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Premedication with simethicone and N-acetylcysteine for improving mucosal visibility during upper gastrointestinal endoscopy in a Western population

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ABSTRACT

Background and study aim Pre-endoscopic use of a preparation with tensioactive and mucolytic agents improved gastric mucosa visualization in Eastern studies. Data on Western population are scanty.

Patients and methods This prospective, endoscopist-blinded, randomized study enrolled patients who underwent esophagogastroduodenoscopy in a single center. Before endoscopy patients, were randomized to receive or not receive an oral preparation with simethicone and N-acetylcysteine in water. A pretested score (Crema Stomach Cleaning Score [CSCS]) for gastric mucosa cleaning evaluation was used. In detail, the stomach was divided into the antrum, body, and fundus and a score of 1 to 3 was assigned to each part (the higher the score, the better the preparation), and a total value ≤5 was considered as insufficient. Time between endoscope insertion and clean achievement (mouth to clean time) or the end of examination (mouth to mouth time) was recorded.

Results A total of 197 patients were enrolled. The mean overall CSCS value and mucosal cleaning in all parts was better in treated patients than in controls. Prevalence total score ≤5 was significantly lower in patients treated before endoscopy. Need for water flush occurred less frequently in treated patients ($P<0.0001$). The mouth to clean time was lower in the treated than in the control group (2.3 ± 1.6 vs 3.8 ± 1.6 min; $P<0.001$), whereas no significant difference in mouth to mouth time emerged.

Conclusions Data from this study show that premedication with simethicone and N-acetylcysteine results in significantly better endoscopic visualization of gastric mucosa, and the proposed CSCS could be useful for standardizing this evaluation.

Introduction

Gastric cancer is the fifth leading cause of cancer in the world and the third leading cause of cancer-related death, responsible for over 1 million new cases and 783,000 deaths, according to the latest report [1]. Albeit the incidence is falling in different countries, the number of newly diagnosed cases remains high and is predicted to continue growing, mainly due to aging of the population [2]. Moreover, gastric cancer incidence has increased in younger individuals (<50 years) in both low- and

high-incidence populations [2]. Considering that screening programs are cost-effective only in high-risk populations, identification and surveillance of gastric precancerous lesions at endoscopy and diagnosis of cancer in an early stage represent the only reasonable procedures for improving survival [3]. It is counterintuitive that a clean gastric mucosa is crucial for achieving such a purpose. However, bubbles, bile, debris, and mucus often compromise optimal endoscopic visualization, reducing the potential detection of superficial, minor elevations or depressions on the mucosal surface. While grading the visualization of mucosa at colonoscopy is an indicator of procedure quality [4], the vision obtained during upper endoscopy is neither routinely assessed nor clearly defined. However, recent UK guidelines endorsed the use of pre-endoscopic preparation to increase quality of upper gastrointestinal endoscopy in the Western world [5].

Some studies conducted on Eastern cohorts highlighted the useful role of tensioactive and mucolytic agents as preparation before upper endoscopy [6, 7]. Simethicone and N-acetylcysteine (NAC) are antifoaming and mucolytic agents, respectively, that act by decreasing surface tension, breaking the bonds between molecules and helping the clearance of foam and other gastric content. Oral premedication 10 to 30 minutes before endoscopy seems to be effective in reducing procedure time, obtaining superior mucosal visualization, and decreasing the amount of water used during endoscopy [8]. Only a few non-Asian experiences have been reported in the latest years with this technique, therefore, more data are needed to identify the real advantage of this procedure in Western countries [9, 10]. Therefore, we designed this prospective study with the aim of assessing the efficacy of premedication in improving gastric mucosa inspection by using a novel, specifically conceived scale.

Patients and methods

Patients

This was a prospective, endoscopist-blinded, randomized study performed in consecutive adult patients who underwent upper endoscopy at a single center, irrespective of indication. Patients with previous gastric surgery were excluded. In our center, upper endoscopy with use of a pre-endoscopic medication has been routine practice since May 2017, when it was initiated on the basis of experience reported mainly in Eastern centers, whereas no preparation was previously used according to the common practice in Western centers. Because no experimental drugs were administered, no adjunctive costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received, our Investigational Review Board waived formal review and approval, deeming the study to be adherent with existing clinical practice. The study was performed according to the guidelines for Good Clinical Practice and the Declaration of Helsinki (1996 version, amended October 2000). Each patient consented to anonymous use of their clinical data for scientific purposes.

Pre-endoscopic preparation

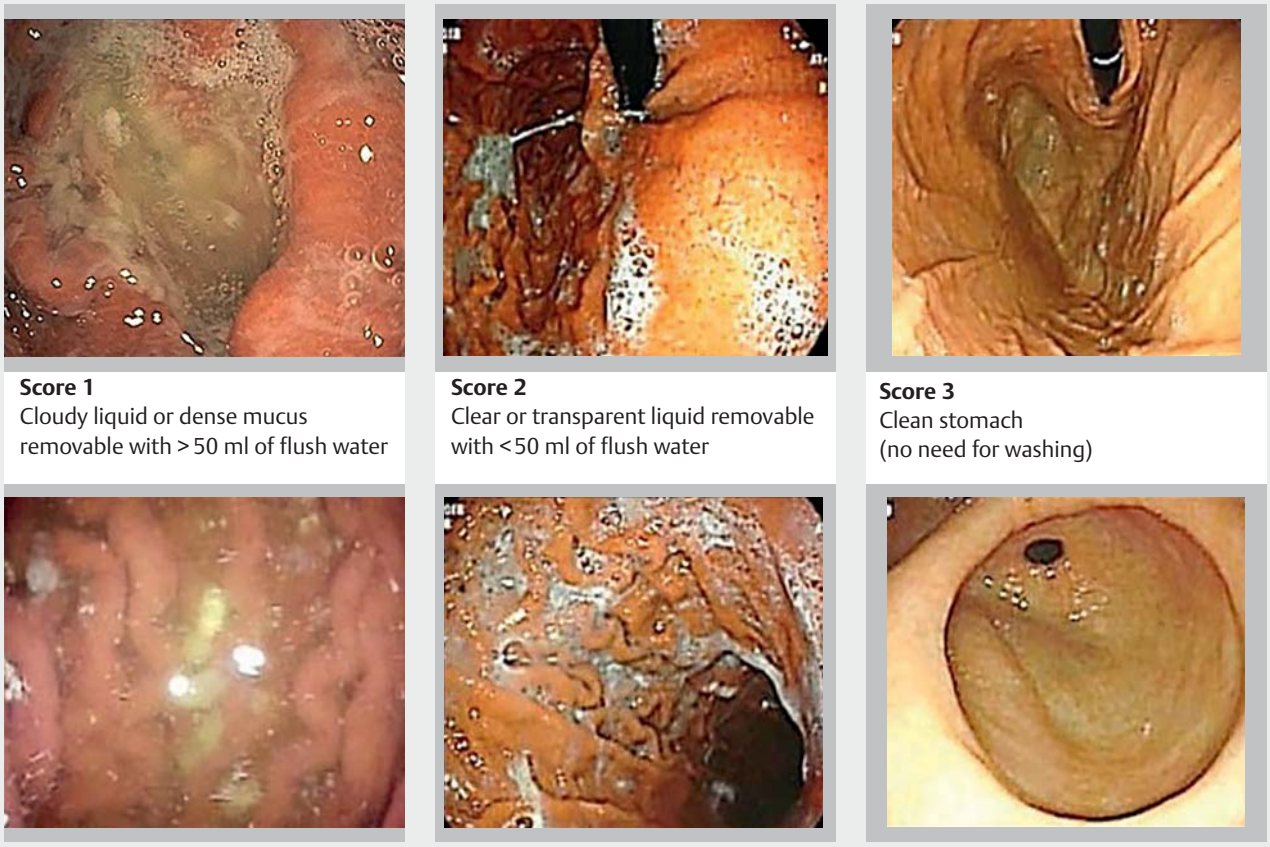
Before endoscopy, patients were randomly assigned to receive (treated group) or not (control group) a preparation, with allocation ratio 1:1. It was prepared with 2 mL simethicone (Mylicon, Johnson & Johnson SpA) and 600 mg NAC (Fluimucil, Zambon Italia) dissolved in 45 mL of warm water as prepared by a nurse. The solution was orally administered 20 minutes before endoscopy to patients, and the procedure of rollover was performed at the bedside during the waiting time. Controls underwent endoscopy without pre-endoscopic preparation.

Mucosal cleaning score

All endoscopic examinations were performed with white light imaging (WLI) by using the VP-7000 plus BL-7000 System ELUXEO videoendoscope with EG 760 R gastroscopes (FUJIFILM Corporation, Tokyo, Japan), under conscious sedation. Four skilled endoscopists (M.G., I.E., A.S., L.C.), performed gastroscopies blinded to the premedication, and graded gastric mucosa visualization by using a specific, previously arranged scale, which we named the Crema Stomach Cleaning Score (CSCS). In detail, the stomach was divided into the antrum, body, and fundus for cleaning evaluation, and a score of 1 to 3 score was assigned to each part, so that the total score ranged from 3 to 9 and a total value ≤ 5 was arbitrarily considered insufficient cleaning (▶ **Fig. 1**). To get good interobserver agreement before the study start, the four participating endoscopists examined a training set of 20 videos corresponding to different degrees of cleaning, and scores were discussed until agreement was reached. At the end of training, a different set of 20 videos was administered to the same endoscopists and the interobserver agreement was calculated using the Kappa statistic. This statistic measures agreement greater than chance and can range from – 1 to 1; a value of 0 indicates statistical independence and a value of 1 indicates perfect agreement among observers. We used the classification of the concordance based on the Kappa value proposed by Landis and Koch based on a 6-point score from a power of concordance poor, less than < 0, to the best concordance ranging from 0.8 to 1 [11]. The *k* statistics for interobserver agreement among the four endoscopists were excellent ($k = 0.91$). For each examination, time between the insertion of the endoscope and the achievement of a clean stomach (mouth to clean time) and the end of the examination (mouth to mouth time) were recorded. The amount of water needed to achieve optimal mucosal visualization was calculated as a surrogate indicator of cleaning. Any adverse event (AE) that occurred during endoscopy or recovery was registered.

Statistical analysis

Categorical variables are described as absolute frequency and percentage. Continuous variables with normal distribution are described as mean ± standard deviation (SD), whereas continuous variables without normal distribution are given as median and range. The Kolmogorov-Smirnov test was used to evaluate the distribution of the continuous variables. Data were not normally distributed and non-parametric tests were used. The



▶ **Fig. 1** Crema Stomach Cleaning Score (CSCS).

Mann-Whitney test was used for continuous variables, and the chi-square test was used for categorical variables. At the time we planned the present study, there were only three randomized studies [9, 10, 12]. Based on data from these studies, a 20 % difference between pre-endoscopic medication and controls was expected. Therefore, a sample size of 62 patients per arm was calculated with an α error of 0.05, β error of 0.2, and statistical power of 0.8. Taking into consideration that 10 % of the cases could have been excluded for any reason, we calculated that a total of 140 patients needed to be enrolled (70 patients per arm).

Results

A total of 200 consecutive outpatients were randomly assigned to receive treatment or not. Three patients in the treatment group were eventually excluded from statistics because of poor tolerance during endoscopic examination. Demographic and clinical characteristics of enrolled patients did not differ between groups (▶ **Table 1**). The mean overall *CSCS* score was significantly higher in treated patients than in controls (7.6 ± 1.5 vs 6 ± 0.7, $P < 0.001$). Similarly, mucosal cleaning was better in all parts of the stomach (fundus: 2.7± 0.6 vs 2.2 ± 0.7; body: 2.3 ± 0.8 vs 1.8 ± 0.7; antrum: 2.7 ± 0.6 vs 2.1 ± 0.8; all comparisons: $P < 0.001$) following pre-endoscopic preparation. As shown in ▶ **Table 2**, prevalence of a score of 1 in each gastric portion and a total score ≤ 5, indicating imperfect mucosal visualization was significantly higher in controls than in patients treated before endoscopy. Similarly, the need for water flush occurred more frequently in controls (86 out of 100) than in treated patients (47 out 97) (86 % *vs* 48 %; $P < 0.0001$), and the amount of water used during endoscopy was significantly higher (Mean: 128.1 ± 101.5 *vs* 43.7 ± 62.1 ml; $P < 0.001$) Finally, we observed a statistically significant ($P < 0.001$) difference in mouth to clean time between the treated group (2.3 ± 1.6 min) and the controls (3.8 ± 1.6 min), whereas no significant difference in mouth to mouth time emerged (9.4 ± 3.8 *vs* 9.8 ± 2.1 min; $P = 0.18$). No AEs were reported in either study group.

Discussion

Upper endoscopy represents the gold standard for diagnosis of gastric benign and malignant lesions [13]. Accurate detection of precancerous or early neoplastic lesions in the stomach is crucial for prognosis, representing the only way to reduce mortality in those populations where screening programs are not cost-effective [3]. Unfortunately, missing a diagnosis of gastric cancer has been reported [14], and it is due to different factors. Localization of the lesion (i.e. cardia region), sampling error, histopathological misinterpretation, poor-quality equipment,

▶ **Table 1** Demographic and clinical characteristics of the enrolled patients.

	Treated patients	Control patients
Number of patients	97	100
Age (mean ± SD)	59 ± 16	55 ± 19
Male (%)	51 (53)	48 (48)
Upper endoscopy indication (%)		
Gastroesophageal reflux symptoms	63 (63)	65 (65)
Dyspepsia	24 (25)	27 (27)
Peptic ulcer follow-up	4 (4)	2 (2)
Gastric cancer follow-up	3 (3)	2 (2)
Barrett's Esophagus follow-up	1 (1)	3 (3)
Vomiting	2 (2)	0
Upper gastrointestinal bleeding	1 (1)	1 (1)
Dysphagia	1 (1)	0
Upper endoscopy findings (%)		
Duodenal ulcer	2 (2)	1 (1)
Gastric ulcer	4 (4)	2 (2)
Gastroduodenal erosions	18 (18)	14 (14)
Gastric polyps > 1 cm	7 (7)	6 (6)
Cancer	0	0

No statistically significant difference emerged.

▶ **Table 2** Prevalence of insufficient preparation in either one section (score 1) or all sections (score ≤ 5) according to Crema Stomach Cleaning Score[1] evaluation.

	Treated patients	Control patients	*P* value
Score = 1	28 (29)	80 (80)	< 0.001
Fundus (%)	4 (4)	17 (17)	
Body (%)	18 (19)	38 (38)	
Antrum (%)	6 (6)	25 (25)	
Score ≤ 5	11 (11)	33 (33)	< 0.001

[1] See text for Crema Stomach Cleaning Score; N (%)

and unsatisfactory patient sedation are factors potentially involved [14, 15]. However, a larger percentage of missed diagnoses have been associated with poor endoscopic performance, namely error in detecting mucosal abnormality or lesions [15]. Regrettably, in several Western countries, the detection rate remains low not only for early gastric cancer, but also for T1 cancer [16]. Poor visualization of gastric mucosa might represent a modifiable source of missing lesions. Pre-endoscopic preparation was found to be useful in improving gastric mucosa visualization and helping endoscopists detect subtle or flat lesions [7, 17] and its use has been endorsed to increase the quality of upper endoscopy in the Western world [5]. However, experience with this practice is still limited in non-Asian countries, and only four Western studies were included in a recent meta-analysis [18]. Data from the present study showed that pre-endoscopic use of a 45-mL solution of simethicone and N-acetylcysteine significantly improves visualization of the gastric mucosa as compared to no gastric preparation. This difference was particularly evident for gastric body and antral mucosa visualization. Our results add information to the limited data available from non-Asian studies [18]. With use of the preparation, the number of procedures in which washing was required and the volume of flush used were significantly decreased, and a significant reduction was observed in mouth-to-clean time, but not mouth-to-mouth time. This may mean that a longer time was spent in observing gastric mucosa in prepared patients rather than in cleaning the stomach, with obvious advantages. Indeed, a direct correlation between timing in exploring mucosa and the rate of detection of lesions has been reported [19]. Moreover, better mucosal visibility offers more benefit in finding gastric mucosal lesions [18]. Therefore, our results confirm that endoscopists should pay greater attention to gastric preparation, which should represent a recognized quality indicator, as suggested [5].

Another relevant aspect of our study is the proposal of a specific cleaning score – the CSCS – for assessing gastric mucosa visualization. To our knowledge, no standard scale for mucosal cleaning assessment has yet been identified. In most previous studies, a four-point scale for each part of the stomach was proposed, with some difference in division of gastric areas [7, 20]. Unlike these scales, in which a higher score correlated with poor vision, we proposed the CSCS following the same principle as the Bowel Boston Preparation Score [4]. Our choice was motivated by the great familiarity of Western endoscopists with use of increasing scales in identifying the cleaning of the mucosa, and in using a three-point scale instead of a four-point scale. We believe that this scale can be easily applied in clinical practice and help endoscopists to assess mucosal visibility and standardize the comparison of different preparations in future studies.

The lack of difference in prevalence of macroscopic lesions detected in the two groups was expected. In fact, the present study aimed to evaluate gastric mucosal visibility with or without a preparation, therefore, it was methodologically designed and statistically powered for that purpose, similar to previous studies [9, 12]. A much larger sample size would have allowed detection of a significant difference, considering that in a multicenter Italian study of 1,054 consecutive patients, the prevalence of peptic ulcer was 1.6 % and of gastric cancer was only 0.28 % [21]. Therefore, specific and larger studies are needed to assess whether pre-endoscopic preparation can increase the diagnostic yield of upper endoscopy in Western countries.

Conclusion

In conclusion, data from this study suggest that premedication with simethicone and N-acetylcysteine facilitated significantly better endoscopic visualization of gastric mucosa and that the proposed CSCS may be useful for standardizing this evaluation.

Competing interests

The authors declare that they have no conflict of interest.

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