

Cohorts of premedication for endoscopy of the upper gastrointestinal tract with simethicone, N-acetylcysteine, *Hedera helix* and visual scale validation

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Abstract

Quality parameters for upper gastrointestinal endoscopy have introduced intraprocedural indicators, including adequate mucosal visualization free of saliva, mucus, or bubbles, which may increase the possibility of early-stage injury detection. The use of mucolytics and anti-foaming agents has shown great efficiency variability depending on the type of solution, concentrations, exposure times and visibility scale applied. **Objectives:** To determine the effectiveness of different premedication solutions for cleaning the digestive mucosa; to validate, by means of an interobserver concordance test, a new scale for the adequate visualization of the mucosa (TVMS) for the esophagus, stomach, and duodenum; and to report adverse events or complications associated with the solutions used and the procedures performed. **Material and methods:** Prospective, comparative cohort study. 412 adult patients, ASA I and ASA II, were included for diagnostic endoscopy under conscious sedation. They were distributed in 6 similar cohorts and divided into two groups: non-premedication, 2 in C1 (fasting 6 to 8 hours) and C2 (water 100 mL) cohorts; premedication, 4 C3 to C6 cohorts (C3: water 100 mL + simethicone 1000 mg; C4: water 100 ml + simethicone 200 mg + N-acetylcysteine 600 mg; C5: water 100 ml + simethicone 200 mg + N-acetylcysteine 1000 mg; C6: water 100 ml + simethicone 200 mg + *Hedera helix* 70 mg). The solution was swallowed 15 to 30 minutes passing through the cricopharyngeus muscle. The Kappa test was performed to measure interobserver concordance of the TVMS scale. **Results:** Of 412 patients, 58 % were female; 23 % (136) were included in the C1 and C2 cohorts; and 67 % (276) were in the C3 to C6 cohorts. The average exposure time to each solution was 24.4 minutes. The wash volume for proper visualization was significantly different between the two groups. In premedicated patients, 75.6 mL of solution were used, while in patients without premedication, 124 mL were used ($p = 0.000$), with an excellent quality of TVMS of 88.7% versus 41.4%, respectively. The C4 cohort (water 100 mL + simethicone 200 mg + N-acetylcysteine 600 mg) was the most effective with a significant difference ($p = 0.001$) compared with the C1 (fasting) and C2 (placebo with water 100 mL) cohorts. It also had better efficiency compared to the C3, C5 and C6 cohorts in that order. There were no adverse events or complications associated with endoscopy, sedation, or premedication products. **Conclusions:** The most effective solution as a premedication to achieve excellent visibility of the digestive mucosa was that used in the C4 cohort (SIM 200 + NAC 600 + H₂OR 100 mL). The proposed TVMS scale is a very complete and easy tool to apply by more than one observer. Premedication ingested, with anti-foam, mucolytic and water up to 100 mL, between 15 and 30 minutes before endoscopy, is safe under the conditions described in this study.

Keywords

Premedication, Simethicone, N-acetylcysteine, Esophagogastroduodenoscopy, TVMS, Interobserver agreement.

INTRODUCTION

Upper gastrointestinal endoscopy has pre-, intra- and post-procedure quality indicators (1-3). Therefore, during the procedure, it is essential to enhance visualization of the upper digestive mucosa, which is usually obstructed by saliva, mucus, bubbles and gastric fluid.

In 1964, Koga and Arakawa (4) conducted early gastric cancer studies using contrast enhancement during roentgenographic examination and eliminated visibility artifacts using pronase, a mucolytic enzyme used later by Ida *et al.* in 1991 for gastroscopy (5).

The effectiveness of pronase (a product difficult to obtain outside Japan, China, and Korea) has made premedication a standard practice for upper gastrointestinal endoscopy. To this end, products such as N-acetylcysteine (NAC), which is a widely accessible mucolytic, are used alone or combined with simethicone-dimethicone (SIM) (6-9) due to its anti-foaming properties (10). However, there is no clarity on the dosages and results of this method in the literature.

The variability of reports depends, in part, on how mucosa visualization is measured. Two meta-analyses (11,12) showed a great disparity in the applied visualization scales, namely the gastric total visibility scale (TVS used only for the mucosa of the stomach segments) (6, 13, 14) and the total mucosal visibility score (TMVS, which includes the esophagus or duodenum) (15). The quantitative expression of the scales is particularly difficult, resulting in confusion and hard-to-remember figures. For this reason, proposals have been made to convert those figures into items that can be used in qualitative scales that are easy to remember and use (excellent, adequate, inadequate) (7).

Premedication to improve the quality of visualization aims to detect early lesions in the esophagus, duodenum, and stomach. This is of great importance to our area in the search for early or incipient gastric cancer, considering that it is the seventh most common cancer worldwide. (16) In 2018, it had a global incidence of 1 033 701 cases, whereas in Colombia, it was the leading cause of death from cancer in men and the fourth in women (17). Early detection and intervention have increased survival rates in eastern countries by more than 90%, compared to approximately 10% to 20% for advanced stomach cancer at 5 years (18-20).

Liquid SIM was used for several years as the only premedication. Nevertheless, encouraging but inconsistent results obtained when combining SIM with NAC (including two recent Colombian publications) (21, 22) and reported in international research led to establish the objectives of the present study: to determine the best effectiveness of various premedication solutions, one of which included an unstudied mucolytic (*Hedera helix* [HH]); to validate a new scale adapted for visualization of esophagus,

stomach, and duodenum; and to report adverse events and complications related to endoscopy and conscious sedation solutions used.

MATERIALS AND METHODS

Patient selection

The study comprises 6 prospective, comparative cohorts treated in a secondary care outpatient center in Bogotá. It was conducted between May 1 and July 31, 2019, in patients aged 18 years or older, who were informed of the objective of the study and signed an informed consent form. The patients underwent diagnostic upper gastrointestinal endoscopy due to clinical suspicion of dyspepsia, gastroesophageal reflux disease, unstudied dysphagia, malignancy or gastric or esophageal cancer. Cases were classified as ASA 1 or 2, according to the American Society of Anesthesiology (ASA).

Exclusion criteria were tumor or non-tumor lesions generating impassable strictures or pyloric syndrome, therapeutic endoscopy, active or recent gastrointestinal bleeding, pregnancy, gastroparesis, and known allergic reactions to premedication or sedation drugs.

The protocol followed the dispositions of the Helsinki Declaration and was approved by the ethics committee of the unit, which stressed two aspects. First, after the final assessment of the premedication, all preparations that were not scored as excellent had to be taken to that level by mucosal clearance using a 0.1 % SIM water solution in the volume required to achieve excellent mucosal clearance; thus, all participants were under the same conditions regarding the possibility of detecting early or advanced lesions. Then, after reviewing the safety of a single, small dose of HH and the beneficial effects seen in the cleaning of the digestive mucosa in some uncontrolled patients who had ingested it for pulmonary symptoms, it was decided to approve cohort No. 6, which combines HH with SIM, with the result being proposed as an off-label recommendation.

Study design

The sample included 412 patients in 6 cohorts (Figure 1) (minimum sample size of 355 for a 97% confidence level and maximum permissible error of 5%, based on a population of 1 440 patients treated in the previous 2 years).

All patients were allocated using simple randomization (by a coordinating nurse) and had a minimum fasting time of 8 hours. The coordinating nurse supervised the intake of each solution 15 to 30 minutes before passing through the cricopharyngeal muscle. With the administration of local

oropharyngeal anesthesia, all procedures were performed under balanced propofol sedation (8 mg/kg) and remifentanyl (4 µg/kg) in ASA 1 and 2 patients. Allergic drug reactions, respiratory depression requiring positive pressure ventilation and pulmonary aspiration were considered major adverse events, according to the published institutional protocol (23).

Patients were divided into two groups: non-exposure (no premedication) and exposure (premedication). Two cohorts were allocated to the non-exposure group (C): C1: No solution (NS) and C2: Water (H₂O) 100 mL. Four cohorts were allocated to the exposure group (C): C3: 100 mL water + 1000 mg simethicone (H₂O + SIM 1000); C4: 100 mL water + 200 mg simethicone + 600 mg N-acetylcysteine (H₂O + SIM 200 + NAC 600); C5: 100 mL water + 200 mg simethicone + 1000 mg N-acetylcysteine (H₂O + SIM 200 + NAC 1000); and C6: 100 mL water + 200 mg simethicone (SIM) + 70 mg *Hedera helix* (HH) (H₂O + SIM 200 + HH 70), with similar numbers of patients in each cohort (Figure 1).

Mucosal visibility score

A mixed (qualitative and quantitative) total mucosal visibility scale (TVMS), modified based on the Elvas qualitative system (7), which derives from the McNally quantitative system, was adopted (24). Scores from 1 to 4 were established depending on mucosal cleanliness for 7 sites of the upper digestive tract (1 esophageal, 4 stomach and 2 duodenum), whose total amounts (between 7 and 28) were brought to three qualitative levels (excellent, adequate, and inadequate). Although there are certain similarities, there

is a clear difference with respect to other published scales (Table 1) (15, 25-30).

Mucosa was washed with water and simethicone at very low dilution (0.1%) only after completing the visualization of the 7 sites, although washing earlier could have modified the score considering the anatomical continuity of the segments and the three organs (Figure 2).

The value ranges were 1 to 4:

1. no mucus or bubbles;
2. with floating or non-adherent mucus or scanty, suctionable bubbles that do not obstruct vision;
3. with adherent mucus or abundant, non-suctionable bubbles that obstruct vision and require less than 50 mL of water to clear;
4. with adherent mucus or abundant, non-suctionable bubbles that obstruct vision and require more than 50 mL of water to clear.

Total scores ranged from 7 to 28 points, which were grouped into three qualitative groups: excellent preparation (7 to 14 points), adequate preparation (15 to 21 points) and inadequate preparation (22 to 28 points).

TVMS was assessed simultaneously by CB (endoscopist, with more than 120 000 endoscopies performed) and YW (nurse, with more than 32 000 endoscopies performed), in two equal, private, and independent forms that were handed over to the coordinating nurse immediately after completing the endoscopy. The required volume of lavage during the endoscopy was quantified. Considering the variability of the time required for biopsy and the assessment of high-risk or malignant lesions, it was decided not to include the total endoscopy time (31).

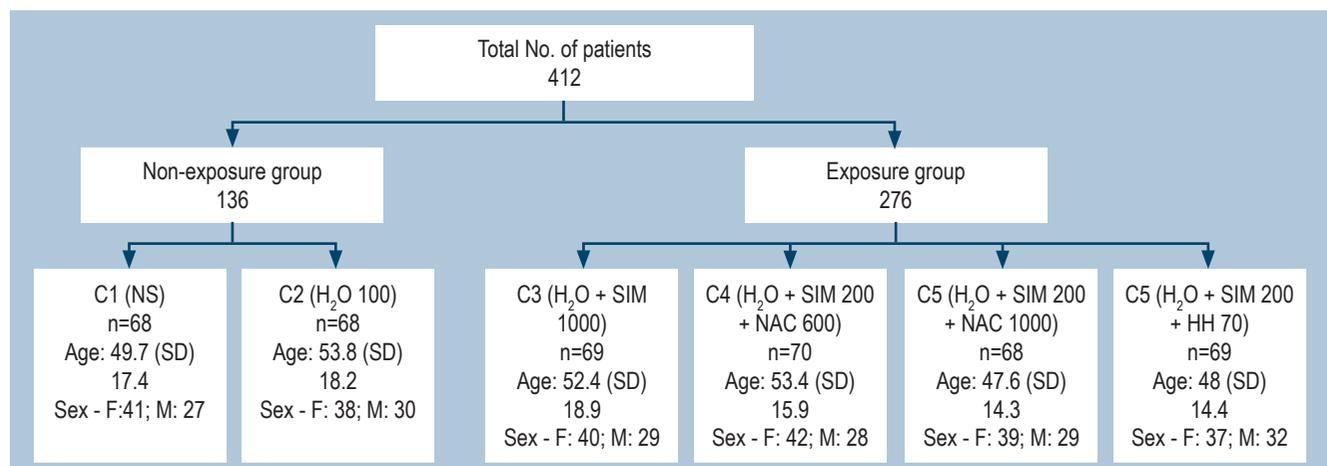


Figure 1. Sociodemographic characteristics of the 6 cohorts. SD: standard deviation; HH: *Hedera helix*; H₂O: water; NAC: N-acetylcysteine; NS: no solution; SIM: simethicone.

Table 1. Comparison between mucosal visibility scales (7)

| Scale and reference | Sites evaluated | Score | Score | Score |
|---|---|--|---|--|
| Quantitative and Qualitative Scale, Blanco et al. (Current study) | 7 sites: esophagus, 4 gastric sites (fundus, proximal body, distal body, and antrum), duodenal bulb, and D2. 4 scores per site: 1. No mucus or bubbles. | Excellent: 7 to 14 points. Completely clean mucosa or requires only aspiration. 2. With floating or non-adherent mucus or sparse, suctionable bubbles that do not obscure vision. | Adequate: 7 to 21 points. Washing with less than 50 mL is required at a maximum of 3 sites. 3. Adherent mucus or abundant, non-suctionable bubbles that obstruct vision and require less than 50 mL of water to clear. | Inadequate: 7 to 28 points. Washing with more than 50 mL is required at 3 or more sites. 4. Adherent mucus or abundant, non-suctionable bubbles that obstruct vision and require more than 50 mL of water to clean. |
| Elvas et al. (7) | 3 sites: esophagus, stomach and duodenum. | Excellent non-adherent mucus and clear vision of the mucosa (included in the use of aspiration). | Adequate adherent mucus that obstructs mucosal vision and requires washing with water. | Inadequate thick mucus or food residue not susceptible to aspiration. |
| Scale A: Bhandari et al.(25), Lee et al.(26), Chang et al.(15) | 7 sites: esophagus, 4 gastric sites (fundus, proximal body, distal body, and antrum), duodenal bulb, and D2. | Score 1: no adherent mucus and clear mucosal vision. | Score 2: thin coating of mucus, without obstructing vision. | Score 3: Score 3: adherent mucus obstructing vision. |
| Scale B: Bertoni et al. (27), McNally et al. (24) | 6 sites: esophagus, fundus, body, incisura, antrum, and duodenum (or jejunum if gastrojejunostomy has been performed). | Score 1 or 2: no or minimal foam and bubbles. | Score 3: moderate amount of foam or bubbles. | Score 4: abundant amount that darkens the mucosal surface (need for washing). |
| Scale C: Kuo et al. (28), ASL et al. (29), Chang et al. (30) | 4 gastric sites : fundus, proximal body, distal body and antrum. | Score 1 or 2: non-adherent mucus or small amount that does not obstruct vision. | Score 3: large amount of mucus with less than 50 mL of water for clearance. | Score 4: large amount of mucus with more than 50 mL of water for clearing. |

*Adapted from: Elvas L *et al.* Endoscopy. 2017;49(2):139-145.

Statistical analysis

A univariate analysis was performed and presented according to the nature of the variable. The Kruskal-Wallis test was used to evaluate hypothesis testing by exposure subgroups due to the lack of normality of the variables analyzed. An exploratory multivariate analysis was carried out to determine the effect of exposure on the digestive mucosa visibility scale through a simple linear regression model; age, sex, endoscopic flush volume, and premedication time were the predictive variables. Variables were significant in the model when the *p* value was <0.05 and the most parsimonious model was sought. In addition, both TVMS evaluators performed a concordance analysis using the Chi-square test of independence (χ^2) and a one-sample proportion hypothesis test for agreement greater than 70 % for the mucosal visibility scale; subsequently, the kappa index was estimated for the categorical variable (excellent, adequate, inadequate) (1). Data was processed in R software version 3.2.0.

RESULTS

A total of 412 patients with a mean age of 51 years were included (SD: 17), of whom 58 % (n = 237) were female. 23% (n = 136) were allocated to the non-exposure cohorts 1 and 2 (non-premedication), while 67% (n = 276) were assigned to the exposure cohorts 3 to 6 (premedication). The mean exposure time (period between solution intake and cryoparyngeal passage) was 24.3 minutes (SD: 4.4). In these distributions, there were no significant differences in *p* value. In turn, the endoscopic flush volume required to achieve excellent visibility shows a significant difference in premedication cohorts (mean 75.6 mL; SD: 51.5) versus non-premedication (mean 124.9 mL; SD: 76.5) (*p*=0.000) (Table 2).

In turn, in both non-premedication cohorts (C1 and C2), the mean endoscopic flush volume was between 123 and 126 mL for 82% to 87% of patients in each cohort (95% confidence interval [CI]). In contrast, in premedication patients (C3, C4, C5 and C6), the mean was between 59 and 84 mL for 32 % and 43 %, respectively (95 % CI),

while the group C4 (H₂O + SIM 200 + NAC 600) required the lowest volume (**Figure 3**).

When performing the cohort-to-cohort comparison, significant differences were found between C1 (NS) and the premedication cohorts C4 and C5, showing that, with the use of these two solutions, mucosal visibility is better when less additional water volume is required (**Table 3**).

When converting the quantitative score of the TVMS to qualitative classification, including all cohorts, an excellent

visibility percentage was obtained in 72 %, adequate in 26 % and inadequate in 2 %, for all patients. This result made it necessary to rule out inadequate visibility for subsequent analysis, as its minimum expected count was 33.67 patients (according to Pearson's χ^2 tests) (**Table 4**).

Having said this, it is evident that for premedication cohorts (C3 to C6), 88.7% excellent visibility was achieved compared to 41.4% of the two non-premedication cohorts (**Table 5**).

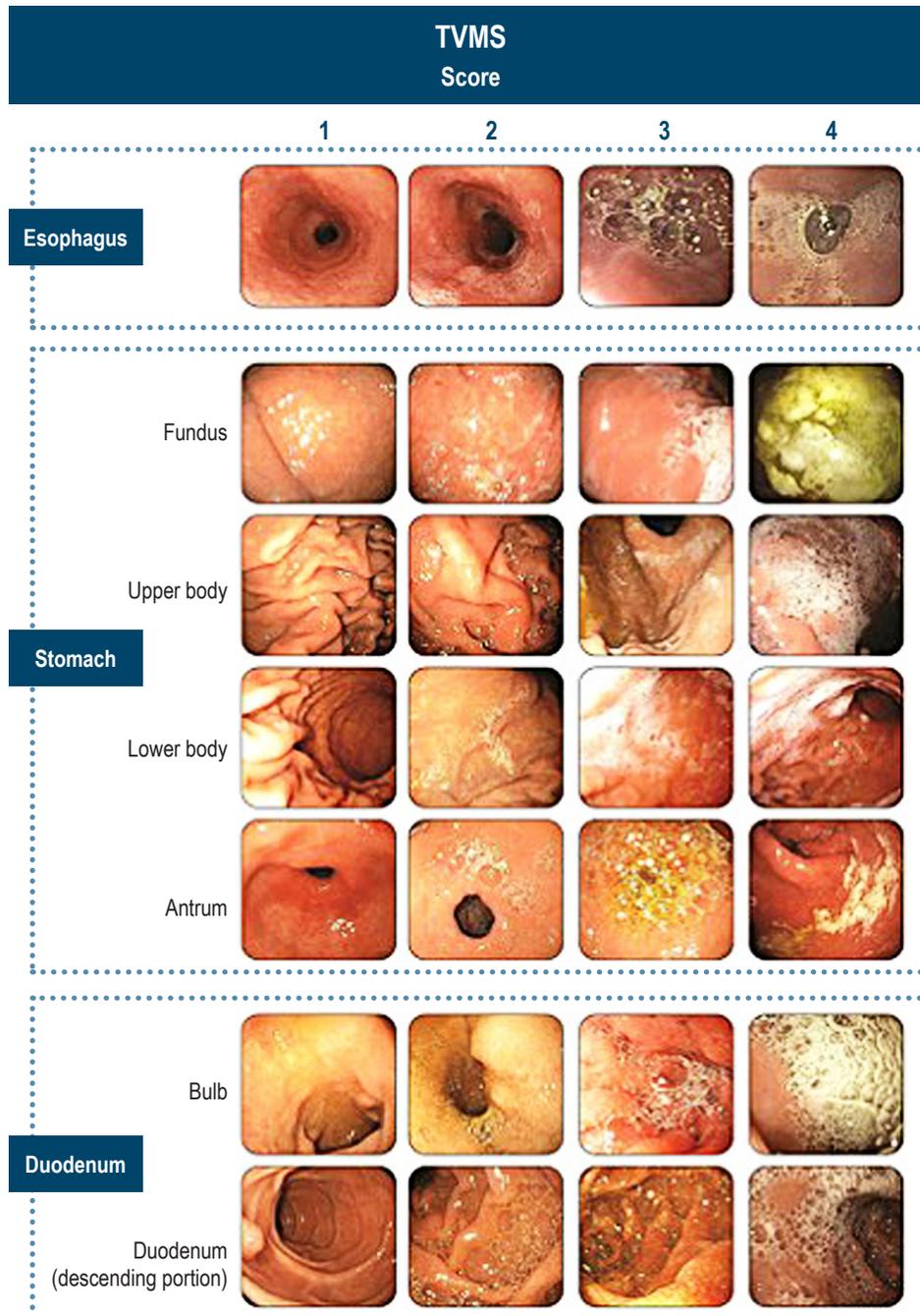


Figure 2. Total Visibility of the Upper Digestive Mucosa Scale (TVMS).

Table 2. Sociodemographic characteristics of the study population

| Characteristics | Premedication | | p value |
|---|------------------------|--------------------------|---------|
| | No (n = 136) (23%) | Yes (n = 276) (67%) | |
| Sex (female, male) | 79 (33.3) 57 (32.6) | 158 (66.7) 118 (67.4) | 0.871 |
| Average age (SD) | 52.1 (17.9) | 50.2 (16.1) | 0.304 |
| Total premedication time (n = 345) mean (SD) min. | 24.4 (4.3) | 24.2 (4.4) | 0.683 |
| Endoscopic flush volume (n = 215) Mean (SD) | 124.9 (76.5) | 75.6 (51.5) | 0.000 |

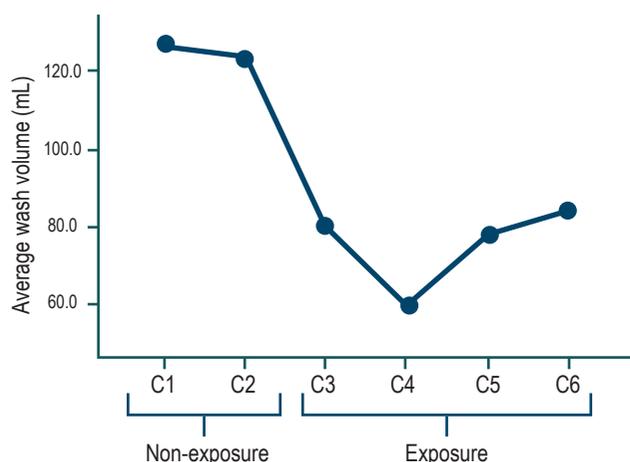


Figure 3. Association between premedication and intra-procedure endoscopic flush (mL of water with 0.1% simethicone).

In turn, when comparing the qualitative quality of visibility cohort by cohort, cohort C4 (H₂O + SIM 200 + NAC 600) was found to be associated with the best visibility (excellent in 92.9%). The second-best cohort was C3 (H₂O+SIM 1000; 89.9 %), followed by C5 (H₂O + SIM 200 + NAC 1000; 88.1 %) and C6 (H₂O 100 mL + SIM 200 mg + HH 70 mg; with 84.1 %). The latter is less efficient than the other solutions but twice as effective as when no premedication is administered (C1) or when only water is used (C2) (Table 6).

The χ^2 test was applied to the scores given by the two TVMS evaluators, obtaining insufficient evidence to think that the results are independent. This was corroborated with the proportions hypothesis test, in which a value of $p=0.0000$ was obtained, allowing us to reject the null

Table 3. Multiple comparisons between premedications and endoscopic flush volume

| Cohort (I) | Cohort (J) | Mean differences (I-J) | P value | 95%CI |
|--|---|------------------------|---------|-------------------|
| C1 (NS) | C2 | 2.70 | 1.000 | -32.917: 38.317 |
| | C3 | 45.95 | 0.066 | -1.737: 93.643 |
| | C4 | 66.35 | 0.001* | 20.793: 111.910 |
| | C5 | 48.44 | 0.039* | 1.516: 95.374 |
| | C6 | 42.84 | 0.050* | .029: 85.647 |
| | C2 (H ₂ O) | C1 | -2.70 | 1.000 |
| C3 | | 43.25 | 0.104 | -4.783: 91.289 |
| C4 | | 63.65 | 0.001* | 17.731: 109.572 |
| C5 | | 45.74 | 0.064 | -1.535: 93.026 |
| C6 | | 40.14 | 0.085 | -3.056: 83.332 |
| C3 (H ₂ O+SIM 1000) | | C1 | -45.95 | 0.066 |
| | C2 | -43.25 | 0.104 | -91.289: 4.783 |
| | C4 | 20.40 | 0.900 | -35.409: 76.206 |
| | C5 | 2.49 | 1.000 | -54.440: 59.424 |
| | C6 | -3.11 | 1.000 | -56.702: 50.471 |
| | C4 (H ₂ O + SIM 200 + NAC 600) | C1 | -66.35 | 0.001* |
| C2 | | -63.65 | 0.001* | -109.572: -17.731 |
| C3 | | -20.40 | 0.900 | -76.206: 35.409 |
| C5 | | -17.91 | 0.937 | -73.065: 37.252 |
| C6 | | -23.51 | 0.780 | -75.212: 28.185 |
| C5 (H ₂ O + SIM 200 + NAC 1000) | | C1 | -48.44 | 0.039* |
| | C2 | -45.74 | 0.064 | -93.026: 1.535 |
| | C3 | -2.49 | 1.000 | -59.424: 54.440 |
| | C4 | 17.91 | 0.937 | -37.252: 73.065 |
| | C6 | -5.61 | 1.000 | -58.517: 47.303 |
| | C6 (H ₂ O + SIM 200 + HH 70) | C1 | -42.84 | 0.050 |
| C2 | | -40.14 | 0.085 | -83.332: 3.056 |
| C3 | | 3.11 | 1.000 | -50.471: 56.702 |
| C4 | | 23.51 | 0.780 | -28.185: 75.212 |
| C5 | | 5.61 | 1.000 | -47.303: 58.517 |

*Tukey's HSD test. The difference in means is significant at the 0.05 level. HSD: honestly-significant-difference.

hypothesis that was posed as less than 70%. The analysis for the categorical variable showed a 98 % agreement with a kappa index of 0.8952, indicating a very good interobserver agreement (Table 7 and Figure 4).

Regarding the safety of the study, there were no adverse events in any of the 412 patients in relation to intolerance, hypersensitivity, bronchospasm, angioedema, exanthema, pruritus, hypotension, nausea, vomiting, diarrhea, or allergies associated with the use of SIM, NAC, and HH. There were also no allergic reactions, phlebitis or respiratory depression with propofol and remifentanyl during sedation. It should be noted that no cases of bronchoaspiration

Table 4. TVMS quality distribution (Overall TVMS)

| Qualitative visibility distribution | n = 412 (%) |
|-------------------------------------|-------------|
| Excellent (7 to 14) | 297 (72.1) |
| Adequate (15 to 21) | 106 (25.7) |
| Inadequate (22 to 28) | 9 (2.2) |

Table 5. Distribution of premedication and non-premedication cohorts vs. mucosal visibility quality according to TVMS

| Cohorts | TVMS visibility quality | | Total (%) |
|--------------------------------|-------------------------|---------------------|-----------|
| | Excellent (7 to 14) | Adequate (15 to 21) | |
| | n (%) | n (%) | |
| Premedication (C3, C4, C5, C6) | 244 (88.7) | 31 (11.3) | 275 (100) |
| No premedication (C1, C2) | 53 (41.4) | 75 (58.6) | 128 (100) |
| Total | 297 (73.7) | 106 (26.3) | 403 (100) |

Table 6. Cross-table cohort distribution (C1, C2, C3, C4, C5, C6) vs. excellent and adequate TVMS visibility quality

| Cohorts | TVMS visibility quality | | Total n (%) |
|--|-------------------------|---------------------|-------------|
| | Excellent (7 to 14) | Adequate (15 to 21) | |
| | n (%) | n (%) | |
| C1 (NS) | 25 (40.3) | 37 (59.7) | 62 (100.0) |
| C2 (H ₂ O) | 28 (42.4) | 38 (57.6) | 66 (100.0) |
| C3 (H ₂ O+SIM 1000) | 62 (89.9) | 7 (10.1) | 69 (100.0) |
| C4 (H ₂ O + SIM 200 + NAC 600) | 65 (92.9) | 5 (7.1) | 70 (100.0) |
| C5 (H ₂ O + SIM 200 + NAC 1000) | 59 (88.1) | 8 (11.9) | 67 (100.0) |
| C6 (H ₂ O + SIM 200 + HH 70) | 58 (84.1) | 11 (15.9) | 69 (100.0) |
| Total | 297 (73.7) | 106 (26.3) | 403 (100.0) |

Table 7. Interobserver agreement on the visibility score with the proposed TVMS

| Quality rating with TVMS | Interobserver agreement (evaluators) | | Total n |
|--------------------------|--------------------------------------|--------|---------|
| | Yes | No | |
| | n (%) | n (%) | |
| Excellent (7 to 14) | 289 (98) | 7 (2) | 296 |
| Adequate (15 to 21) | 97 (94) | 6 (6) | 103 |
| Inadequate (22 to 28) | 8 (62) | 5 (38) | 13 |
| Total | 394 | 18 | 412 |

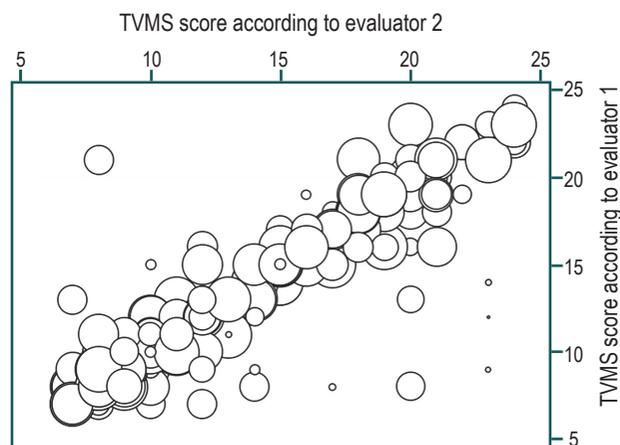


Figure 4. Bubble plot of interobserver agreement in visibility scores with TVMS.

during conscious sedation were reported, considering that in 5 of the 6 cohorts, patients ingested 100 mL of fluid between 15 to 30 minutes prior to the start of endoscopy (mean 24.2 minutes).

DISCUSSION

This comparative cohort study confirmed that the highest score for excellent visualization of the upper gastrointestinal mucosa was associated with the use of premedication with 600mg NAC + 200mg SIM + 100mL water, ingested between 15 and 30 minutes prior to cricopharyngeal passage with the endoscope. Premedication with SIM with or without NAC has been extensively studied in meta-analyses and systematic reviews. Lee, Du, and Fu (12) conducted a study in 5 750 patients and the combination of SIM and NAC showed better TVMS compared to SIM alone. Both SIM + NAC and SIM alone were more efficient than water alone (mean differences [MD] = -0.14 [-0.25, -0.03]; $p=0.01$), with no adverse events (using SIM or dimethicone at doses of 40 to 200 mg and NAC between 200mg and up to 1000mg, compared to control groups with water between 5mL and 100mL). All reported TVMS, except for one that presented a qualitative scale with scores of excellent, adequate and inadequate (6).

In another meta-analysis, Sajid *et al.* (11) included 654 patients with or without SIM +/- NAC and found an association of improvement (*odds ratio* [OR]: 0.43; 95% CI [0.28: 0.68] $z=3.65$; $p=0.003$) in mucosal visibility when premedication was used. Another group of 364 patients was analyzed and it was found that the use of SIM +/- NAC was associated with an improvement in mucosal visibility score compared with the group in which SIM was not used (standardized mean difference [SMD]: -1.66; 95%CI:

-1.93, -1.40; $z=12.12$; $p=0.00001$). Although the quality of visualization according to the TVMS was higher in the 4 cohorts of solutions used versus fasting or water use (88.7 % vs 41.4 %), the best premedication was used in cohort C4 ($H_2O + SIM 200 + NAC 600$), with an endoscopic flush volume of 59.9 mL. These values are lower than and significantly different from non-premedication cohorts C1 and C2 ($p > 0.001$), with a yield of 92.9%, which is higher than values in groups C3 (89.9%), C5 (88.1%) and C6 (84.1%), but with no significant difference between them.

Our previous experience, applied in cohort C3 ($H_2O + SIM 1000$), showed the second-best efficiency, with excellent visibility in 89.9 %, comparable to the reports by Bertoni (27) and Chang (30). This contrasts with another publication in which liquid simethicone was used at low doses and volume [1mL liquid simethicone (100mg) in 5mL of water, administered 30 minutes before endoscopy], in which the authors reported excellent visualization in 51.9% (9), a figure only slightly higher than that found in the present study with fasting or water alone, which is why this scheme is not recommended.

The result of cohort C5 ($H_2O + SIM 200 + NAC 1000$), which had the third best performance, showed that the NAC + SIM combination was not dose-dependent on increased NAC and that, therefore, its concentration of 600mg is sufficient and even better than using 1000mg for excellent visualization. Cohort C6 ($H_2O + SIM 200 + HH 70$), with *Hedera helix* at a low single dose of 70mg (used off-label as an alternative to NAC) achieved a percentage of excellence of 84.1%, higher than non-premedication in C1 (40.3%) and C2 (42.4 %), although its mean flush volume (83.4mL) did not show a significant difference compared to them. It thus leaves the window open for future tests of its efficiency, at other concentrations and in a controlled study, since it may be a safe and cost-effective alternative.

Upper GI endoscopy performed with six- to eight-hour fasting only had adequate visibility quality in 25.7%, i.e., 1 out of 4 patients will require washing in at least 3 sites of their upper digestive tract (with an average volume of 125 mL). In Chile, under the same conditions, an average of 52mL of water (range 0 to 400 mL) were required, evaluating only 4 sites, all in the stomach (14). The use of only water as premedication (cohort C2 [$H_2O 100 mL$]) showed no significant difference compared to fasting, with a slightly lower clearance volume than fasting (mean 123mL vs. 126mL). That study did not confirm that the use of 100mL of water worsened TVMS either (6), implying that water spread the mucus over a larger area of the stomach, without diluting mucus or bubbles.

Regarding the second objective of the study, it was possible to provide a new adapted and improved TVMS by taking into account 7 evaluation sites (1 in the esophagus, 4 in the

stomach, 1 in the duodenal bulb and 1 in the second portion of the duodenum), extending the idea of the need for excellent visibility beyond the stomach, which would allow the detection of lesions other than incipient gastric cancer in the early phase. Quantitative to qualitative TVMS conversion was performed in a simple way: each of the 7 sites was assigned scores from 1 to 4, for a total of between 7 and 28; scores of 1 and 2 mean that there was no bubble, saliva, or mucus residue (1) or that, at most, these residues were suctionable (2). The score range for excellent visibility was then between 7 and 14, a condition that only required suctioning or a minimal amount of irrigation (less than 50mL). For adequate visibility, the range was established between 15 and up to 21 points, a condition in which bubbles, mucus, or saliva were not completely suctionable and required cleaning irrigation (in a volume less than 50mL, changing the score from 2 to 3) at more than 4 sites and up to 7 sites. Inadequate visibility was considered when the range was between 22 (6 sites required volume less than 50mL and 1 site required more than 50mL) and 28 (7 sites with endoscopic flushes greater than 50mL); these scores led to recommend the interruption of the procedure and rescheduling it.

Once the scale was understood, its applicability and validity were confirmed by the interobserver agreement result, according to the TVMS, with an agreement of 98% when visibility was excellent and 94% when visibility was adequate. The mixed scale (qualitative and quantitative) aimed to facilitate the comparison of the effect of the solutions used as premedication. Its construction included concepts published by various authors: from Chang *et al.* (30), an endoscopic flush volume of more or less than 50mL; from Lee *et al.* (26), the 7 washing sites, including the esophagus and duodenum; from the classic scales of Kuo *et al.* (28) and Asl *et al.* (29), scoring grades from 1 to 4, only for the 4 sites of the stomach (which differs from our scale in that they used a volume of more or less 30mL); and from the scale of Elvas *et al.* (7), the three qualitative grades. It was also a useful tool to meet the recent requirement to report mucosal visualization as an intraprocedural quality parameter (3).

Concerning the third objective, there were no adverse events or complications associated with the endoscopy procedure, nor with the three products used (SIM, NAC, and HH) in the premedication solutions of cohorts C2 to C6. There were also no allergies or respiratory depression with propofol and remifentanyl in any of the patients. Regarding sedation, and in agreement with the studies by Koeppe *et al.* (32) and Da Silva *et al.* (33), who reported water intake of 200mL to 410mL up to 1 hour prior to endoscopy with only a subjective observation of more free liquid in the stomach, our study did not find any case of pulmonary aspiration. Thus, the results showed that premedication using volume, dilutions, times, physiological conditions, and

under the conscious sedation scheme, as published in 2017 (23), is a safe and beneficial practice.

One of the limitations of the study is the involvement of a single gastroenterologist, a situation that could not be solved given the conditions of the institution. However, this could be compensated with pre-study training and knowledge of both the TVMS scale and premedication solutions with 100 patients and the participation of the entire team, including the co-evaluation nurse. To conclude, the low concentration of SIM used in the cleaning fluid agrees with publications describing the presence of SIM residues inside the endoscope, despite high-level reprocessing, which could promote bacterial growth (34, 35).

The study adhered to the Position statement of the Gastroenterological Society of Australia (2019), in which “given the evidence of improved quality of endoscopic imaging and polyp detection, without evidence of clinical adverse events over decades of use, we believe that continued use of simethicone is appropriate, and it can be administered through any endoscope channel.” Therefore, its recommendations are as follows: the use of SIM is reasonable since it improves the visibility of the gastric and colonic mucosa and facilitates the detection of adenomas during colonoscopy (level of evidence IA, grade of recommendation A); the smallest effective amount of simethicone should be used for the lavage fluid, that is, 2 to 3 mL of 120 mg/mL added to one liter of sterile water (level of evidence IV, grade of recommendation D); SIM can be administered orally or through any irrigation channel (level of evidence IV, grade of recommendation D); and strict adherence to endoscope reprocessing protocols is essential, especially immediate precleaning decontamination in patient-care areas, including postprocedural irrigation and prompt initiation of manual or mechanical cleaning (level of evidence IIB, grade of recommendation B) (36).

CONCLUSIONS

Using premedication with SIM alone or mixed with mucolytics such as NAC or HH (the latter, an off-label recommendation) allows better visibility rates than performing a fasting or water-only digestive endoscopy. Of the 4 solutions studied, the one with the best results was SIM 200 mg + NAC 600 mg + water 100 ml, achieving excellent visibility quality of 92.9 %; however, the other 3 solutions also have excellent results above 84.1 %. The proposed TVMS scale, which includes 7 sites with 4 scores and converted to 3 qualitative scores (excellent, adequate, and inadequate) is an easy-to-apply tool that is more complete than previously published scales. The premedication scheme including up to 100 mL, ingested between 15 and 30 minutes before endoscopy, is a safe exposure in ASA I and II adult patients who undergo the procedure under conscious sedation. The use of the mucolytic *Hedera helix* is a different and less expensive alternative, although less efficient than NAC.

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