The add-on N-acetylcysteine is more effective than dimethicone alone to eliminate mucus during narrow-band imaging endoscopy: a double-blind, randomized controlled trial

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Abstract

Objective. Recent studies have shown that pronase can improve mucosal visibility, but this agent is not uniformly available for human use worldwide. This study aimed to assess the efficacy of N-acetylcysteine (NAC), a mucolytic agent, in improving mucus elimination as measured by decreased endoscopic water flushes during narrow-band imaging (NBI) endoscopy.

Material and methods. A consecutive series of patients scheduled for upper gastrointestinal endoscopy at outpatient clinics were enrolled in this double-blind, randomized controlled trial. The control group drank a preparation of 100 mg dimethicone (5 ml at 20 mg/ml) plus water up to 100 ml, and the NAC group drank 300 mg NAC plus 100 mg dimethicone and water up to 100 ml. During the endoscopy, the endoscopist used as many flushes of water as deemed necessary to produce a satisfactory NBI view of the entire gastric mucosa. Results. In all, 177 patients with a mean age of 51 years were evaluated in this study. Significantly lesser water was used for flushing during NBI endoscopy for the NAC group than the control group; 40 ml (30–70, 0–120) versus 50 ml (30–100, 0–150) (median (interquartile range, range), p = 0.0095).

Conclusions. Considering the safety profile of NAC, decreasing the number of water flushes for optimal vision and unavailability of pronase in some areas, the authors suggest the use of add-on NAC to eliminate mucus during NBI endoscopy.

Key Words: mucolytic agent, N-acetylcysteine, narrow-band imaging, randomized controlled trial

Introduction

Early detection of gastric cancer can be achieved through various diagnostic techniques such as chromoendoscopy or narrow-band imaging (NBI) with or without high-magnification endoscopy [1]. During NBI, the presence of foam, bubbles or mucus in the gastrointestinal tract can obstruct mucosal visualization. To improve mucosal visualization, it is necessary to have a pre-endoscopic drink that reduces mucus and foam. Dimethicone (dimethylpolysiloxane, DMPS) has been reported as an effective defoaming agent in many trials [2,3]. In addition to upper endoscopy, dimethicone has also been used in colonoscopy and capsule endoscopy [4] to eliminate bubbles and reduce artifacts during endoscopic ultrasound (EUS) [5].

Recent studies have shown that the addition of a mucolytic agent such as pronase further improves visualization of the mucosa [6–8]. In Japan, patients are therefore given pronase before their endoscopic procedure. However, pronase is not uniformly available for human use in the rest of the world. N-Acetylcysteine (NAC) is widely used as a mucolytic agent in respiratory diseases. It is administered as a spray or as a dissolved sodium bicarbonate tablet in low doses of...
200–500 mg [9]. NAC has been shown to break the disulfide bonds that stabilize extracellular proteins in the mucus in vitro; this changes the viscoelasticity of the mucus and reduces gastric barrier mucus thickness [10]. A previous study has suggested that the reduction of mucus thickness by NAC increased eradication rates of Helicobacter pylori owing to improved delivery of antibiotics [11]. NAC was also reported to soften gastric phytobezoars that are frequently cemented with mucus allowing easier fragmentation by mechanical devices [12]. The present study aimed to assess the efficacy of NAC in improving mucus elimination by decreasing endoscopic water flushes during NBI endoscopy.

Methods

Patients

This double-blind, randomized controlled trial was carried out from January to May 2012 at a medical center in Taiwan. A consecutive series of patients scheduled for upper gastrointestinal endoscopy for upper gastrointestinal symptoms at an outpatient clinic were enrolled in this study. Patients with a history of upper gastrointestinal surgery, gastric malignancy or pregnancy were excluded. Sealed envelopes were used by an attendant nurse to randomly allocate patients into one of the two groups according to the treatment. The patients in the control group drank a preparation of 100 mg dimethicone (5 ml at 20 mg/ml) plus water up to 100 ml, and those in the NAC group drank 300 mg NAC (Synmosa Corp., Ltd., Taiwan) plus 100 mg dimethicone and water up to 100 ml. The authors obtained the written informed consent from all the participants. The Health Research Ethics Committee of the Department of Research at Mackay Memorial Hospital approved this study (MMH-I-S-163).

Premedication and endoscopic procedure

All the liquid solutions were prepared in the same opaque bottles and were taken before endoscopic procedure under supervision of an attendant nurse. The patients then awaited endoscopy in a sitting position in the waiting room. All patients were unaware of their groups and the content of liquid solutions. A single, experienced endoscopist blinded to the patients’ group and premedication performed the endoscopic procedures. Upper endoscopy was performed with a standard endoscope (Olympus GIF H260; Olympus Medical Systems Corp., Tokyo, Japan) with an NBI light source. The evaluation of the entire stomach was initially performed in a standardized manner with conventional white light (CWL) endoscopy to exclude obvious lesions. After removal of excess gastric contents by suction (Figure 1A), the endoscopist was then free to use as many flushes as deemed necessary with a 50 ml syringe to produce a satisfactory view of the mucosa with no adherent mucus (Figure 1B–D). When the required water flush was more than 50 ml, water was reloaded from the syringe. The endoscope was then positioned at the
pylorus, and the NBI light source was turned on. The entire gastric mucosa of the antrum and body was carefully scanned by NBI. If no adherent mucus on the gastric mucosa was observed using CWL (Figure 2A), but an obvious amount of mucus was located on the gastric mucosa during narrow-band imaging (B), extra water was flushed to ensure adherent mucus was eliminated as measured by both conventional white light (C) and narrow-band imaging (D) settings.

**Statistical analysis**

The sample-size calculations showed that 80 participants were required for each treatment group (160 patients overall) to detect a 20-ml decrease in the water flushed, from 60 to 40 ml, and a power of 80%, two-tailed \( \alpha \) error of 5%. Allowing for a 15% attrition rate, the authors aimed to recruit 200 participants. Two-tailed tests with a significance level of 0.05 were conducted. Continuous data of age was calculated and was reported as mean ± standard deviation (SD). Categorical variable of gender was described using frequency distributions and was reported as \( n \) (%). The non-parametric method of Wilcoxon rank sum test was used to compare the difference of flush water and duration from preparation to procedure and showed as median and interquartile range (IQR). Statistical analysis was performed between the two groups using the Statistics Analysis System (version 9.2. SAS Institute Inc., Cary, NC, USA).

**Results**

**Demographic data and exclusion criteria**

In all, 200 patients (100 patients in each group) were enrolled in the study after providing written informed consent. Eighteen patients in the NAC group and five patients in the control group were excluded because of hemostasis procedures, biopsy required, active bleeding or food retention. The remaining 177 patients evaluated in this study (82 patients in the NAC group and 95 patients in the control group) had a mean age of 51 years.

**Number of flushes required and safety profile**

No significant differences were observed in age or gender between both the groups. The water used for flushing was significantly lesser during NBI endoscopy for the NAC group than for the control group; 40 ml (30–70, 0–120) versus 50 ml (30–100, 0–150) (median (IQR, range), \( p = 0.0095 \). Pulmonary aspiration or allergy reaction following NAC treatment was not detected in the study group.

**Discussion**

This study aimed to assess the efficacy of premedication with NAC, a mucolytic agent, in improving mucus elimination as measured by decreased

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**Figure 2.** The entire gastric mucosa of the antrum and body was carefully scanned by NBI. If no adherent mucus was observed on the gastric mucosa as measured using conventional white light (A), but an obvious amount of mucus was located on the gastric mucosa during narrow-band imaging (B), extra water was flushed to ensure adherent mucus was eliminated as measured by both conventional white light (C) and narrow-band imaging (D) settings.
water flushes during NBI endoscopy. Magnification endoscopy combined with NBI is more accurate than CWL endoscopy in diagnosing gastric cancer on the basis of the following criteria: disappearance of fine mucosal structure, microvascular dilation and heterogeneity [13]. During endoscopy, the visualization of mucosa can be obstructed by foam, bubbles or mucus. For optimal visualization, mucosal hygiene is more important for NBI than CWL endoscopy. To the best of the knowledge, this is the first study describing this novel approach.

Premedication with dimethicone before upper endoscopy is commonly used to improve visibility of the gastric mucosa. It is administered after the addition of 80–100 ml of warm water. However, a significant amount of mucus can remain and adhere to the gastric mucosa interfering with mucosal visibility. Currently, mucolytic agents in combination with dimethicone have proved effective in eliminating gastric mucus and bubbles when used 20 min before conventional endoscopy [7]. NAC is a mucolytic agent that has been shown to change the viscoelastic properties of gastric mucin in vitro. A previous study has shown that the total mucosal visibility score did not significantly differ between the group with pronase and that with NAC [14]. The authors of this study also recommended that NAC could be a substitute for pronase in areas where the latter was unavailable. Regarding the relative lower cost of dimethicone and NAC per patient herein than pronase, the authors suggest use of NAC to eliminate mucus during NBI endoscopy.

A scoring system modified by Kuo et al. [7] and Chang et al [14] allocated scores from 1 to 4 based on mucosal visibility. Scores are measured for four domains of the stomach (the antrum, upper part of the greater curvature, lower part of the greater curvature and gastric fundus), with the total score known as the “total visibility score” (TVS). Score 1 means no adherent mucus on the gastric mucosa, score 2 means a little amount of mucus on the gastric mucosa without obscuring the vision, score 3 means a large amount of mucus on the gastric mucosa with less than 50 ml of water required to clear the mucus and score 4 indicates that more than 50 ml of water is required to clear the mucus. The difference in the scoring system used in the two studies was that Kuo et al. used 30 ml whereas Chang et al. used 50 ml of water for the criteria distinguishing scores 3 and 4.

The authors did not use the TVS method to assess the cleanliness and visibility for several reasons. First, separate assessment of all four domains of the study as mentioned above is time consuming and difficult to evaluate. Furthermore, the ranking of the visibility scores is extremely subjective with inter-observer biases. In this study with NBI endoscopy, it was found that water flushing with either 30 ml (as used by Kuo et al. in their study) or 50 ml (as used in the study by Chang et al.) was not sufficient for completely clear visualization of the mucosa. In the authors’ evaluation, more water was required to flush for optimal visualization, with a median of 40 ml in the NAC group and 50 ml in the control group. When the required water flush was more than 50 ml, water was reloaded from the syringe. In the NAC group, only 24% of patients needed more than one reloading of the water as compared with 48% of patients in the control group.

Instead of TVS, the authors assessed the efficacy of NAC in improving mucus elimination as measured by decreased endoscopic water flushes during NBI endoscopy. During NBI endoscopy, the goal is to complete visualization of the gastric mucosa. This need for complete mucosal clearance for NBI endoscopy indicates that the TVS scoring system is inadequate. Further, concerns, among Western endoscopists, of an increased risk of aspiration during the procedure were not realized during the practices. Moreover, no significant interactions or adverse reactions were reported with NAC.

In non-sedative endoscopy, this is a very long duration for patients to tolerate the procedure, especially if performing a variety of diagnostic techniques such as chromoendoscopy or NBI with or without high-magnification endoscopy. NAC can eliminate gastric mucus because of its property of breaking the disulfide bonds of proteins in the mucus. Eliminating the gastric mucus by NAC can reduce the need for additional manipulation such as washing. This will in turn reduce the number of flushes made by endoscopists in their attempt to clear the mucus, allowing more time for the observation of the gastric mucosa.

Taking into account the good safety profile of NAC and unavailability of pronase in some areas, the authors suggest NAC as a mucolytic agent to eliminate mucus during NBI endoscopy. Whether the use of NAC in NBI endoscopy will achieve a higher detection rate of early cancers or improved clinical outcomes is yet to be determined, and well-designed large clinical trials are required in the future to evaluate this.

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References


