Original Article

Visualization of mucosa by gastroscopy evaluation using pre-preparation procedure with simethicone

[Visualización de la mucosa por evaluación gastroscópica usando un procedimiento de pre-preparación con simeticona]

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Abstract

Context: A solution of simethicone administrated orally before the scan endoscopy procedure is recommended as a good means to reduce the bubbles interference.

Aims: To evaluate the reliability, reproducibility and effectiveness of simethicone pre-treatment before endoscopic exploration of patients not diagnosed with malignant digestive pathologies.

Methods: The study was organized in two stages. Time zero was a retrospective reanalysis of data from 58 randomized patients (age 15-90 years) who had been evaluated by endoscopy without simethicone (Control group), and 66 patients (Simethicone group) who were recruited and received 62 mL of a simethicone pre-preparation drink, 30 min before examination. The second stage, using procedure with simethicone, was continued and after 6 months at the beginning, 88 subjects were randomized. Stability in the results was demonstrated with simethicone. Statistical analysis was performed using SPSS v.21.

Results: Analysis of comorbidities were represented with the highest prevalence being high blood pressure, diabetes mellitus, long-term depression, obesity and hypothyroidism. Results demonstrated similarity among endoscopist and between analysts within the same group (examination time, images resolved and with the best quality, by mucosal areas). However, these variables were different between groups, such that valuation quality was improved with simethicone, even 6 months after the initial evaluation.

Conclusions: Use of simethicone as a pre-preparation drink 30 min before the endoscopy evaluation improves the quality of images and reduces the time of operation.

Keywords: endoscopy; gastrointestinal; gastroscopy; simethicone; surfactant.

Resumen

Contexto: La solución de simeticona es recomendada administrarla por vía oral, antes del procedimiento exploratorio endoscópico, como una buena alternativa para reducir las interferencias de las burbujas.

Objetivos: Evaluar la confiabilidad, reproducibilidad y efectividad de la simeticona como pre-tratamiento antes de la evaluación endoscópica en pacientes no diagnosticados por patologías digestivas malignas.

Métodos: El estudio se organizó en dos etapas. Tiempo cero fue un análisis retrospectivo de los datos de 58 pacientes seleccionados aleatoriamente (15-90 años) quienes habían sido evaluados mediante el procedimiento de endoscopia sin simeticona (grupo Control) y 66 pacientes (grupo Simeticona) fueron reclutados y recibieron 62 mL de solución de simeticona, 30 min previos a la exploración. En la segunda etapa, la aplicación de simeticona se extendió y después de 6 meses del inicio, se seleccionaron 88 sujetos. La estabilidad en los resultados se demostró con simeticona. El análisis estadístico se realizó por SPSS v.21.

Resultados: El análisis de comorbilidad demostró una mayor prevalencia en hipertensión arterial, diabetes mellitus, depresión a largo plazo, obesidad e hipotiroidismo. Los resultados demostraron similitud entre endoscopistas y entre analistas, dentro del mismo grupo (tiempo de exploración, imágenes resueltas y con la mejor calidad, por áreas de mucosa). Estas variables fueron diferentes entre los grupos, de modo que la calidad de la valoración mejoró con simeticona, incluso, 6 meses después del inicio de la evaluación.

Conclusiones: Es posible el uso de simeticona como tratamiento previo a la exploración; mejorando la calidad de las imágenes y reduciendo el tiempo de operación.

Palabras Clave: endoscopia; gastrointestinal; gastroscopia; simeticona; surfactante.

INTRODUCTION

Endoscopic procedure is an essential contribution for detecting gastric cancer at initial states (Fernández-Urien et al., 2017). Cancer in Spain remains one of the causes with the highest incidence, prevalence and mortality. In 2018, it had become the leading cause of mortality in men and the second cause in women (27%) and one of the factors causing the greatest disability in patients. Although the incidence in different types of cancer such as colorectal, breast, and lung is the most significant; it would be convenient to pay attention to the incidence of stomach cancer, among others that are not within the preventive diagnostic system (Díaz-Rubio, 2019).

Continuous lavage of luminal bubbles with water does not consistently result in improved mucosal assessment and can result in increased bubble formation. Simethicone is commonly used as a defoaming agent during endoscopic procedures because improves mucosal visibility; but concerns regarding simethicone use during gastrointestinal endoscopy have been circulating for several years. Following reports of simethicone residue in endoscope channels despite high level disinfection, an endoscope manufacturer recommended that it not be used due to concerns of biofilm formation and a possible increased risk of microorganism transmission. However, a detailed mucosal assessment is essential in performing high-standard endoscopic procedures. The British Society of Gastroenterology advised in 2017 that the concentration of simethicone should be kept to a minimum and that it be administered orally or via the biopsy port and not via the water bottle or flushing pump (Devereaux et al., 2019).

Visualization of the gastric mucosa can be interfered by bubbles, even though patients are fasting for 6 h, prior to gastroscopy examination. Some clinical studies propose the prior preparation of the subject supplying a solution with simethicone (50 mL water, 1000 mg N-acetylcysteine, 60 mg simethicone) 5-10 min before (Basford et al., 2016) or 20 min before (10 mL 4% N-acetylcysteine and 2 mL with 133.3 mg simethicone) (Royero, 2018) to reduce these troubles without the usual intervention of mucosal washing, during the scan.

Prior use of simethicone as pre-preparation drink for a best scan is not extended in the Spanish health system.

The present work reports a randomized controlled study to evaluate the degree of visualization of the mucosa and image capture, during the pre-endoscopy preparation with simethicone (Aero-red), compared to the usual protocol.

MATERIAL AND METHODS

Subjects and methods

Subjects were informed about the objective, procedure and they were included by consent. Criteria for the selection of subjects were according to the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects and the indications for examination: iron deficiency anaemia, family history of gastric cancer, ulcer background check, dysphagia, dyspepsia, abdominal pain, epigastralgia, rectal bleeding, gastroesophageal reflux (GER), toxic syndrome, vomiting, nausea and epilepsy were included. Pregnant women were excluded from the study. The project design and all documents were proved by Dr. Reyes Moreno, head of Digestive Diseases Service of Inca Hospital, Balearic Islands (president of Spain Asociation Against Cancer in Balearic Islands, Spain).

In the first phase of the study (Time zero), 124 subjects (15-90 years) undiagnosed from malignant digestive pathologies were selected at random for either examination: a group without a previous preparation (Control group, n = 58); and a second group who received previous preparation with simethicone (2 mL of oral drops Aero-red 100 mg/mL in 60 mL of water), 30 min before the procedure (Simethicone group, n = 66) (Fig. 1).

The endoscopist was blinded to the preparation used and the excess fluid in the stomach was removed via the endoscope suction channel. A total of 126 determinations were made, and digital images were analysed. The quality of the images was assessed according to the scale: from 1 (best) to 4 (worst), for 4 localization zones: distal esophagogastric junction (DEPGU), gastric proximal body (GPB), antrum (A) and duodenum (D). The score was similar to the valuation proposed by Ahsan et al. (2011) (Fig. 1):

1. No air bubbles.

2. There are a small number of bubbles that do not interfere in the evaluation.

3. There are a considerable amount of air bubbles and foam, must be cleaned for evaluation.

The evaluation of the mucosa is not reliable and requires of abundant cleaning due to the presence foam or air bubbles.
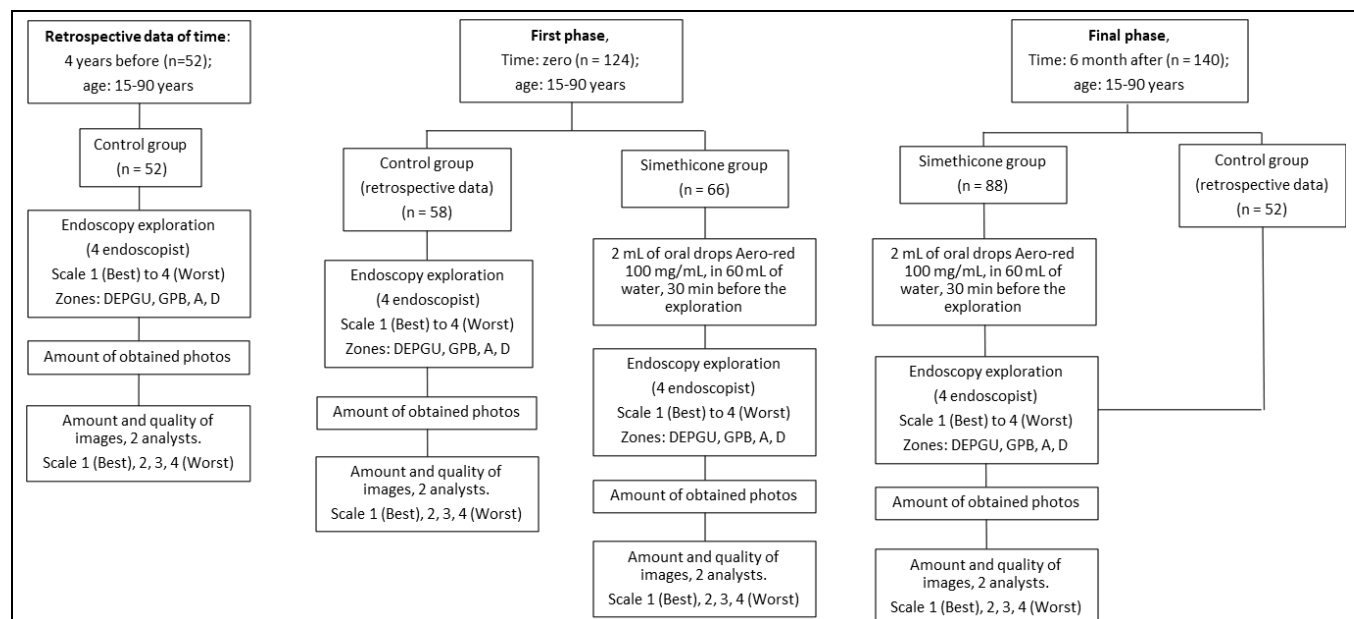
Figure 1. Flowchart of the study.

Scale: from 1 (best) to 4 (worst), for 4 localizations. Zones: distal esophagogastric junction (DEPGU), gastric proximal body (GPB), antrum (A) and duodenum (D).

Statistical analysis

The process was carried out by four gastroscopists (two of them as evaluators of digital images). The evaluators were blinded to the origin of digital images. Results were statistically analysed by SPSS v.21. A two-tailed p-value less than 0.05 was considered statistically significant for association analysis (Person coefficient, *Chi*-square test, *kappa* κ coefficient).

In the months following the first stage, the process of applying pre-preparation with simethicone was continued. In separated trial, six months later (Time 6 month), 140 subjects were randomized by the same inclusion criteria for either examination: without simethicone (Control group, n = 52) and with a pre-examination procedure (Simethicone group, n = 88) to assess the stability of the protocol performance. Based on the results of previous Time zero procedure without simethicone, were compared to quality of retrospective digital images obtained in 52 patients, 4 years before, analysed using SPSS v.21 (Fig. 1).

RESULTS

The quality assurance of analysis in both endoscopy procedures consisted of demonstrating the security of method, control of repetitions necessary due to interferences caused by bubbles, precision between analysts and time of endoscopy scan. In a first stage, we analysed some variables that could be affected by the pre-preparation use of simethicone: duration of endoscopy scan, the number of images that could be assessed and the precision of the analysis of digital images by specialists.

In our study, both groups were randomized: Retrospectively in Control, and prospectively in the Simethicone group. Underlying diseases most frequent in the population of interest were high blood pressure, diabetes mellitus, long-term depression, hypothyroidism and obesity. The most frequent indications were dyspepsia, vomiting, epigastralgia, gastric common femoral artery, dysphagia, abdominal pain or the combination of several of them. Table 1 reports the indications for esophagogastroduodenoscopy (EGD) for the diagnostic of patients and underlying diseases.

The studies developed by Bastford et al. (2016) and Royero (2018) were important to define the strategy and the score system in our study. Each scan generated four images of mucosal areas, and each image was evaluated on a scale of 1 to 4 depending on the interference caused by bubbles during gastric evaluation. Fig. 2 shows digital images obtained for the worst case without simethicone (Fig. 2A) and the scale of visualization in each mucosal area of patients prepared with simethicone (Fig. 2E).

In our first stage (Time zero), two repetitions were sometimes undertaken to improve quality (one for every 29 subjects), in the Control group, while Simethicone group no repetitions were necessary. In the second study, six months later, there was no repetition in either group.

Table 1. Demographic characteristics, indications for endoscopy examination and underlying diseases of groups.

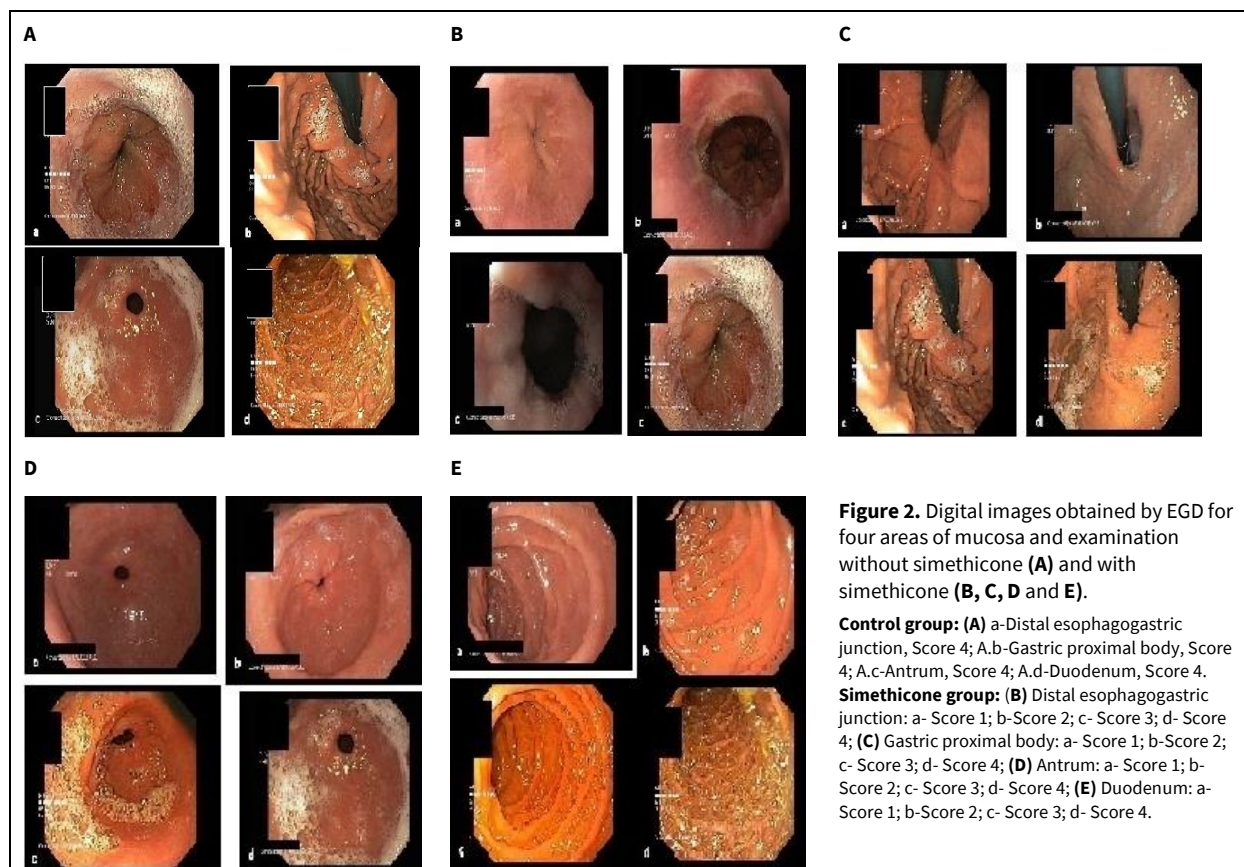| Variable	Control group (n = 58)	Simethicone group (n = 66)	Variable	Control group (n = 58)	Simethicone group (n = 66)
Age (years)			**Comorbidities (%)**		
Minimum	15	19	Diabetes mellitus	17	8
Maximum	90	86	High blood pressure	19	26
Range	58 ± 19	55 ± 15	Long-term depression	7	14
Indication (%)			Obesity	5	2
Epigastralgia	6	8	Dementia	3	0
Dyspepsia	15	32	Hypothyroidism	5	5
Dysphagia	5	5	Cardiopathy disease	0	2
Abdominal pain	5	5	Migraine/ Sinusitis	3	2
Rectal bleeding	2	0	Anaemia	2	0
Vomiting	10	0	Chronic renal failure	2	0
Nausea	2	0	Anxiety	2	3
Toxic syndrome	2	2	Bronchitis/Asthma	2	2
Gastroesophageal reflux (GER)	5	19	Chronic obstructive pulmonary disease	2	2
Iron deficiency anaemia	3	8	Heart attack	2	0
Family history of gastric cancer	3	2	Hepatitis B/Hepatitis C/SIDA	2	0
Ulcer background check	2	0	Pulmonary pneumonia	0	2
Gastric common femoral artery	0	12	Psoriasis	0	2
Iron deficiency	3	3	Fibromyalgia	2	0
Suspect to celiac disease	0	2	Osteoarthritis	2	0
Abdominal distension	0	5	Goiter	2	0
Chronic gastritis	0	2	Sciatic pain	2	0
Barrett´ mucosa	0	2	Ulcerative colitis	2	0
Anaemia	3	0	Irritable Bowel Syndrome	3	0
Aphonia	2	0	Thyrotoxicosis	2	0
Caustic intake	2	0	Herpes simplex virus	2	0
Upper gastrointestinal bleeding (UGB)	2	0	**Total comorbidities (%)**	**90**	**70**
Suspicion of hereditary hemochromatosis (HH)	2	0			

Examination time, endoscopists, methods and analysts of images (Time zero)

Some quality and safety indicators suggested by López-Picazo et al. (2017) as useful to facilitate improvement in digestive tract endoscopy units are summarized in Table 2.

A box plot analysis of the examination times required by two endoscopists and for groups (Control and Simethicone group) is shown in Fig. 3A-B. In this analysis, no differences between groups were apparent, but the Control group was not normally distribution. The U-Mann Whitney test was therefore applied for independent samples (in examination time). These results confirm significance between Control and Simethicone groups (Table 2), with ranges of 2-6 min using simethicone (73% of scans included in this range of time) and 3-8 min (71% of examinations) using the conventional method (significance between groups $p = 0.0001$). In the latter case, there were

Figure 2. Digital images obtained by EGD for four areas of mucosa and examination without simethicone **(A)** and with simethicone **(B, C, D** and **E)**.

Control group: (A) a-Distal esophagogastric junction, Score 4; A.b-Gastric proximal body, Score 4; A.c-Antrum, Score 4; A.d-Duodenum, Score 4.
Simethicone group: (**B**) Distal esophagogastric junction: a- Score 1; b-Score 2; c- Score 3; d- Score 4; **(C)** Gastric proximal body: a- Score 1; b-Score 2; c- Score 3; d- Score 4; **(D)** Antrum: a- Score 1; b- Score 2; c- Score 3; d- Score 4; **(E)** Duodenum: a- Score 1; b-Score 2; c- Score 3; d- Score 4.

patients in whom the scan without simethicone was extended due to interference by the bubbles (point out of range), and in which the mucosal lavage was used (Fig. 3A-B, Control group).

The same analysis was extended to the number of digital images resolved. From 126 scans for both groups (two repetitions of the same patient in Control group), a total of 504 images should be expected for each endoscopist (Control: 240 images and Simethicone: 264 images). The first endoscopist obtained 82% of expected images in Control and 93% in Simethicone group. The number of digital images showed association with the type of preparation of the patients (χ^2 = 17.536; p = 0.001). In this way, when 4 images were obtained, the best results were achieved in 81% of scans on patients with simethicone while in the Control group, only 44% of scans with all 4 images were achieved. Comparison among endoscopists did not show significance by U-Mann Withney test (Table 2). In fact, the joint analysis of expected images obtained by both endoscopists suggested a 12% improvement, using simethicone as pre-preparation procedure (Table 2).

Quality of images, analysts and examination methods (Time zero)

Reliability, reproducibility or consistency of measurements is a fundamental principle of study preci-

sion. In the research process, there are sources of potential error. Researchers need to reduce those related to the measurement of variables to ensure confidence in the results and conclusions (Manterola et al., 2018). An intervention or instrument is reliable, precise or reproducible when its measurements generate the same results at different times, scenarios and populations under the same conditions (Manterola et al., 2018). In our case, it was important to demonstrate consistent results with different analysts undertaking digital image evaluation as indirect tests of accuracy. We included two specialists as images analysts, with different numbers of years of experience, gathered in digestive examination (Analyst 1 with 9 years and Analyst 2 with 16 years).

The first outcome of our study is no significant difference between analysts in the evaluation of images in all mucosal areas (score) for both methods of examination (Control and Simethicone groups) (Table 2, Precision between analysts). However, the quality of score depends on the scan method for all mucosal areas (Table 2; Effectiveness of method, Fig. 4). Fig. 4A-B show the distribution of scores by areas for each analyst and study group. It is evident that the number of images with the best quality (score 1) increased using pre-preparation procedure with simethicone, for all mucosal areas; therefore, it improves the quality of final valuation.

Table 2. Summary of statistical parameters that allowed the characterization of the reference system (Control group) and the procedure proposed for endoscopy (Simethicone group).

Quality Assurance	Control group	Simethicone group	Practical results
1. Analysis at time zero			
1.1. Repetitions due to interferences caused by bubbles	Two repetitions were presented to improve quality (one for every 29 subjects) (n = 58)	No repetition was necessary for the number of patients randomized (n = 66)	Accessibility. Low frequency of repetitions increases the possibility of attending to a greater number of patients
1.2. Precision between endoscopists:	There were not differences between endoscopist:		Similar results regardless of human factor
Examination time	U-Mann Withney test (p = 1.000)		
Amount of images resolved	U-Mann Withney test (p = 0.735)		
1.3. Duration of procedure (min)	5.5 ± 2.58 (3-8)	3.83 ± 1.77 (2-6)	
1.4. Efficiency of examination method /effectiveness:	There were differences between group		
Examination time	U-Mann Withney test (U = 2412; Z = -5.37; p=0.0001).		Less time consuming during the scan, using simethicona.
Amount of images resolved	U-Mann Withney test (U = 3191; Z = -4.457; p=0.0001)		
Both endoscopists (%)	78	90	12% improvement, using simethicona.
Amount of expected images (n)	480	528	
Amount of obtained images (n)	364	476	
1.5. Precision between analysts:	No significance between analysts	No significance between analysts	Similar results regardless of human factor and complexity of the mucosal area
Scores assigned by each analyst:	*Chi*-squared test:	*Chi*-squared test:	
DEPGU	$\chi^2 = 1.557$; p = 0.817	$\chi^2 = 2.030$; p = 0.845	
GPB	$\chi^2 = 1.245$; p = 0.742	$\chi^2 = 2.320$; p = 0.803	
Antrum	$\chi^2 = 2.487$; p = 0.647	$\chi^2 = 6.472$; p = 0.263	
Duodenum	$\chi^2 = 1.844$; p = 0.764	$\chi^2 = 9.529$; p = 0.090	
1.6. Effectiveness of method:	There was significance; therefore, there was association among Score, mucosal area and examination method (Control and Simethicone groups):		Pre-preparation procedure with simethicone improves the quality of final valuation (Fig. 3)
Scores assigned by each analyst	*Chi*-squared test:		
DEPGU	$\chi^2 = 31.432$; p < 0.0001		
GPB	$\chi^2 = 17.548$; p = 0.004		
Antrum	$\chi^2 = 38.518$; p < 0.0001		
Duodenum	$\chi^2 = 41.981$; p < 0.0001		
1.7. Degree of overlapping between analyst* (Time zero):			Best results of similitude for pre-preparation procedure with simethicone
Scores assigned by each analyst	*Kappa* index (Concordance)	*Kappa* index (Concordance)	
DEPGU	$\kappa = 0.704$; p < 0.0001 (S)	$\kappa = 0.472$; p < 0.0001 (Mod)	
GPB	$\kappa = 0.151$; p = 0.003 (I)	$\kappa = 0.528$; p < 0.0001 (Mod)	
Antrum	$\kappa = 0.104$; p = 0.091 (I)	$\kappa = 0.528$; p < 0.0001 (Mod)	
Duodenum	$\kappa = 0.083$; p = 0.159 (I)	$\kappa = 0.666$; p < 0.0001 (S)	
1.8. Security	There were no adverse events	There were no adverse events associated with the use of simethicone prior to the examination.	No adverse events related to simethicone effect with anaesthesia.

Table 2. Summary of statistical parameters that allowed the characterization of the reference system (Control group) and the procedure proposed for endoscopy (Simethicone group) (continued…)

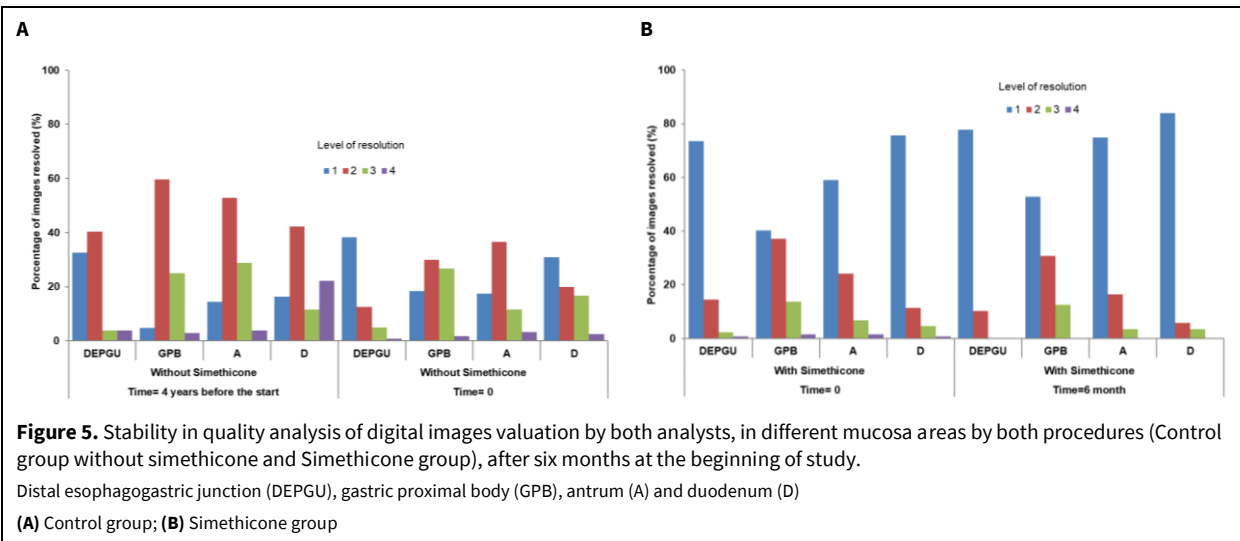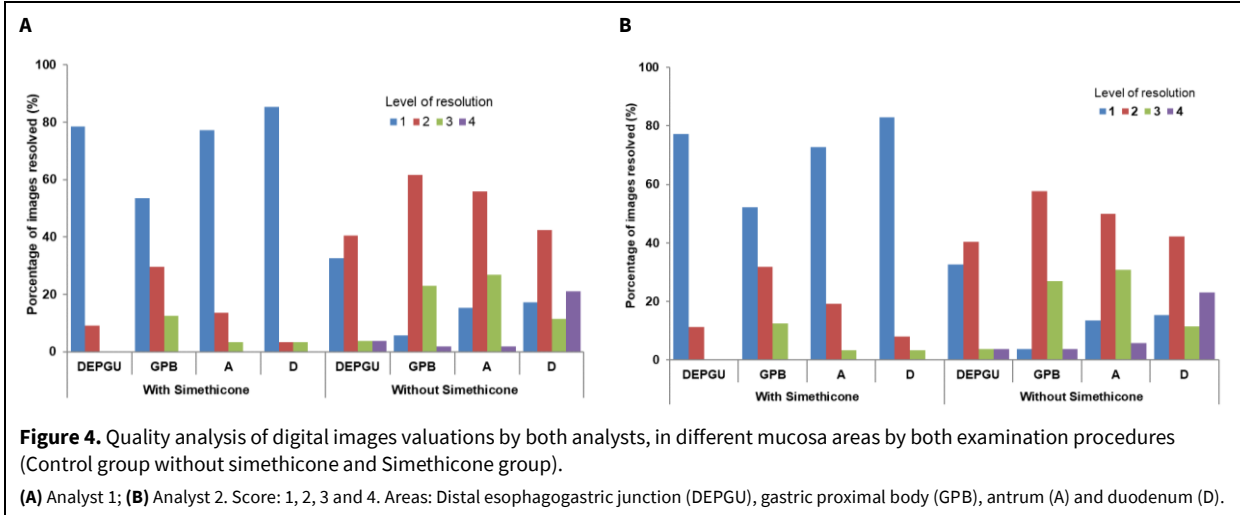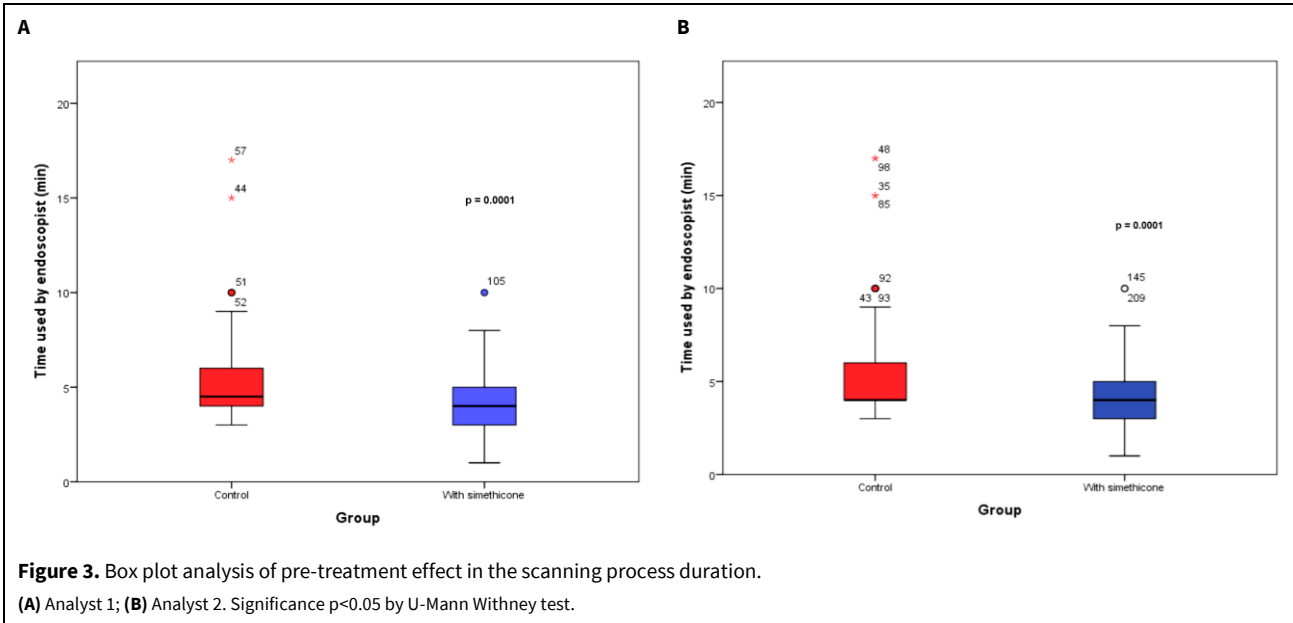| Quality Assurance	Control group	Simethicone group	Practical results
2. Stability of results after 6 months			
2.1. Precision between analysts:	No evaluate by the study		Similar results regardless of human factor and complexity of the mucosal area, with simethicone
Scores assigned by each analyst		*Chi*-squared test:	
DEPGU		$\chi^2 = 147.220$; $p < 0.0001$	
GPB		$\chi^2 = 212.729$; $p < 0.0001$	
Antrum		$\chi^2 = 214.951$; $p < 0.0001$	
Duodenum		$\chi^2 = 184.966$; $p < 0.0001$	
2.2. Degree of overlapping between analyst* (Time = 6 months):	No evaluate by the study		Validity of study with simethicone, after 6 months (Fig. 4B)
Scores assigned by each analyst		*Kappa* index (Concordance)	
DEPGU		$\kappa = 0.908$; $p < 0.0001$ (NP)	
GPB		$\kappa = 0.870$; $p < 0.0001$ (NP)	
Antrum		$\kappa = 0.833$; $p < 0.0001$ (NP)	
Duodenum		$\kappa = 0.760$; $p < 0.0001$ (S)	
3.1. Degree of overlapping between analyst* (Time = 4 years before the start):		No evaluate by the study	Validity of study without simethicone, 4 years after the start (Fig. 4A)
Scores assigned by each analyst	*Kappa* index (Concordance)		
DEPGU	$\kappa = 1.000$; $p < 0.0001$ (NP)		
GPB	$\kappa = 0.832$; $p < 0.0001$ (NP)		
Antrum	$\kappa = 0.782$; $p < 0.0001$ (S)		
Duodenum	$\kappa = 0.921$; $p < 0.0001$ (NP)		
3.2. Increased photo recovery with score 1 (% per year of study)	Time = 4 years before the start - Time zero	Time zero -Time = 6 months	More likely to improvement the quality of results with simethicone (Fig. 4)
DEPGU	1.25	10	
GPB	3.25	26	
Antrum	1	32	
Duodenum	3.75	16	

Note: Endoscopists were who performed the scans and the analysts selected the images and processed these. Distal esophagogastric junction (DEPGU), gastric proximal body (GPB), antrum (A) and duodenum (D)

* Agreement degree, according to Manterola et al. (2018):

Kappa index of Cohen (κ)	Agreement degree
<0.00	No agreement (NA)
0.00-0.20	Insignificant (I)
0.21-0.40	Medium (Me)
0.41-0.60	Moderate (Mod)
0.61-0.80	Substantial (S)
0.81-1.00	Nearly perfect (NP)

The second outcome for our study is that although it is not possible to determine the degree of accuracy using simethicone compared to a reference method; we have could determine the agreement in the score from both analysts; so, in each of the groups. The best results were obtained in Duodenum area, with higher concordance; and moderated concordance for DEPGU, GPB and Antrum) (Table 2; Concordance between analyst). Thus, the use of simethicone improves the results of the evaluation, expressed as an increase in the coincidence of the data obtained by analysts who evaluated the same images.

Figure 3. Box plot analysis of pre-treatment effect in the scanning process duration.

(A) Analyst 1; **(B)** Analyst 2. Significance p<0.05 by U-Mann Withney test.

Figure 4. Quality analysis of digital images valuations by both analysts, in different mucosa areas by both examination procedures (Control group without simethicone and Simethicone group).

(A) Analyst 1; **(B)** Analyst 2. Score: 1, 2, 3 and 4. Areas: Distal esophagogastric junction (DEPGU), gastric proximal body (GPB), antrum (A) and duodenum (D).

Figure 5. Stability in quality analysis of digital images valuation by both analysts, in different mucosa areas by both procedures (Control group without simethicone and Simethicone group), after six months at the beginning of study.

Distal esophagogastric junction (DEPGU), gastric proximal body (GPB), antrum (A) and duodenum (D)

(A) Control group; **(B)** Simethicone group

Quality of images, analysts and examination methods (Time 6 months)

After the first analysis, pre-preparation with simethicone procedure was continued six months later. In the second part of the study, the study was repeated with a significant increase in *kappa* values for the group with simethicone (Table 2, Overlap between analyst Time = 6months) and a significant increase in the quality of the image evaluation, which corresponds to a greater number of images with score 1 (Fig. 5B).

Fig. 5A demonstrated that far from improving the quality of the images without simethicone, since four years before to after six months of the start of our study; a greater number of images were obtained with score 2 and 3. In this case, we estimated that the improvement of quality without simethicone is 1-4% per year while with simethicone is 10-32% per year, depending on the mucosal area.

The practice acquired in the procedure and the close coordination between endoscopists and analysts, who participated in this study, have increased the number of good quality images and all four areas required.

DISCUSSION

Currently, there are a number of indicators and statistical analyses that demonstrate the reliability of a method to be used in clinical diagnosis (Manterola et al., 2018). We have selected the principal indicators regarding the possible benefits in effectiveness, safety and efficiency of the method in the endoscopy procedure.

In our study, the reliability (precision) among endoscopists and between analysts served as a reference to verify the safety of the results and to minimise of errors attributed to the human factor. Inter-endoscopist reliability is that which occurs in the same process during patient manipulation, to maximise the number of images that characterize the four mucosal areas. Inter-observer reliability occurs when two observers evaluate the same image independently.

Adequate inter-analyst precision was obtained, and the concordance in image assessment was the best premise to demonstrate that simethicone contributed to an improvement in the evaluation.

Several gastroenterology associations and committees have considered the risks and benefits of simethicone when formulating four recommendations and suggested there are no published reports of adverse events related specifically to its use, delivered either orally or via any endoscope channel. An assessment of the risks and benefits supports the continued use of simethicone during endoscopic procedures. Met-analysis carried out by Sajid and Chedgy (2018) suggested that the assessment of the included studies using multi-dimensional pathways like the use of "risk of bias assessment" tool by the Cochrane Collaboration, scoring systems, evidence from the GRADE-pro tool recommended by the Cochrane Collaboration brought overall strength of evidence may be considered high.

CONCLUSION

Our results confirm that the use of simethicone (Aero-red) as a pre-preparation drink 30 min before the endoscopy evaluation: improves the quality of images, recovers a higher number of images, and reduces the time of operation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

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Contribution	Ortega-Moya SP	Martínez-Cabrera I	Telles Guzmán M	Iyo Miyashiro E	Reyes Moreno J
Concepts or ideas	x	x			
Design	x	x			
Definition of intellectual content	x	x			
Literature search	x	x			
Experimental studies	x		x	x	x
Data acquisition	x	x	x	x	x
Data analysis	x	x			
Statistical analysis		x			
Manuscript preparation	x	x			
Manuscript editing	x	x			
Manuscript review	x	x	x	x	x