4%)		
Alcohol consumption				80.772	<0.001
No	1359 (93.7%)	638 (88.0%)	721 (99.4%)		
Yes	91 (6.3%)	87 (12.0%)	4 (0.6%)		
History of gastrointestinal disease				5.314	0.021
No	1115 (76.9%)	539 (74.3%)	576 (79.4%)		
Yes	335 (23.1%)	186 (25.7%)	149 (20.6%)		
Family history of gastrointestinal disease				0.485	0.486
No	1034 (71.3%)	523 (72.1%)	511 (70.5%)		
Yes	416 (28.7%)	202 (27.9%)	214 (29.5%)		

Abbreviations: N/A = not applicable; SD = standard deviation

* Data are shown as No. (%), unless otherwise specified

TABLE 2. Gastroscopy visibility scores of the study groups[*] [†]

	Experimental group (n=725)	Control group (n=725)	*t*
Oesophagus	1.15±0.45	2.02±0.20	-47.435
Cardia	1.11±0.37	2.00±0.14	-60.981
Gastric fundus	1.14±0.44	2.08±0.42	-41.252
Gastric body	1.16±0.47	3.02±0.18	-99.957
Gastric antrum	1.08±0.32	2.25±0.52	-51.587
Gastric angle	1.06±0.28	2.36±0.57	-54.964
Duodenum	1.06±0.30	2.19±0.80	-35.639

[*] Data are shown as mean±standard deviation
[†] All P<0.001

TABLE 3. Effect of pronase on visibility score[*]

	Partial regression coefficient (β)	Standard error	*t*
Oesophagus	0.747	0.032	23.355
Cardia	0.798	0.026	31.189
Gastric fundus	0.843	0.040	21.184
Gastric body	1.860	0.033	57.207
Gastric antrum	0.971	0.039	25.009
Gastric angle	1.185	0.041	28.836
Duodenum	0.950	0.055	17.428

[*] All P<0.001

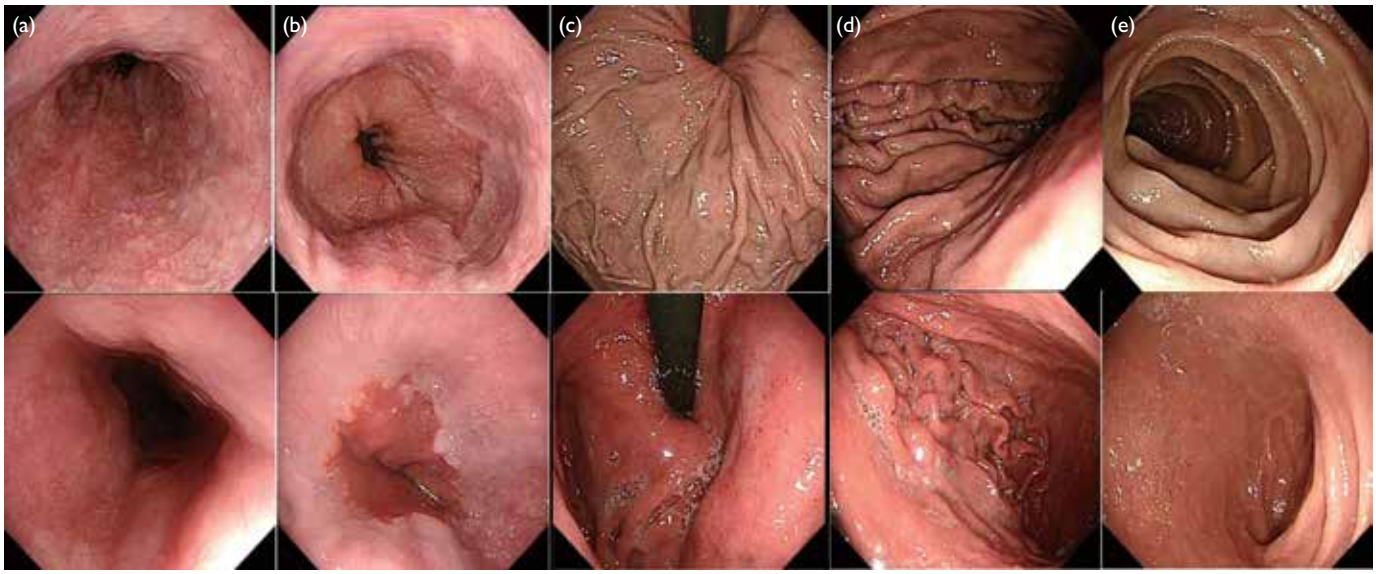

FIG. Images of each part of the stomach under gastroscopy: (a) oesophagus, (b) cardia, (c) fundus, (d) corpus, and (e) duodenum. Upper and lower images show experimental and control groups, respectively

variable and group assignment as the independent variable; adjustments were conducted for sex, age, marital status, education level, smoking status, alcohol consumption, history of gastrointestinal disease, and family history of gastrointestinal disease. After adjustment for these confounding factors, the visibility scores for all regions of the stomach remained significantly higher in the control group than in the experimental group (P<0.001 for all visibility scores) [Table 3].

Lesion and early cancer detection rates

Chi squared test analyses revealed that the detection rates of precancerous lesions (including atrophic gastritis, intestinal metaplasia, and low-grade intraepithelial neoplasia[5]) and early cancer were significantly higher in the experimental group than in the control group (77.5% vs 62.5%; P<0.001) [Table 4].

Multivariable binary logistic regression analysis was performed with early cancer detection as the dependent variable and group assignment as the independent variable; adjustments were conducted for sex, age, marital status, education level, smoking status, alcohol consumption, history of gastrointestinal disease, and family history of gastrointestinal disease. The likelihood of early cancer detection was significantly higher in the experimental group compared with the control group, with an odds ratio of 3.840 (95% confidence interval=1.204-12.241; P=0.023) [Table 5].

Examination time

Average gastroscopy times were 6.52±2.51 minutes

TABLE 4. Rates of lesion detection in the study groups*

	Detection condition†					Detection rate
	No lesions	Atrophic gastritis	Intestinal metaplasia	Low-grade intraepithelial neoplasia	Early-stage cancer	
Experimental group (n=725)	163 (22.5%)	375 (51.7%)	123 (17.0%)	42 (5.8%)	22 (3.0%)	77.5%
Control group (n=725)	272 (37.5%)	323 (44.6%)	92 (12.7%)	23 (3.2%)	15 (2.1%)	62.5%
Overall (n=1450)	435 (30.0%)	698 (48.1%)	215 (14.8%)	65 (4.5%)	37 (2.6%)	70.0%
χ^2			42.535			39.018
P value			<0.001			<0.001

* Data are shown as No. (%), unless otherwise specified

† For patients with two or more gastrointestinal lesions, only the most severe lesion was recorded. Lesion severity was ranked as follows: low-grade intraepithelial neoplasia > intestinal metaplasia > atrophic gastritis[5]

TABLE 5. Comparison of early cancer detection rates between the study groups

	Partial regression coefficient (β)	Standard error	Statistical value (Wald)	P value	Odds ratio (95% CI)
Control group			Reference level		
Experimental group	1.345	0.592	5.172	0.023	3.840 (1.204-12.241)

Abbreviation: 95% CI = 95% confidence interval

in the experimental group and 10.03±1.23 minutes in the control group. Gastroscopy time significantly differed between the two groups (t=33.81; P=0.001).

Adverse reactions

No adverse reactions, such as nausea, vomiting, dyspnoea, or facial flushing, were reported in either group.

Discussion

Currently, approximately 90% of primary gastric cancers in China are diagnosed at an advanced stage.[6] The prognosis of affected patients is closely related to the timing of diagnosis and treatment. Despite surgical intervention, the 5-year survival rate for patients with advanced gastric cancer remains <30%.[7] After treatment, the 5-year survival rate for patients with early gastric cancer exceeds 90%, and cure may be achieved.[8] However, the rates of early diagnosis and treatment of gastric cancer in China are <10%, substantially lower than rates reported in Japan (70%) and South Korea (50%).[9] In Wuwei, the incidence and mortality rates of gastric cancer remain among the highest in the country; gastric cancer ranks first among malignant tumours in the city.[10] Screening for upper gastrointestinal cancer is one of the most effective methods for population-level detection of early-stage cancer. Since 2010, Wuwei Tumour Hospital has implemented an upper gastrointestinal cancer screening programme (endoscopy combined with tissue biopsy) in Wuwei. Improvements in the detection rates of precancerous lesions and upper gastrointestinal cancer are key objectives of this screening initiative.

Gastroscopy is currently a widely used method for the clinical diagnosis and treatment of gastrointestinal diseases. A clear endoscopic field of vision is essential for accurate diagnosis and effective treatment by endoscopists. To optimise gastroscopy outcomes and enhance visibility within the stomach, bubbles and mucus must be removed. The use of pronase in combination with defoaming agents is recommended by the *Consensus on Early Gastric Cancer Screening and Endoscopic Diagnosis and Treatment in China*[11] and the *Guidelines for Endoscopic Diagnosis of Early Gastric Cancer* (2019 edition) developed by the Japan Gastroenterological Endoscopy Society.[12]

Lee et al[13] demonstrated that administering pronase 10 to 20 minutes before gastroscopy significantly improved the visibility of the endoscopic visual field and reduced the number of water washes required. Similarly, a multicentre randomised controlled study by Liu et al[14] indicated that the combination of pronase and dimethicone significantly enhanced the visibility of the upper gastrointestinal mucosa. Pronase has also been utilised in narrow-band imaging endoscopy. A randomised controlled study by Cha et al[15] compared the effects of orally administering pronase and simethicone 10 minutes before narrow-band imaging endoscopy on mucosal

visibility and diagnostic performance. The results showed that mucosal visibility within the proximal stomach was significantly better in the pronase group than in the simethicone group.[15] In the present study, the visibility scores for all sites in patients who received pronase were approximately 1 point, indicating minimal mucus adhesion. After adjustment for confounding factors, multiple linear regression analysis confirmed that visibility scores remained significantly lower in the pronase group than in the control group at all sites; this finding further validated the effectiveness of pronase. The present study also revealed that the average endoscopic examination time was significantly shorter (approximately 5 minutes) in the pronase group than in the control group. This reduced examination time was attributed to the near-complete absence of mucus adhesion after pronase administration, which decreased the number of rinses needed during the procedure. The shorter examination also enhanced patient comfort and increased compliance for subsequent screenings.

Zhang et al[16] and Gao et al[17] conducted retrospective analyses of 25 314 patients who underwent gastroscopy at Nanfang Hospital of Southern Medical University and 166 260 patients at Bazhong Central Hospital, revealing early cancer detection rates of 0.2% and 0.62%, respectively. Zhang et al[1] performed a follow-up analysis of individuals in Liangzhou District in Wuwei who underwent upper gastrointestinal cancer screening in 2017; they observed an early cancer detection rate of 2.8%.[1] In the present study, lesion detection rates for the experimental and control groups were 77.5% and 62.5%, respectively; corresponding early cancer detection rates were 3.0% and 2.1%. These percentages align with findings from the previous study in Wuwei[1] and are substantially higher than those reported for other regions.[16,17] The present results suggest that in Wuwei, a region displaying one of the highest incidences of upper gastrointestinal cancer in China, early cancer screening should be actively promoted. Furthermore, the detection rates of precancerous lesions and early cancer can be improved by using endoscopy combined with tissue biopsy.

The efficacy of pronase in improving the endoscopic visual field is well established, but studies investigating its impacts on the detection rates of precancerous lesions and early cancer have yielded inconsistent results.[14,18,19] Chen et al[18] conducted a randomised controlled trial that enrolled older patients undergoing gastroscopy; they found that the detection rate of minimal-change lesions was higher in the pronase group than in the control group (45.2% vs 27.5%; P<0.05).[18] Lee et al[19] demonstrated that the use of pronase when rinsing a lesion during endoscopy significantly increased the tissue depth of endoscopic biopsies and improved the anatomical localisation of biopsy sites, thereby enhancing the accuracy of disease diagnosis. In the present study, the detection rates of precancerous lesions and early cancer were significantly higher in the experimental group than in the control group (P<0.001). After adjustment for confounding factors, multivariable logistic regression showed that the likelihood of detecting early cancer was significantly greater in the experimental group than in the control group (odds ratio=3.840; P=0.023) [Table 5]. This finding indicates that pronase pretreatment before gastroscopy can enhance the detection rates of precancerous lesions and early cancer. The enhancement may be attributed to the clear visual field provided by pronase, which facilitates accurate selection of biopsy sites and improves recognition of minimal-change lesions. Gastroscopy physicians have substantial daily workloads and manage large numbers of patients requiring treatment. The use of pronase reduced the time required for endoscopy, potentially improving patient compliance with clinical microscopy.

Limitations

As an early cancer screening study, this investigation had a relatively small sample size; therefore, the findings require further validation in large-scale clinical studies. Cluster randomisation was used in this study, leading to baseline differences between groups; however, adjustments for these factors were included in the statistical analyses. The gastroscopy procedures were performed by highly skilled endoscopists. The generalisability of the findings to all endoscopists warrants additional investigation.

Conclusion

Pronase pretreatment before gastroscopy improves visual field clarity, reduces examination time, increases the detection rates of precancerous lesions and early cancer, and demonstrates good safety. This approach is beneficial for early cancer screening in regions with a high incidence of upper gastrointestinal cancer. The practical value of this method requires confirmation in large-scale clinical studies.

Author contributions

Concept or design: Z Wu, S Li, G Wang.
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Drafting of the manuscript: Z Zhang.
Critical revision of the manuscript for important intellectual content: Z Wu.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This research was approved by the Medical Ethics Committee of Wuwei Cancer Hospital, Wuwei, Gansu, China (Ref No.: 2019-Ethical review-11). The trial was registered with the Chinese Clinical Trial Registry (Ref No.: ChiCTR2200064855). Informed consent was obtained from all study participants, including consent for the publication of their anonymised data and clinical photos.

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