

Efficacy of premedication with activated Dimethicone or N-acetylcysteine in improving visibility during upper endoscopy

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Abstract

AIM: To assess the efficacy of N-acetylcysteine (NAC) and activated Dimethicone in improving endoscopic mucosal visibility.

METHODS: A total of 148 patients were randomly allocated into four groups to receive one of the following premedications: group A: 100 mL water alone; group B: activated Dimethicone plus water (up to 100 mL); group C: NAC plus water (up to 100 mL); and group D: activated Dimethicone and NAC plus water (up to 100 mL). A single endoscopist blinded to the patients group assessed the gastric mucosal visibility scores (range 1-4) at four sites. The sum of the scores from the four sites was considered as the total mucosal visibility score (TMVS).

RESULTS: The patients in group B showed a significantly lower TMVS than those of groups A and C ($P < 0.001$). The TMVS in patients of group D was significantly lower than that of groups A and C ($P < 0.001$). The TMVS did not significantly differ between groups B and D ($P > 0.05$). The difference between TMVS of groups C and A was not significant ($P > 0.05$).

CONCLUSION: Premedication with activated Dimethicone 20 min prior to the upper endoscopy leads to the best visibility. NAC does not improve visualization by itself.

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Key words: Dimethicone; N-acetylcysteine; Simethicone; Upper endoscopy

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INTRODUCTION

Studies recently demonstrated a declining trend in gastric cancer incidence throughout the world; yet, it is still the second most common cause of mortality due to malignant diseases^[1]. As detecting the cancer at the early stage has a great impact on its potential curability, mass screening programs are implementing in Japan with the highest rate of the disease. Although the real effect of this approach on mortality is said to be little by some, studies conducted in Japan favor endoscopic mass screening especially by the advent of new minimally invasive procedures such as endoscopic mucosal resection for cancers detected at early stages^[2-5].

Foam, bubbles, and mucus accumulated in the upper gastrointestinal tract can interfere with clear mucosal visualization and pose potential risk of missing early or subtle lesions. That is why anti-foam and bubble-bursting

agents are widely used in gastrointestinal endoscopic centers particularly in Japan where it is common. This is a routine practice neither in the country where this study was conducted nor in the West, probably in fear of some presumed risk of pulmonary aspiration^[6].

Simethicone [Dimethylpolysiloxane (DMPS) or activated Dimethicone] was proved to be a good defoaming agent for pre-endoscopic usage to remove bubble and mucus^[7,8]. Pronase, a proteolytic enzyme isolated in 1962 from the culture filtrate of *Streptomyces griseus*, is another agent whose efficiency as a premedication for improving the visual field of endoscopy devoid of foam and mucus has been investigated and is now being used routinely in Japan's endoscopic centers. It is better to be used in combination with DMPS and bicarbonate to yield more improvement in visibility^[9,10].

Other than upper endoscopy, Simethicone has been studied to be used in colonoscopy as an additive to other bowel preparations to eliminate bubbles^[11,12], in capsule endoscopy as small bowel preparation for the same goal^[13,14], and in endoscopic ultrasonography to reduce artefacts and increase the accuracy of the modality^[15,16].

Currently, N-acetylcysteine (NAC), a mucolytic agent, in combination with DMPS has shown to be effective in elimination of gastric mucus and bubbles when used 20 min prior to endoscopy, improving visualization of the gastric mucosa^[17]. Owing to the lack of any study surveying the efficiency of NAC independently, the present study aimed to compare the effect of this compound and activated Dimethicone (Simethicone) with placebo and together as premedications for gastroscopy.

MATERIALS AND METHODS

This double-blind, randomized, placebo-controlled study was carried out from April to August 2010. Amongst all the consecutive patients referred to our out-patient endoscopy clinic, 148 patients were enrolled in the study after giving a written informed consent. The patients with a history of upper gastrointestinal surgery, gastric cancer, gastrointestinal bleeding, caustic ingestion, pregnancy, diabetes mellitus, asthma, and allergic reactions were excluded from the study. This study was approved in the ethics committee of the local university.

The patients were randomly allocated into four different groups (using random blocks) with peculiar liquid premedication for each one: (1) group A, 100 mL water; (2) group B, 100 mg, 2.5 mL, activated Dimethicone (Dimetin, Tolid Daru co., Tehran, Iran) plus water up to 100 mL; (3) group C, 600 mg N-acetylcysteine (ACC, Hexal AG, Holzkirchen, Germany) in water up to 100 mL; and (4) group D, 100 mg, 2.5 mL, activated Dimethicone and 600 mg N-acetylcysteine plus water up to 100 mL.

All the liquid solutions were prepared in the same opaque bottles and taken about 20 min prior to endoscopic procedure under supervision of an informed attendant nurse. All patients were unaware of their groups and the type of liquid solutions. Then the patient awaited

endoscopy in sitting position in the endoscopy waiting room.

All the endoscopic procedures were performed by a single, experienced endoscopist blinded to the patient's group and premedication. The endoscopies were done at a relatively fixed period of time in a clinic affiliated with Shiraz University of Medical Sciences, using a video endoscope (EPK 1000 PENTAX, Japan).

During endoscopy, four distinct domains of the stomach including the antrum, the upper part of the greater curvature, the lower part of the greater curvature, and the gastric fundus were evaluated separately for mucosal visibility. Scoring from 1 to 4 for each domain, known as visibility score, was defined based on the modified form of Kuo *et al.*^[9] scoring system like the one used by Chang *et al.*^[17] as follows: (1) score 1, no adherent mucus on the gastric mucosa; (2) score 2, little amount of mucus on the gastric mucosa, but no obscuring vision; (3) score 3, large amount of mucus on the gastric mucosa, with less than 50 mL of water to clear; and (4) score 4, large amount of mucus on the gastric mucosa, with more than 50 mL of water to clear.

The sum of visibility scores of all four domains is considered as the TMVS for each patient.

Statistical analysis

The demographic characteristics were assessed using a χ^2 test, ANOVA, or one-way analysis of variance. The visibility scores of all the four groups were analyzed using Kruskal-Wallis and Mann-Whitney pairwise comparisons. *P* value < 0.05 was considered statistically significant.

RESULTS

From a total of 148 patients enrolled in the study, 77 (52%) were male and 71 (48%) female. Then, 38, 37, 37 and 36 patients were randomly assigned to groups A, B, C and D, respectively. The mean (\pm SD) age was 42.2 ± 13.9 in group A, 44.3 ± 18 in group B, 44.6 ± 16.4 in group C, and 41.8 ± 17.5 in group D. The mean age in the whole study population was 43.2 ± 16.4 . The most common reason for endoscopy in all the groups and also in the total population was dyspepsia (65.5% in total). Moreover, the second most common cause in all the patients was acid reflux (12.8%). All demographic data encompassing sex distribution per group and reason for endoscopy are shown in Table 1. There was no statistically significant difference (*P* > 0.05) among groups regarding age and gender.

The mean of TMVS in group A was 9.50 ± 2.55 , in group B 5.11 ± 1.28 , in group C 8.41 ± 2.10 , and in group D 5.39 ± 1.71 . The total mean ranks in groups A, B, C and D were 109.96, 41.69, 98.39 and 46.24, respectively (the lower the rank, the better the visibility). The difference among the mean ranks was statistically significant (*P* < 0.001). Group B showed the least visibility scores at different locations of the stomach and also the least

Table 1 Demographic characteristics of patients in each group

Group	A	B	C	D
Number	38	37	37	36
Age(yr; mean ± SD)	42.2 ± 13.9	44.3 ± 18.0	44.6 ± 16.4	41.8 ± 17.5
Female: Male (n)	18:20	19:18	16:21	18:18
Cause of endoscopy				
Dyspepsia	25	28	21	23
Reflux	6	5	4	4
Screening for cancer	7	0	5	4
Others	0	4	7	5

No significant difference between each two groups regarding age and gender. Group A received water, group B received activated Dimethicone plus water, group C received N-acetylcysteine plus water, and group D received activated Dimethicone and N-acetylcysteine plus water.

Table 2 The mean rank¹ of any group of patients in distinct domains of stomach

Group	A	B	C	D
Antrum	102.82	48.91	91.74	53.19
Lower part of the greater curvature	103.43	51.24	88.00	53.99
Upper part of the greater curvature	100.17	48.49	92.43	55.71
Fundus	102.21	51.43	90.96	52.04

¹The lower the mean rank, the better the visibility.

Table 3 Mean mucosal visibility score at different sites and total mean mucosal visibility scores in any group separately (mean ± SD)

Group	A	B	C	D
Antrum	2.39 ± 0.94	1.22 ± 0.53 ^{a,b}	2.05 ± 0.78	1.28 ± 0.51 ^{c,d}
Lower part of the greater curvature	2.26 ± 0.89	1.14 ± 0.34 ^{a,b}	1.89 ± 0.87	1.19 ± 0.46 ^{c,d}
Upper part of the greater curvature	2.47 ± 0.79	1.38 ± 0.54 ^{a,b}	2.35 ± 0.94	1.53 ± 0.69 ^{c,d}
Fundus	2.37 ± 0.75	1.38 ± 0.54 ^{a,b}	2.11 ± 0.65	1.39 ± 0.54 ^{c,d}
Total (TMVS)	9.50 ± 2.55	5.11 ± 1.28 ^{a,b}	8.41 ± 2.10	5.39 ± 1.71 ^{a,b}

^aP < 0.001 vs group A; ^bP < 0.001 vs group C; ^cP < 0.05 vs group A; ^dP < 0.05 vs group C; a, b, c, d: Kruskal-Wallis and Mann-Whitney pairwise comparisons. TMVS: Total mucosal visibility score.

mean TMVS which were all significantly lower than those of groups A and C (P < 0.001). The patients in group D had significantly lower visibility scores for separate gastric domains (P < 0.05) and showed lower mean TMVS than group A and C too (P < 0.001). Groups B and D did not differ significantly in scores (P > 0.05). Despite the fact that patients in group C achieved lower scores than group A patients, the difference was not significant at all (P > 0.05). The mean rank, the mean mucosal visibility scores at separate sites, and the mean TMV scores in distinct groups are depicted in Table 2 and 3, respectively. No adverse reaction was detected during the study in any group.

DISCUSSION

Esophagogastroduodenoscopy or upper endoscopy re-

mains commonplace for the evaluation of upper gastrointestinal tract disorders. One of the major applications of this modality is to discern gastric cancer at early stages. This is of paramount importance because of the direct effect of early diagnosis of gastric cancer on patients' future survival, quality of life, and management. A case series from Britain, reported by Sue-Ling *et al*^[18] showed a 5 year survival rate of 98% for patients detected at early stages of gastric cancer and survived operation. On the other hand, rapid diagnosis is not guaranteed by doing upper endoscopy alone even in a wide range. Suvakovic *et al*^[19] in 1997 remarked that open-access gastroscopy by itself was not sufficient to increase early gastric cancer pick-up; moreover, more awareness from general practitioners, more experience in endoscopy, and high sensitivity for biopsying are important among others too. Besides, foam, bubbles, and mucus accumulated on gastric mucosa are postulated to play a role by blurring visual field during endoscopy. So, it seems prudent to make use of some agents before endoscopy to eliminate these troubles and enhance the precision and accuracy of endoscopy in showing subtle abnormalities.

Simethicone (activated Dimethicone or activated Methylpolysiloxane), commonly used for relief of bloating and gas with no significant adverse reaction or interaction^[20], is a safe adjunct to endoscopic premedications. It works via decreasing the surface tension of bubbles of air and dispersing them without remarkable absorption in the gastrointestinal system^[20]. The effectiveness of Simethicone has already been proved in some other trials as a defoaming agent^[7,8]. Recently, Keeratchananont *et al*^[22], though using a different grading scale and including the esophagus and duodenum in their study, concluded that 133.3 mg (2 mL) of liquid Simethicone in 60 mL water 15-30 min prior to procedure could improve the visibility and reduce the number of flushings required for removing the mucus significantly. They also showed that using Simethicone prior to endoscopy would cut down the duration of the procedure and consequently lead to more satisfaction to both physician and patient. Similarly in our study, those patients in group B who received 100 mg activated Dimethicone in water showed better visualization compared to group A that received only simple water as placebo. The amount of water to be given with Simethicone had been a matter of debate. We used of a fixed volume of water in all our patient groups to remove the possible role thereof; however, in two clinical trials it was shown that there was no significant difference in visibility between those who received Simethicone alone or with 100 mL water^[9,17].

Pronase is a proteolytic enzyme commonly used in Japan as a premedication in combination with bicarbonate and Gascon (Simethicone)^[6]. Fujii *et al*^[10] came to the conclusion that the solution of 100 mL water, 20 000 units Pronase, 1 gm bicarbonate, and 80 mg DMPS was more effective than DMPS alone in improving visibility during conventional endoscopy and chromoendoscopy. They showed that this would decrease duration of endoscopy. Kou *et al*^[9] in a similar study proved that Pronase would

improve visualization much better than DMPS only when used in combination with bicarbonate and DMPS. They vividly concluded that Pronase without DMPS was of no use. Pronase is not routinely used in this country and was not the scope of the study.

NAC is a mucolytic and antioxidant agent acting via its free sulfhydryl group to lower the mucus viscosity^[21]. Nor significant interaction neither adverse reaction has been reported with oral preparations. In this study, those patients with a history of asthma and Diabetes Mellitus were excluded. This study is the only one in which the effect of NAC alone has been investigated and compared to Dimethicone and placebo. The patients in group C who received 600 mg NAC in 100 mL water did not show any betterment in visibility scores (8.41 ± 2.10 vs 9.50 ± 2.55 in group A). Combination of NAC and Dimethicone in group D demonstrated better visualization than simple water in group A. But this combination was not superior to Dimethicone alone in group B. We supposed that this was the effect of Dimethicone appearing in group D as in group B and NAC had no effect. In contrast to our results, Chang *et al.*^[17] concluded that the mixture of 400 mg NAC and 100 mg DMPS plus water up to 100 mL is more effective than DMPS alone or DMPS in water in a significant manner. They also recommended that NAC could be a substitute for Pronase where it was unavailable. In their study, the mean of the total visibility score in the patients who received NAC plus DMPS was 6.5 ± 2.2 (vs 5.39 ± 1.71 in this study) and in those receiving DMPS with water 7.6 ± 2.6 (vs 5.11 ± 1.28 in this study). The scoring system was exactly similar in the two studies though performed by different endoscopists. All these compounds were proved not to affect the result of rapid urease tests using Campylobacter-like organism tests^[9,17].

In conclusion, regarding the lower cost of Dimethicone (activated) (one third that of NAC per patient herein) and lack of Pronase, we suggest the routine use of 100 mg activated Dimethicone in water up to 100 mL twenty min prior to upper endoscopy here and all other areas where Pronase is not available. To clarify the exact benefits of NAC requires further trials.

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COMMENTS

Background

Upper endoscopy is a routine and widely-used procedure to evaluate upper gastrointestinal tract. Since foam and air bubbles can impair visibility, some anti-foam agents such as Simethicone and Pronase are used as premedications prior to endoscopy.

Research frontiers

Activated Dimethicone (Simethicone) has been shown to be effective in reducing

foam and bubbles in the stomach. N-acetylcysteine (NAC) is a mucolytic drug that is supposed to be efficacious too. This study aims to compare the efficacy of these agents in improving visibility.

Innovations and breakthroughs

Activated Dimethicone was shown to be effective. In contrast to prior findings our study showed that NAC was not able to improve visibility when used alone. Furthermore, combination of NAC and Dimethicone did not differ from Dimethicone alone in providing more clear visualization. This is the first study in which the efficacy of NAC was investigated independently as a premedication.

Applications

Usage of activated Dimethicone prior to upper endoscopy is of benefit for improving mucosal visibility; however, N-acetylcysteine seems not to be effective if used alone. Thus, activated Dimethicone should be considered as a premedication before upper endoscopy especially in areas where other agents are lacking.

Peer review

This is a nice study. It is well composed, balanced, documented and the English spelling is good.

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