Use of N-acetylcysteine plus simethicone to improve mucosal visibility during upper GI endoscopy: a double-blind, randomized controlled trial

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Background and Aim: Upper GI endoscopy (UGE) is essential for the diagnosis of gastrointestinal diseases. Mucus and bubbles may decrease mucosal visibility. The use of mucolytics could improve visualization. Our aim was to determine whether premedication with simethicone or simethicone plus N-acetylcysteine is effective in improving visibility during UGE.

Methods: This was a randomized, double-blinded, placebo-controlled trial with 2 control groups: no intervention and water 100 mL (W); and 3 intervention groups: simethicone 200 mg (S); S + N-acetylcysteine (NAC) 500 mg (S+NAC500); and S + NAC 1000 mg (S+NAC1000). The solution was ingested 20 minutes before UGE. Gastric visibility was evaluated in 4 segments with a previously described scale. A score of less than 7 points was defined as adequate visibility (AV). Water volume was used to improve visibility, and adverse reactions were evaluated as a secondary outcome. Multiple group comparison was performed using non-parametric one-way analysis of variance (ANOVA).

Results: Two hundred thirty patients were included in the study, 68% female, mean age 49 years. The most common indication for UGE was epigastric pain/dyspepsia (33%). AV was more frequent in the S+NAC500 and S+NAC1000 groups (65% and 67%) compared with no intervention (44%, $P = .044$) and water (41%, $P = .022$). The gastric total visibility scale (TVS) was significantly better in the S+NAC500 and S+NAC1000 groups compared with water ($P = .03$ and $P = .008$). Simethicone was not different from no intervention and water. S+NAC1000 required less water volume to improve visibility. No adverse reactions from the study drugs were observed.

Conclusions: Premedication with S+NAC500 and S+NAC1000 improves visibility during UGE. The use of simethicone did not show improvements in gastric visibility. TVS was worse in patients using water alone. (Clinical trial registration number: NCT 01653171.) (Gastrointest Endosc 2018;87:986-93.)

Abbreviations: IQR, interquartile range; NAC, N-acetylcysteine; S, simethicone; TVS, total visibility scale; UGE, upper gastrointestinal endoscopy.

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INTRODUCTION

Upper GI endoscopy (UGE) is one of the main diagnostic tests for the evaluation and follow-up of gastrointestinal diseases.[1] One of the key elements is complete visualization of the gastric mucosa,[2] which is particularly important for early recognition of gastric cancer.[3] Mucus, foam, and bubbles pooled in the upper GI tract interfere with adequate endoscopic visualization. Many anti-foaming and mucolytic agents are widely used in endoscopic centers mainly in Japan,[4] where their use is standard, unlike western countries. Moreover, most patients attending for UGE are fasting, according to recommended preprocedure instructions.[5]

Several agents have been proven to improve gastric mucosal visibility. Simethicone has been found to be a good anti-foaming agent before endoscopy to remove mucus and bubbles.[6-8] More recently, N-acetylcysteine (NAC), either alone or in combination with simethicone, has proven to be effective in removing mucus and gastric bubbles when used 20 minutes before UGE, improving the visualization of the gastric mucosa.[9,10] Other agents, such as Pronase (MilliporeSigma, Burlington, Mass, USA), have also been described as useful for this purpose and are widely used in Asian countries, but they are not generally available in western countries.[11] Given the comparative nature of these studies, most have compared anti-foaming agents with water as placebo. The impact of anti-foaming agents compared with fasting alone, the most common condition in western countries, has not been evaluated yet.

The aim of our study was to evaluate the use of anti-foaming agents in preparation for UGE, comparing differences in the visualization of the gastric mucosa in patients prepared with simethicone or NAC plus simethicone with water alone or no intervention.

METHODS

Patients

From July 2012 to August 2013, all patients undergoing ambulatory diagnostic UGE were invited to participate in the study. Adults capable of giving informed consent were included. Exclusion criteria were history of upper GI tract surgery, gastric cancer, deep sedation with propofol, need for therapeutic endoscopy and emergency procedures, recent upper GI bleeding, caustic ingestion, pregnancy, diabetes mellitus, asthma, and allergic reactions to the medications used in the study.

Study design

This was a parallel assignment, double-blinded, placebo-controlled randomized controlled trial. The study protocol was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of our Academic Hospital (School of Medicine, Pontificia Universidad Católica de Chile). The study was registered at ClinicalTrials.gov (NCT:01653171). The manuscript was written in accordance with the CONSORT guidelines.[12]

Randomization and concealment

The attending doctors were responsible for obtaining informed consent before UGE. Participants were randomly assigned following simple randomization procedures (GraphPad QuickCalcs) to 1 of 5 groups. The randomization sequence was managed by a statistician not participating in the endoscopic evaluation of the patients and blinded to the investigators.

Interventions

Patients were randomized to 5 groups: (1) no intervention; (2) 100 mL of water (W); (3) W + simethicone (S) 200 mg; (4) W + S + NAC 500 mg (S+NAC500); and (5) W + S + NAC 1000 mg (S+NAC1000) (Fig. 1).

Patients, technical staff, endoscopists performing the procedure, and data collectors were blinded. For this purpose, all liquid solutions were prepared in opaque containers of similar appearance. The participants received the assigned solution 20 minutes before the procedure under the supervision of a trained nurse.

All patients were given standard recommendations before the procedure: at least 8 hours of liquid and solid fasting and 72 hours of suspension of anti-secretory medications. Local pharyngeal anesthetic solution was used immediately before the procedure.

Gastric visibility assessment

During endoscopy, gastric visibility was evaluated in 4 segments (gastric antrum, lower gastric body, upper gastric body, and fundus), using a scale ranging from 1 to 4 points: (1) no adherent mucus in the gastric mucosa examined; (2) a small amount of mucus in the gastric mucosa examined that does not hinder vision; (3) a large amount of mucus in the gastric mucosa examination, which can be washed thoroughly with less than 50 mL of water; (4) a large amount of mucus in the gastric mucosa examined, which cannot be cleaned completely with up to 50 mL of water on that gastric site, and would require more water for washing. The sum of the visibility scores for the antrum, lower gastric body, upper gastric body, and fundus was defined as the total visibility scale (TVS), ranging from 4 to 16 points, as defined in previous publications by Kuo et al,[11] Asl and Sivandzadeh,[9] and Chang et al[10] (Fig. 2).

In a preliminary phase of the study, the 9 participating endoscopists were shown images corresponding to different degrees of cleanliness of gastric mucosa, and scores were discussed until agreement was reached. Subsequently, an online survey of 20 gastric images from different sections of the stomach was conducted separately by endoscopists participating in the study and each image was graded according to the TVS score, and Cohen's kappa (k) coefficient with quadratic weighting was used to grade the interobserver agreement for TVS.[13] Endoscopic

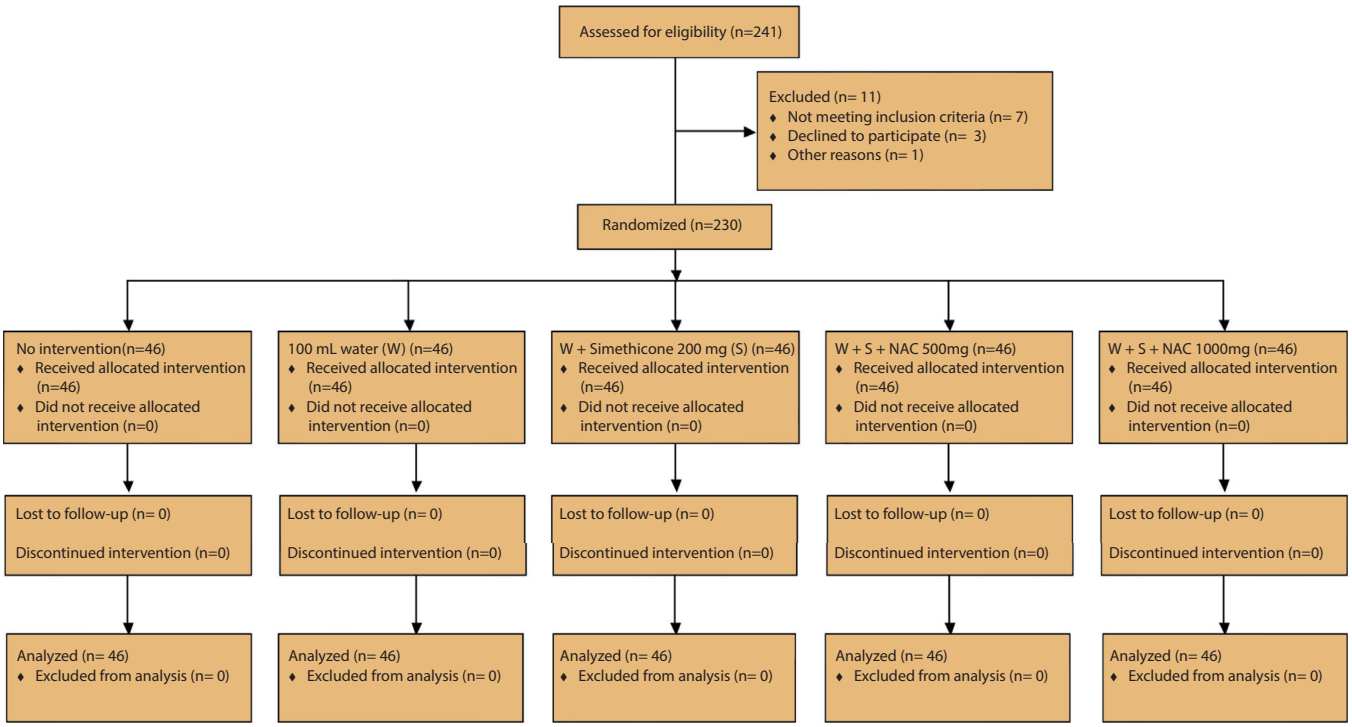


Figure 1. Flowchart. Eligibility criteria, allocation, and follow-up for the study groups, according to the CONSORT guidelines.[12]

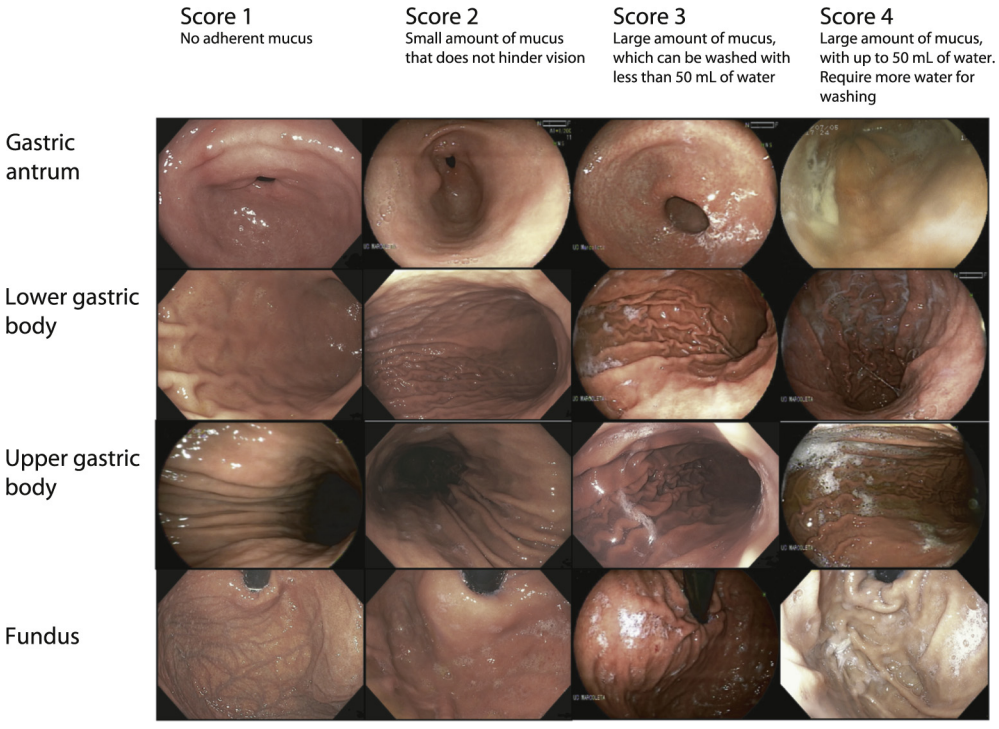


Figure 2. Gastric total visibility scale (TVS). Each segment of the stomach was evaluated with a score of 1-4, giving a total TVS score as the sum of all the segments evaluated. Time to complete the procedure and amount of water used to achieve adequate visibility was also assessed.

examinations were performed in the endoscopy unit of our center using high-definition video-endoscopes (Fujino-nEG-530FP, Japan).

Outcomes measures

Endoscopic visualization was considered to have adequate visibility (AV) when the TVS was less than 7

TABLE 1. Baseline characteristics of the study patients (n = 230)

Variables	Percentage/mean	No intervention	Water	Simethicone	S+NAC500	S+NAC1000
Female (%)	68 (156/230)	44 (20/46)	41 (19/46)	46 (21/46)	65 (30/46)	67 (31/46)
Age (years), median (IQR)	49 (35-82)	55 (41-70)	47.5 (33-68)	48.5 (33-77)	48 (41-70)	46 (31-70)
Indication for upper gastrointestinal endoscopy						
Epigastric pain/dyspepsia	75/230	10/46	14/46	23/46	16/46	12/46
GERD	61/230	15/46	10/46	12/46	15/46	9/46
Gastric cancer screening	16/230	5/46	6/46	0	0	5/46
Follow-up upper gastrointestinal endoscopy	9/230	2/46	0	0	0	7/46
Anemia	6/230	0	0	2/46	0	4/46
Other	63/230	14/46	16/46	9/46	15/46	9/46

S+NAC500, Simethicone + N-acetylcysteine 500 mg; *S+NAC1000*, simethicone + N-acetylcysteine 1000 mg; *IQR*, interquartile range.

points and insufficient visibility (IV) when the TVS was 7 points or higher, as primary outcome.

Secondary outcomes were (1) the amount of water used to allow suitable visualization of gastric mucosa; (2) time to complete the UGE (from the time of oral intubation until complete removal of the endoscope; (3) as a safety outcome, the presence of adverse reactions to the study drugs was assessed; and also the occurrence of respiratory, cardiovascular, or endoscopic adverse events. After the endoscopic procedure, patients were observed for at least 90 minutes before being discharged. Patients were instructed to communicate with the investigators and the endoscopic unit in the event of late adverse reactions.

Follow-up of endoscopic findings and results for biopsy samples (when taken) were registered whenever available after completion of the study. Endoscopic lesion findings were considered positive when the endoscopist described atrophy, metaplasia, granular gastropathy, ulcers, neoplasia, polyps, and large erosions. Positive findings also included minor findings such as erythema or small isolated erosions that were confirmed as inflammation in biopsy samples.

Sample size estimation

A sample size calculation was performed using Epidat v.4.0 based on a previous study of similar design.[9] Considering an alpha error of 5% with power of 80%, assuming a difference of 30% in the proportion of patients with AV between intervention and control groups (70% vs 40%, respectively), the calculated sample size was 40 patients per study arm. Considering that our study had 5 arms, the required sample size was 200 patients. To account for an estimated 15% loss to follow-up after randomization, the total study sample size was 230 patients. Although TVS is a numerical variable, we decided to calculate the sample size using TVS as a binary outcome. First, a priori we did not have detailed information about the distribution of TVS; therefore, assuming a normal distribution to compare means could be inappropriate. In addition, previous studies have not established the minimal clinically important difference for the TVS of gastric mucosa. The binary outcome approach enabled us to calculate a sample size regardless of the distribution of TVS, with enough power to detect minimal differences in terms of TVS as a numerical variable.

Statistical analysis

Categorical variables were described with percentages and proportions. Continuous variables were described as the mean and standard deviation or the median and interquartile range (IQR). The chi-squared test or the Fisher exact test was used to compare categorical variables and the proportion of AV among the study groups. The Shapiro-Wilk normality test was performed to assess the distribution of the primary and secondary outcomes variables. The Mann-Whitney non-parametric test was performed to compare differences in TVS between control groups and intervention groups. Non-parametric one-way analysis of variance (ANOVA) (Kruskal-Wallis) adjusted by Dunn's multiple comparisons test was conducted to compare the TVS across all the study groups. A two-tailed *P* value of less than .05 between groups was considered statistically significant. The statistical analysis was performed using SPSS v.20.0 (SPSS Inc, IBM, Armonk, NY, USA) and GraphPad Prism (GraphPad Software, La Jolla, Calif, USA).

RESULTS

Two hundred forty-one patients were assessed to enter the study protocol. Two hundred thirty patients were enrolled in the study; consequently 46 patients were randomly assigned to each of the 5 groups and received the allocated intervention. There were no losses to follow-up or discontinued interventions throughout the study (Fig. 1). One hundred fifty-six patients (68%) were female and the mean age of study population was 49 years. The most common indication for UGE was epigastric pain/dyspepsia (33%), followed by gastroesophageal reflux (27%). Table 1 presents the general characteristics of the patients. No differences in general characteristics were observed between groups.

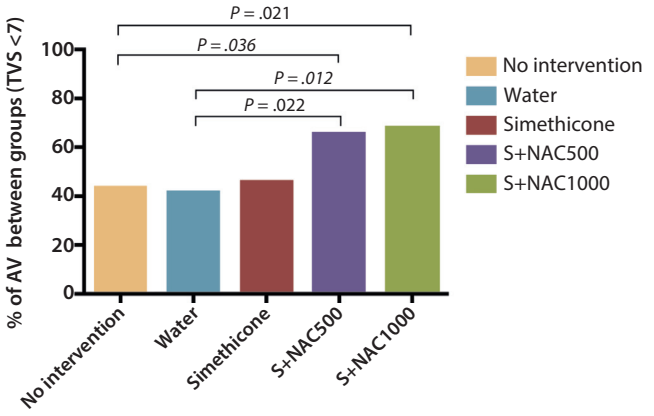
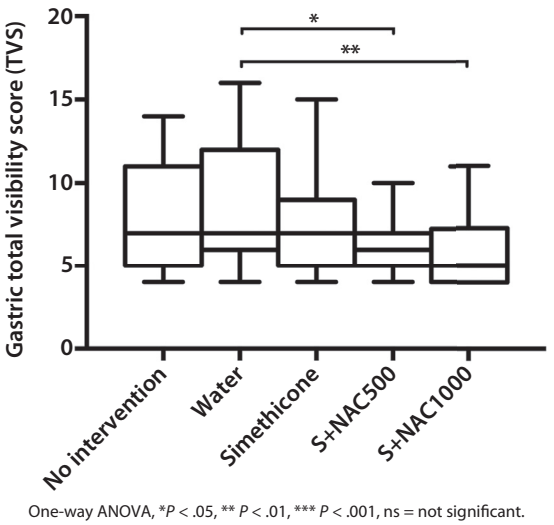


Figure 3. Percentage of adequate visibility (AV) for the study groups.



One-way ANOVA, *$P < .05$, ** $P < .01$, *** $P < .001$, ns = not significant.

Figure 4. Comparison of TVS score between intervention and control groups in the adjusted analysis. Total gastric visibility score was better in the S+NAC500 and S+NAC1000 groups compared with the water group.

When considering a TVS cut-off of 7 points for AV (<7 points) or IV (≥7 points), 53% (121/230) of the overall study sample had an AV score. The lowest proportion of AV was seen in the water group: 41% (19/46). AV was more frequent in the groups that used S+NAC500 and S+NAC1000 compared with the no-intervention group (65% and 67% compared with 44% in the no-intervention group, $P = .036$ and $P = .021$) and the water group (65% and 67% vs 41% in the water group, $P = .022$ and $P = .012$). AV in the simethicone group (46%) was no different from the no-intervention and water groups ($P = .834$ and $P = .674$) (Fig. 3).

The median TVS in the overall study sample was 5 (IQR, 5-14). The median TVS was higher in the water group (7; IQR, 6-14), followed by the no-intervention group (7; IQR, 5-12), then the simethicone group (7; IQR, 5-10), the S+NAC500 group (6; IQR, 5-10), and the S+NAC1000 group (5; IQR, 4-11).

The TVS score was compared between study groups. TVS score was no different between the 2 control groups (no intervention and water; $P = .3$). No differences were noted when comparing the no-intervention group with the simethicone group ($P = .56$). However, the TVS scores for the S+NAC500 and S+NAC1000 groups were significantly better than for the no-intervention group ($P = .034$ and $P = .019$, respectively).

When comparing the water group with the simethicone group, no differences were noted ($P = .14$). The TVS scores for the S+NAC500 and S+NAC1000 groups were lower than for water group ($P = .0034$ and $P = .0015$, respectively).

The TVS score between intervention groups was also analyzed. In the unadjusted analysis, the S+NAC1000 group had a lower TVS score than the simethicone group ($P = .046$). In control groups, the TVS score was worse in the water group than in the no-intervention group.

In one-way ANOVA analysis adjusted by Dunn's multiple comparisons test, the TVS score was only significantly better in the S+NAC500 and S+NAC1000 groups compared with the water group ($P = .028$ and $P = .0086$, respectively) (Fig. 4). No differences were noted in the intervention groups compared with the no-intervention group after adjusting for multiple comparisons (Table 2).

As a secondary outcome, the median amount of water used to allow adequate visualization of gastric mucosa was 50 mL (IQR, 0-330 mL) in the overall study sample. The median amount of water used was higher in the water group (90 mL; IQR, 10-200 mL). Comparison between groups showed a significantly lower use of water in the S+NAC1000 group ($P = .035$). The group using simethicone did not show a difference compared with no intervention or water groups regarding the amount of water used.

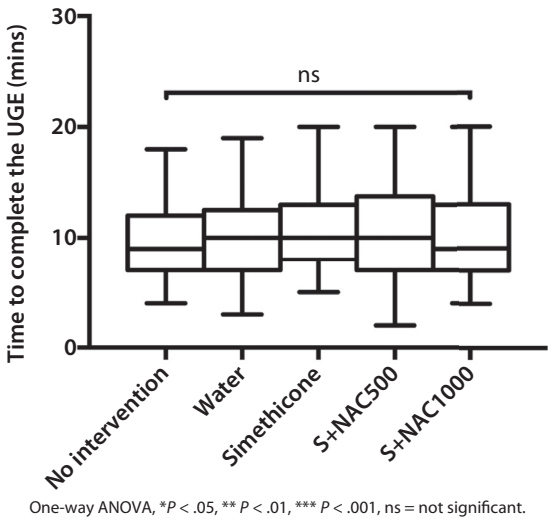
The median time to complete the UGE was 10 minutes (IQR, 7-23 minutes) in the overall sample. There were no differences between groups in total time to complete UGE ($P = .818$), although the group that required least time to complete visualization of the entire gastric mucosa was the group that used S+NAC1000 (median, 9 minutes; IQR, 7-13 minutes) (Fig. 5).

Endoscopic findings on detection of gastric lesions were evaluated after the completion of the study and compared between groups. Follow-up for endoscopic lesion findings and biopsy sample results (when obtained) was available for 86% of patients included in the study. The intervention groups taken together (S, S+NAC500, S+NAC1000) had a higher rate of lesion detection in UGE compared with the water only group (32% [37/115] in the intervention groups vs 14% [6/42] in the water group; $P = .027$). When considering the S+NAC500 and S+NAC100 groups compared with the water-alone group, there was difference in endoscopic lesion detection (32% [24/76] in the NAC groups vs

TABLE 2. Comparison of total visibility scale score between control and intervention groups

	Uncorrected *P* value*	Adjusted *P* value†
Water vs no intervention	.303	>.99
Simethicone vs no intervention	.557	>.99
S+NAC500 vs no intervention	.034	.1570
S+NAC1000 vs no intervention	.019	.1619
Simethicone vs water	.139	>.99
S+NAC500 vs water	.0034	.028
S+NAC1000 vs water	.0015	.0086
S+NAC500 vs simethicone	.081	>.99
S+NAC1000 vs simethicone	.046	.531
S+NAC500 vs S+NAC1000	.613	>.99

S+NAC500, Simethicone + N-acetylcysteine 500 mg; *S+NAC1000*, simethicone + N-acetylcysteine 1000 mg.
*Direct comparison, Mann-Whitney test.
†Adjusted *P* value by one-way ANOVA adjusted by Dunn's multiple comparisons test to compare TVS scores across all the study groups.



One-way ANOVA, *$P < .05$, ** $P < .01$, *** $P < .001$, ns = not significant.

Figure 5. Time to complete the UGE procedure. No differences in total time was observed among the groups ($P = .818$).

14% [6/42] in the water-alone group; $P = .048$). No difference was observed in lesion detection when the intervention groups were compared with the no-intervention group ($P = .607$). The no-intervention group was also superior for lesion detection than the water group ($P = .024$). The details of the endoscopic findings according to each group of patients are presented in Table 3.

Cohen's kappa (κ) coefficient with quadratic weighting was used to grade the interobserver agreement[13] for the gastric TVS. The kappa coefficient for interobserver agreement on grading gastric mucosal visualization among endoscopists was 0.901. This magnitude of agreement is considered strong.[14]

Adverse reactions

No adverse reaction attributable to the interventions was detected during the study. No allergic reactions or upper respiratory tract aspirations were noted. There were no cardiovascular or endoscopic adverse events in the patients during study period, from administration of the study drug to at least 90 minutes after the UGE procedure was completed. No late adverse reactions were reported.

DISCUSSION

This randomized, double-blind, placebo-controlled trial focusing on improvement of gastric mucosal visualization before upper endoscopy indicates that the use of simethicone plus NAC provides better visualization of the gastric mucosa in UGE. To the best of our knowledge, this is the first study to use a control group of no intervention, and this option should certainly be included in any comparative study dealing with preparation for UGE, because most patients undergo an UGE without any specific preparation in western countries.[5] Our findings suggest that the use of NAC, at both concentrations used in this study, plus simethicone did provide better visualization of the gastric mucosa. We also found that the use of water alone as preparation for upper endoscopy could be detrimental. A potential explanation for this finding could be that water might just move or spread mucus over a wider surface of the gastric mucosa, without having any effect on its dissolution. Improving the quality of the endoscopy procedure is just as important as ensuring access to endoscopy to achieve early detection of cancer.[3,15]

Although the group that required the least time to complete visualization of the entire gastric mucosa was the S+NAC1000 group (median, 9 minutes; IQR, 7-13 minutes), there were no differences between groups in the total time to complete UGE. We should expect a significantly longer procedure time in the groups with a worse cleaning score. This leads us to assume that in the latter groups, the endoscopic visualization could have been of lower quality than for the groups that used S+NAC. Considering that the demand for endoscopic procedures is increasing, and that efficiency must be optimized, it is imperative to incorporate strategies that can improve the quality of the procedures while saving time.

Foam, bubbles, and accumulated mucus over the gastric mucosa make complete visualization during the procedure difficult and may interfere with the endoscopic diagnosis, therefore decreasing the sensitivity of this test. Decreasing the amount of mucus and bubbles is essential to ensure better visualization of the gastric mucosa. Adequate premedication can improve visualization, diminishing the

TABLE 3. Endoscopic findings in upper gastrointestinal endoscopy according to allocation group*

Allocation group	Positive endoscopic findings in UGE (%)	Atrophy	Metaplasia	Granular gastropathy	Ulcers/erosions	Elevated lesion (polyps/neoplasia)	Minor findings†
No intervention	37 (15/41)	2	8	3	2	2	0
Water	14 (6/42)	0	1	1	3	1	1
Simethicone	33 (13/39)	6	4	3	4	1	0
S+NAC500	31 (11/36)	3	3	2	4	3	0
S+NAC1000	33 (13/40)	2	3	4	5	4	0

UGE, Upper gastrointestinal endoscopy; *S+NAC500*, Simethicone + N-acetylcysteine 500 mg; *S+NAC1000*, simethicone + N-acetylcysteine 1000 mg.
*Total number of gastric lesions found during upper gastrointestinal endoscopy examination (there could be more than one finding).
†Minor findings: erythema or small isolated erosions, confirmed as inflammation after biopsy.

need to wash the mucosa during the procedure and saving time.[3] Therefore, it seems appropriate to use agents before endoscopy to eliminate these problems and improve the precision and accuracy of endoscopy in showing subtle abnormalities. Several mucolytic agents have been described as helpful.

Simethicone, used for relief of bloating and gas with no significant adverse reactions in common usage, is a safe supplemental endoscopic premedication. Simethicone causes reduction of the surface tension of the air bubbles and disperses them without significant absorption in the gastrointestinal system. Simethicone's effectiveness as an anti-foaming agent has been demonstrated in several other trials.[16] Also, it has been studied in other scenarios such as colonoscopy,[16,17] in the preparation for capsule endoscopy in the small bowel,[18,19] and in endoscopic ultrasonography where it reduces artifacts and increases the accuracy of the study.[20] However, in our study, the use of simethicone did not show a benefit in the gastric mucosa visibility scale, the amount of water needed for adequate mucosal visualization, or the overall time to complete the procedure in the multiple groups comparison.

NAC is a mucolytic agent and antioxidant that acts through its free sulfhydryl group to lower the viscosity of mucus. NAC either alone or in combination with simethicone has proven effective in removing mucus and gastric bubbles when used 20 minutes before UGE, improving the visualization of the gastric mucosa.[9,21-24] NAC is commonly used to improve the visibility of the mucosa of the esophagus, for the detection of Barrett's, esophagus, and before chromoendoscopy.[25] No significant interactions or adverse reactions have been reported with oral preparations.

More recently, other agents such as Pronase have also been described as useful in this purpose, and are widely used in Japan and Asian countries, but they are not generally available in western countries.[10,11,26]

In our study, the use of NAC plus simethicone, at both concentrations that were studied, did provide better results for visualization of the gastric mucosa. There seems to be a dose-dependent effect with the use of NAC plus simethicone in our study; the use of 1000 mg of NAC was superior to 500 mg of NAC when compared with water or no intervention. Most reports evaluating the use of NAC have used a smaller dose than 1000 mg.[9,21,24] Our study results show that a dose of 1000 mg of NAC is superior to 500 mg for the TVS score compared with water and no intervention, without causing any side effects. Therefore, adopting the use of 1000 mg NAC in endoscopy practice could produce greater improvement in gastric mucosal visibility.

An interesting finding in our study is that the use of water in preparation for endoscopy had a higher TVS score, required more water for adequate mucosal assessment, and had less lesion detection during UGE than all the other groups, including the group with no intervention. Most studies have administered water as a placebo control, ranging from 60 to 100 mL.[6-10,21,22,24] Our results suggest that the use of water alone as preparation for UGE could be detrimental.

Currently, there is no standard validated scale to classify mucosal visualization, and previous studies have used different measures.[21] Our choice was to use the score described by Kuo et al,[11] adapted by Chang et al[10] and Asl and Sivandzadeh[9] based on the methodological considerations of these publications. In our study, the interobserver agreement for the gastric visibility scale was strong.

We believe that this scale can be easily applied to assess and compare different preparations for UGE in clinical studies and in clinical practice; a gastric mucosa visibility scale is needed for these purposes. Validated bowel preparation scales are applied in a routine way nowadays, and we believe there is a role for the use of gastric visibility scales especially in the context of gastric cancer screening in areas with a high incidence of gastric cancer and/or in high-risk conditions such as atrophic gastritis/intestinal metaplasia.[5,27]

Similar to our study, most articles involving the use of anti-foaming agents as premedication in UGE have been designed to evaluate the improvement in gastric mucosal visibility through different scales, and not to assess an increase in detection of gastric lesions. In one study, the rate of gastric lesions reported was higher in the simethicone group but without statistical significance.[21]

Our findings showed that the use of premedication before endoscopy improved the detection of gastric lesions compared with the group that used water alone. There were no differences in lesion detection in the groups that used premedication compared with no intervention. Several considerations should be taken into account regarding lesion detection. First, the study was not designed to find differences in lesions detection, therefore these findings could be incidental. Second, the analysis of the lesions detected and the biopsy results (when obtained) was made after the completion of the study. Although improved mucosal visibility does not necessarily improve clinical outcomes, endoscopic premedication may be helpful for increasing the detection rate of early cancers. Large randomized clinical trials are needed to confirm the utility of gastric premedication for detecting gastric lesions and identifying early gastric cancers.

Our study has some limitations. We cannot compare endoscopic visibility measurements for each patient before premedication to assess the impact of the individual preparations. Our results suggest that the lesion detection rate should improve with the use of adequate preparation with mucolytic agents before UGE; however, this needs to be investigated prospectively.

In conclusion, our findings show that the use of NAC plus simethicone before UGE improves the visibility of the gastric mucosa and reduces the volume of water needed for AV, which may increase the diagnostic yield of the UGE examination.

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