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MINIREVIEWS

Efforts to increase image quality during endoscopy: The role of pronase

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Abstract

Clear visualization of the gastrointestinal mucosal surface is essential for thorough endoscopy. An unobstructed assessment can reduce the need for additional time-consuming manipulations such as frequent washing and suction, which tend to prolong total procedure time. However, mucus, foam, and bubbles often hinder clear visibility during endoscopy. Premedication with pronase, a compound of mixed proteolytic enzymes, has been studied in order to improve mucosal visibility during endoscopy. Although its effects differ according to the location in the stomach, premedication with pronase 10 to 20 min before endoscopy significantly improves mucosal visibility without affecting the accuracy of *Helicobacter pylori* identification. The effects of pronase as premedication also extend to chromoendoscopy, narrow-band imaging, magnifying endoscopy, and endoscopic ultrasonography. In addition, endoscopic flushing with pronase during endoscopy may improve the quantity and the quality of a biopsy to some degree. Although improved mucosal visibility does not necessarily improve clinical outcomes, premedication with pronase may be helpful for increasing the detection rate of early cancers.

Key words: Endoscopy; Premedication; Pronase

Core tip: The present review discusses the role of

pronase in increasing image quality during endoscopy. Premedication with pronase 10 to 20 min before endoscopy significantly improves mucosal visibility without affecting the accuracy of *Helicobacter pylori* identification. The effects of pronase as premedication are also applicable in advanced endoscopic procedures such as narrow-band imaging, magnifying endoscopy, or endoscopic ultrasonography. Although improved mucosal visibility does not necessarily improve clinical outcomes, premedication with pronase may be helpful for increasing the detection rate of early cancers.

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INTRODUCTION

Esophagogastroduodenoscopy (EGD) is commonly performed to diagnose and treat benign and malignant diseases, especially early gastric cancer in the upper gastrointestinal tract. Clear visualization of the gastrointestinal mucosal surface is essential for thorough EGD, particularly when using advanced endoscopic methods such as narrow-band imaging (NBI) or magnifying endoscopy (ME). Furthermore, clear visualization can decrease the need for additional time-consuming manipulations such as frequent washing and suction, which may prolong the total procedure time. In other words, proper premedication before EGD is important to obtain satisfactory visualization of the gastrointestinal mucosa. However, mucus, foam, and bubbles often hinder clear visibility during EGD[1]. To overcome these problems, mucolytic and defoaming agents have been applied in EGD.

In most endoscopic centers, simethicone or dimethylpolysiloxane (DMPS) is commonly used to eliminate bubbles and foam during EGD[1,2]. Simethicone is a mixture of polydimethylsiloxanes that reduces the surface tension of air bubbles and results in the coalescence of small bubbles into larger ones, which may then pass more easily with belching or flatulence[3]. DMPS, which is similar to simethicone, also has the effect of eliminating foam and bubbles. Several studies have shown that simethicone is a suitable premedication to improve the endoscopic view of EGD[4,5]. However, despite premedication with these deforming agents, great deal of mucus can still be encountered during EGD[6].

Pronase, a compound of mixed proteolytic enzymes, was isolated from the culture filtrate of *Streptomyces griseus* in 1962, and has been used as a base material in the preparation of anti-inflammatory and digestive enzymes[7]. Because of its mucolytic effects[8], pronase was used to remove gastric mucus for roentgenographic examination in 1964[9]. It has also been applied as a premedication for endoscopy since 1991[10]. However, the effectiveness of premedication with pronase for improving mucosal visibility during EGD has been the subject of a few clinical trials. Similarly, a limited number of systematic reviews have been performed to address its efficacy in improving mucosal visibility during advanced endoscopy such as NBI or ME as well as conventional endoscopy. Therefore, the aim of this review is to evaluate the role of pronase in increasing imaging quality of various endoscopic examinations based on the published literature.

METHODS TO IDENTIFY STUDIES

Two reviewers (Kim GH and Chung IK) performed a literature search using PubMed and Embase databases. Key words included pronase, premedication, and endoscopy. Relevant review articles were also investigated and additional studies were identified by searching the bibliography of published articles. We focused on studies that described premedication with pronase to increase imaging quality during endoscopy.

THE EFFECTS OF PRONASE ON MUCOSAL VISIBILITY DURING CONVENTIONAL ENDOSCOPY

Table 1 summarizes studies of the effects of pronase as premedication for conventional endoscopy. In most studies, the mucosal visibility score was classified from 1 to 4 (1, no adherent mucus; 2, mild mucus, but not obscuring vision; 3, large amount of mucus obscuring vision; and 4, heavy adherent mucus). All studies showed the superior effects of pronase for improving mucosal visibility in the stomach, but this effect differed according to the location in the stomach. In a recent meta-analysis that included three studies until 2012[11], significant improvement in mucosal visibility was noted only with pronase use in the antrum and fundus. Mucosal visibility in the greater curvature of the upper body did not improve despite pronase premedication, which suggests that this area needs to be cautiously observed[12,13]. In our study, even though the grade of mucosal visibility in the upper body and fundus was high compared to other sites, a significant difference in mucosal visibility grade during EGD was observed in the fundus and upper body of the stomach[7].

Improving visibility can also lead to reduce the need of additional manipulation for washing to clear the surface of the gastrointestinal mucosa, which results in shortening the total EGD procedure time[8,10,13]. However, pronase only induces mucolysis, but itself does not have a defoaming effect. Therefore, if a defoaming agent is used simultaneously as premedication in addition to pronase, it is expected that mucosal visibility will be improved *vs* using pronase alone. In fact, many studies have reported a combination of pronase

Table 1 Summary of studies about premedication with pronase for visualization of the mucosa during conventional endoscopy

Ref.	Year	Study design	Premedication group (*n*)	Mucosal visibility
Fujii *et al*[8]	1998	Prospective	A: DMPS (34) B: DMPS + SB (32) C: DMPS + SB + pronase (34)	C > A, B
Kuo *et al*[6]	2002	Prospective	A: DMPS (34) B: DMPS + water (30) C: Pronase + water (31) D: Pronase + SB + water (32) E: Pronase + SB + DMPS + water (33)	E > A, B, C, D
Chang *et al*[12]	2007	Prospective	A: DMPS (39) B: DMPS + water (35) C: Pronase + SB + DMPS + water (34) D: N-acetylcystein + DMPS + water (39)	C = D > A, B
Bhandari *et al*[30]	2010	Prospective	A: Drinking of simethicone + pronase + water (35) B: Endoscopic flushing of simethicone + water (37) C: Endoscopic flushing of simethicone + pronase + water (40)	A > B, C
Lee *et al*[13]	2012	Prospective	A: DMPS + SB + pronase within 10 min (100) B: DMPS + SB within 10 min (100) C: DMPS + SB + pronase within 20 min (100) D: DMPS + SB within 20 min (100)	A = C > B, D
Woo *et al*[26]	2013	Prospective	A: Pronase + SB + DMPS within 10 min (98) B: Pronase + SB + DMPS between 10-30 min (97) C: Pronase + SB + DMPS at 30 min (99)	A = B > C
Kim *et al*[7]	2015	Prospective	A: Simethicone + SB + pronase (71) B: Simethicone (72)	A > B

DMPS: Dimethylpolysiloxane; SB: Sodium bicarbonate.

with defoaming agents such as DMPS significantly improves visibility during conventional endoscopy or chromoendoscopy[6,8,10]. Therefore, when pronase is used to improve visibility during EGD, we recommend the concurrent use of a defoaming agent.

THE EFFECTS OF PRONASE ON MUCOSAL VISIBILITY DURING ADVANCED ENDOSCOPY

Table 2 summarizes studies that explored the effects of pronase as premedication for advanced endoscopy.

Chromoendoscopy

Chromoendoscopy requires a clear field in order for the dye to bind to the targeted mucosa rather than the overlying mucus[14,15]. Gastric mucus prevents the dye from spraying onto the gastric mucosa and is a frequent source of artifacts during endoscopic imaging. The mucolytic effect of pronase during conventional endoscopy is sustained during chromoendoscopy. In a randomized controlled trial of chromoendoscopy with methylene blue, premedication with pronase came to significantly improve the visibility of the gastric wall both before and after methylene blue spraying and also to significantly shorten the time of the chromoendoscopic examination[8].

NBI and ME

Recently, NBI has been reported to improve the visibility of mucosal structure and the accuracy of detection for precancerous conditions[16]. Like conventional endoscopy, the presence of foam, bubbles, or mucus on the gastric mucosa can obstruct mucosal visualization during NBI endoscopy. Therefore, a premedication with defoaming and mucolytic agents can be an effective method to improve visibility and possibly the diagnostic performance of NBI endoscopy. In our study comparing the visibility score and diagnostic performance of NBI endoscopy for patients with precancerous conditions with or without pronase premedication, a combination of pronase with simethicone significantly improved visibility during NBI endoscopy in the proximal part of the stomach, and it also improved the negative predictive value of NBI endoscopy compared with that of white light endoscopy[17].

ME with NBI (ME-NBI) is reported to have high accuracy for diagnosing corpus gastritis, intestinal metaplasia and early gastric cancer[18-21]. In particular, the microvascular and microsurface patterns observed during ME-NBI are clinically helpful for distinguishing cancerous from noncancerous lesions. As mucosal visibility during EGD is essential in finding subtle mucosal abnormalities associated with early neoplasia, mucosal visibility is especially important during ME-NBI in that this procedure has time-consuming and complicated nature. In a randomized study, we showed that premedication with pronase improved mucosal visibility during ME-NBI of the stomach and reduced the frequency of water flushing needed to clear the mucosa[7].

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) plays an important

Table 2 Summary of studies about premedication with pronase for visualization of the mucosa during advanced endoscopy

Examination	Ref.	Year	Study design	Premedication group (*n*)	Mucosal visibility
Chromoendoscopy	Fujii *et al*[8]	1998	Prospective	A: DMPS (34) B: DMPS + SB (32) C: DMPS + SB + pronase (34)	C > A, B
NBI endoscopy	Cha *et al*[17]	2014	Prospective	A: Pronase + SB (28) B: Simethicone (27)	A > B
ME-NBI	Kim *et al*[7]	2015	Prospective	A: Simethicone + SB + pronase (71) B: Simethicone (72)	A > B
EUS	Sakai *et al*[24]	2003	Prospective	A: DMPS (29) B: DMPS + SB (29) C: DMPS + SB + pronase (29)	C > A, B
	Han *et al*[25]	2011	Prospective	A: Saline (60) B: Pronase + SB (62) C: Pronase + SB + simethicone (61)	B > A > C

NBI: Narrow-band imaging; ME-NBI: Magnifying endoscopy with narrow-band imaging; EUS: Endoscopic ultrasonography; DMPS: Dimethylpolysiloxane; SB: Sodium bicarbonate.

role in assessing benign and malignant gastrointestinal diseases. It is especially useful for diagnosing subepithelial lesions and the staging of early gastric cancer[22,23]. However, artifacts caused by gastric mucus can potentially affect visibility during EUS, which inhibits the ability to evaluate superficial mucosal lesions. Reducing gastric cavity and mucosal surface artifacts caused by mucus may be helpful in improving EUS performance. A randomized study evaluating the effect of pronase in improving EUS images showed that premedication with pronase reduced artifacts during EUS *via* a mucolytic effect that disrupts the surface mucus gel layer of the stomach[24]. In another similar randomized controlled study, premedication with pronase decreased the number of gastric wall and lumen hyperechoic artifacts observed in patients given either saline solution or pronase/simethicone[25]. Unlike pronase, the use of simethicone led to turbidity and echogenicity, which did not improve visibility during EUS. Although a more accurate diagnosis is not necessarily gleaned from better-quality images, obtaining good EUS images through premedication with pronase may lead to improve the diagnostic accuracy for superficial mucosal lesions during EUS.

CONSIDERATIONS IN USING PRONASE AS PREMEDICATION

To improve the effect of pronase on removing gastric mucus, several factors must be considered[10]. First is intragastric pH. Mucolysis by pronase is found to be maximal at pH 6 to 8. Therefore, it is necessary to neutralize the acidity of the gastric juice with a neutralizer such as sodium bicarbonate and to prevent subsequent hypersecretion of gastric juice with an anticholinergic agents such as scopolamine butylbromide[8]. The second consideration is the amount of pronase and the volume of oral solution. Based on previous findings[6,8,10,13], 2000 units or more (usually 20000 units) of pronase and 80 mL to 100 mL of oral solution are needed to achieve adequate effects. The third consideration relates to position change of the patient. Rotation from supine, left or right lateral, to prone position several times is helpful for completely removing gastric mucus[8]. However, in two recent studies, similar effects of pronase were shown without position changes before EGD[12,13]. The argument for not changing position before EGD stems from the fact that the ingested solution flows into the gastric fundus, then gradually into the gastric antrum by the way of the gastric body after premedication with pronase.

When is the optimal time for taking pronase to maximize its mucolytic effect before EGD? In previous studies, premedication with pronase was administered 10 to 20 min before EGD[8,12]. In a recent study comparing premedication times of 10 min and 20 min before EGD, mucosal visibility score did not differ between the two groups[13]. In another recent study evaluating the optimal time of medication with pronase, administration of pronase within 30 min before EGD significantly improved endoscopic visualization compared to administration at 30 min before EGD[26]. These results suggest that if pronase is given within 30 min before EGD, the duration of premedication does not play a significant role in satisfactory mucosa visualization.

OTHER ADDITIVE EFFECTS OF PRONASE

Effect of pronase on Helicobacter pylori

Because *Helicobacter pylori* (*H. pylori*) strains reside in the surface mucous gel layer as well as on the surface of gastric epithelial cells, premedication with pronase could reduce the accuracy of *H. pylori* identification in biopsy specimens *via* its mucolytic effect. However, the use of pronase seems not to influence the identification of *H. pylori* by culture and rapid urease test of biopsy specimens in many studies[6,8,12].

Pronase can disrupt gastric mucus and so reduce the thickness of the surface mucous gel layer, which enhances drug delivery to improve the eradication

rate of *H. pylori*[6,27,28]. Therefore, it is assumed that supplements of pronase in addition to anti-*H. pylori* regimen could increase the eradication rate of *H. pylori*. Earlier randomized controlled studies showed the additive effect of pronase in improvement of *H. pylori* eradication rates[27,28], but a recent randomized controlled study did not confirm this effect[29].

Effect of pronase on gastric biopsy

Although pronase improves visibility, a patient's positioning may prevent it from reaching some portions of the stomach in sufficient quantity. In these situations, the endoscopist aid distribution to the target lesion through endoscopic flushing of pronase. Although endoscopic flushing is not able to provide equivalent improvements in mucosal visibility during EGD when compared with the oral administration of pronase[30], it can be helpful for improving the visibility of a target lesion. Furthermore, patients receiving endoscopic flushing with pronase in a limited area exhibited decrease in thickness of mucus, increase in depth of biopsy, improved anatomical orientation, and improved overall diagnostic assessment of the second biopsy specimens compared with a control group[31]. Therefore, endoscopic flushing with pronase during EGD can be recommended in order to improve the quantity and quality of endoscopic biopsies.

CONCLUSION

During EGD, foam, bubbles, and mucus often obstruct visibility. Premedication is therefore usually administered prior to an endoscopic procedure in order to remove foam and mucus. Satisfactory visibility achieved through premedication with proper agents can reduce the need to carry out flushing during the procedure, thus shortening the duration of an endoscopy. The use of pronase as premedication improves mucosal visualization in advanced endoscopy as well as in conventional endoscopy without affecting the accuracy of *H. pylori* identification. Although the use of pronase does not necessarily result in a higher detection rate of early cancers or improve clinical outcomes, improved mucosal visibility may be helpful for increasing the detection rate of early cancers. Large randomized clinical trials will be needed to confirm the utility of pronase for identifying early cancers.

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