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ARTÍCULO ORIGINAL

Premedication in upper gastrointestinal endoscopy to improve mucosal visualization. A systematic review

Premedicación en endoscopia gastrointestinal alta para mejorar la visualización de la mucosa. Una revisión sistemática

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JL and AC contributed regarding the introduction. The methods were developed by the authors CC and DA. The results were described by FD and LS. Finally, in the discussion and conclusion, all authors reviewed and contributed information.

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The authors declare that they have no conflict of interest.

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ABSTRACT

Objective: This review aims to evaluate the efficacy and safety of premedication comprising mucolytics and/or defoaming agents to improve the quality of visualization during elective upper digestive endoscopy (elective upper GI endoscopy) procedure. **Materials and methods:** A systematic review of the literature contained in electronic databases (Medline/Pubmed, Embase, and Lilacs) was performed to identify randomized controlled trials and systematic reviews that assessed patients undergoing upper gastrointestinal endoscopy (elective upper GI Endoscopy) under sedation, after being premedicated with mucolytics and/or defoaming agents for mucous clearance. A meta-analysis was conducted to determine the relative efficacy and safety profile of such premedication. **Results:** In patients undergoing an elective procedure, premedication with defoaming and/or mucolytic agents improved the visibility score of the gastric antrum during upper GI endoscopy. The use of combined agents such as simethicone vs. water and N-acetyl cysteine (NAC) vs. water showed significant differences in favor of the active substance; however, no significant differences were found between the use of simethicone alone vs. simethicone + NAC. The use of pronase and dimethylpolysiloxane, among others, produced no significant difference (additive effect) in the visualization score. This is associated with the limited number of studies that performed similar comparisons and the heterogeneity of the outcomes. No major adverse effects were reported in the studies that were included regarding safety outcomes (i.e., volume of fluids required for clearance, risk of bronchoaspiration, and disinfection of equipment). **Conclusions:** The results of this review evidence that premedication with simethicone (a drug registered in Colombia for use against functional gastrointestinal disorders; ATC group A03A) is safe and effective for improving the quality of visualization during elective upper GI endoscopy procedures. However, no significant differences were observed in the visualization quality with the use or addition of other agents. The use simethicone should be set as off-label use and should be implemented at the prescriber's discretion. The use of simethicone as a premedication is recommended to improve the endoscopic visualization score in elective procedures.

Keywords: *Premedication; Gastroscopy; Antifoaming Agents; Antiflatulents; Pronation; Simethicone; Dimethylpolysiloxanes; Cysteine (source: MeSH NLM).*

RESUMEN

Objetivo: Esta revisión tiene como objetivo evaluar la eficacia y seguridad de la premedicación que comprende mucolíticos y/o agentes antiespumantes para mejorar la calidad de visualización durante el procedimiento de endoscopia digestiva alta electiva (endoscopia GI superior electiva). **Materiales y métodos:** Se realizó una revisión sistemática de la literatura contenida en bases de datos electrónicas (Medline/Pubmed, Embase y Lilacs) para identificar ensayos controlados aleatorios y revisiones sistemáticas que evaluaron pacientes sometidos a endoscopia gastrointestinal superior (endoscopia GI superior electiva) bajo sedación, después de haber sido premedicados con mucolíticos y/o agentes antiespumantes para la eliminación de la mucosa. Se realizó un metaanálisis para determinar la eficacia relativa y el perfil de seguridad de dicha premedicación. **Resultados:** En pacientes sometidos a un procedimiento electivo, la premedicación con agentes antiespumantes y/o mucolíticos mejoró el puntaje de visibilidad del antro gástrico durante la endoscopia digestiva alta. El uso de agentes combinados como simeticona vs. agua y N-acetil cisteína (NAC) vs. agua mostró diferencias significativas a favor del principio activo; sin embargo, no se encontraron diferencias significativas entre el uso de simeticona sola vs. simeticona + NAC. El uso de pronasa y dimetilpolisiloxano, entre otros, no produjo diferencia significativa (efecto aditivo) en el puntaje de visualización. Esto se asocia al número limitado de estudios que realizaron comparaciones similares y a la heterogeneidad de los desenlaces. No se reportaron efectos adversos mayores en los estudios que se incluyeron con respecto a los desenlaces de seguridad

(es decir, volumen de líquidos requeridos para la depuración, riesgo de broncoaspiración y desinfección del equipo). **Conclusiones:** Los resultados de esta revisión evidencian que la premedicación con simeticona (medicamento registrado en Colombia para su uso en el tratamiento de trastornos funcionales gastrointestinales; grupo ATC A03A) es segura y efectiva para mejorar la calidad de visualización durante procedimientos electivos de endoscopia digestiva alta. Sin embargo, no se observaron diferencias significativas en la calidad de visualización con el uso o la adición de otros agentes. El uso de simeticona debe establecerse como uso fuera de etiqueta y debe implementarse a discreción del médico prescriptor. Se recomienda el uso de simeticona como premedicación para mejorar el puntaje de visualización endoscópica en procedimientos electivos.

Palabras clave: *Premedicación; Gastroscopia; Antiespumantes; Antiflatulento; Pronación; Simeticona; Dimetilpolisiloxanos; Cisteína (fuente: DeCS Bireme).*

INTRODUCTION

Upper gastrointestinal (GI) endoscopy is a common procedure for the diagnosis and treatment of benign and malignant diseases, particularly when associated with early gastric cancer [1]. Therefore, clearly visualizing the mucosa, particularly when using advanced endoscopic methods such as narrow band imaging (NBI) or magnification endoscopy, is necessary.

The presence of mucus, bubbles, and foam in the gastric cavity is a well-known problem in upper GI endoscopy, capsule endoscopy, and colonoscopy [2]. In these procedures, the endoscopist has an altered image of the mucosa, thus requiring procedures such as multiple aspirations of adherent foam and washings during the procedure, which can substantially increase the time required to adequately assess the mucosa under examination and reduce diagnosis precision and patient comfort [3]. Mucosa visibility is a key factor when detecting subtle mucosal abnormalities during a diagnostic endoscopy. This requires physicians to maximize the available technology to improve the quality of visualization [4].

The use of simethicone, N-acetylcysteine, and Pronase decrease the amount of foam and mucus adhered that hinders proper assessment of the mucosa, thereby improving its visibility while reducing the need for washing and aspiration during the procedures. This effectively decreases the assessment duration and the probability of overlooking early lesions in early gastric cancer [5-7].

Therefore, numerous endoscopic centers worldwide commonly use antifoaming agents alone or in conjunction with mucolytic and/or defoaming agents as a method of premedication before performing an esophagogastroduodenoscopy. There is an increasing number of publications in the medical literature regarding the benefits of using these agents; however, thus far, no established protocols regarding the doses of each of the drugs, the volumes to be administered, or the ideal time of administration prior to the procedure have been presented [8].

Different premedication protocols for simethicone have been described in the literature, the most recent of which suggest the use of the following.

- Administering a solution containing 100 mL of water with 80 mg simethicone in liquid form 20 min prior to the procedure [4,9,10].
- 40 mg simethicone chewable tablet + 30 mL of water, administered 15 to 30 min prior to the procedure [11].

The purpose of this review is to act as a reference guide on the current evidence available in terms of the effectiveness and safety of premedicating with simethicone, to help medical specialists in the field of gastroenterology formulate a comprehensive management plan, supported by the best available evidence.

MATERIALS AND METHODS

The protocol of this review was designed following The Cochrane Handbook recommendations [12]; This study is a systematic review, in consequence, no ethical approval was required. As a search strategy, a bibliographic review was performed in the PubMed (Medline), Embase, and Lilacs databases. Unpublished studies (gray literature) were considered using the Clinical Trials database. The Medline/Pubmed search used the MeSH descriptive words listed below in Tables 1, 2 and 3. Initially, the search was not limited by language or type of study design. No limits were used for the search publication period.

Data collection and analysis

Herein, we separately analyze the efficacy and safety results according to each comparator in premedication to improve visualization in upper GI endoscopy for diagnostic purposes.

Selection of studies

Two reviewers independently revised the titles and abstracts of all references obtained from the search strategy using Rayyan online software in the "blind" mode. Studies that clearly did not meet the inclusion criteria were excluded, and full copies of the remaining studies were obtained and reviewed. Disagreements were resolved by discussion between the two reviewers after the "blinding mode" was removed, and the studies were anonymized prior to inspection.

Table 1. Pubmed search strategy.

Search	Query	Items found
#7	Search ((((((((((acetylcysteine[MeSH Terms]) OR pronase[MeSH Terms]) OR simethicone[MeSH Terms]) OR dimethylpolysiloxane[MeSH Terms]) OR defoaming agents[MeSH Terms]) OR antiflatulents[MeSH Terms]) OR cysteine[MeSH Terms])))) AND (((((esophagus/diagnostic imaging[MeSH Terms]) OR gastroscopy[MeSH Terms]) OR Endoscopy, Gastrointestinal[MeSH Terms]) OR duodenoscopy[MeSH Terms])) AND adults[MeSH Terms])) AND premedication[MeSH Terms]	11
#4	Search ((((((((((acetylcysteine[MeSH Terms]) OR pronase[MeSH Terms]) OR simethicone[MeSH Terms]) OR dimethylpolysiloxane[MeSH Terms]) OR defoaming agents[MeSH Terms]) OR antiflatulents[MeSH Terms]) OR cysteine[MeSH Terms]) OR premedication[MeSH Terms])) AND (((((esophagus/diagnostic imaging[MeSH Terms]) OR gastroscopy[MeSH Terms]) OR Endoscopy, Gastrointestinal[MeSH Terms]) OR duodenoscopy[MeSH Terms])) AND adults[MeSH Terms])	309
#3	Search simethicone	444
#2	Search agents, antifoaming	5495

The DeCS descriptive words listed in Table 2 were used for the EMBASE search.

Table 2. Embase search strategy.

Search	Query	Items found
#1	antifoaming agent '/exp OR dimeticone '/exp OR 'acetylcysteine '/exp OR 'simethicone '/exp	31398
#2	'antifoaming agent '/exp OR 'dimeticone '/exp OR 'simethicone'/exp OR 'acetylcysteine'/exp OR 'pronase '/exp OR 'premedication'/exp	159800
#3	'gastroscopy '/exp OR 'duodenoscopy '/exp OR 'gastrointestinal tract examination '/exp OR 'gastrointestinal endoscopy '/exp	182998
#4	'adult'/exp	7840308
#5	#2 AND #3 AND #4	1941
#6	'gastroscopy '/exp OR 'duodenoscopy'/exp OR 'gastrointestinal endoscopy'/exp	140716
#7	'premedication'	26047
#8	'antifoaming agent '/exp OR 'dimeticone'/exp OR 'acetylcysteine '/exp OR 'simethicone '/exp	65555
#9	'antifoaming agent'/exp OR 'dimeticone '/exp OR 'acetylcysteine'/exp OR 'simethicone'/exp OR 'pronase'/exp	68846
#10	#4 AND #8 AND #9 AND #11	15

The descriptive words listed in Table 3 were used for the Lilacs search.

Two reviewers independently extracted the data using a standard form, verified for the agreement before entering Review Manager 5.3 (RevMan 2014). The following information was included: number of participants, drug regimen and treatment, study design (placebo or active control), study duration and follow-up, outcome measures on visualization score, withdrawals, and serious adverse events.

We used the Oxford Quality score as the inclusion criterion [12], which limited the inclusion to studies that were at least randomized and double blind.

The two reviewers jointly assessed the risk for bias for each study, using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions [13], and adapted from the criteria applied by the Cochrane Group. Any disagreement was resolved by discussion.

Table 3. Lilacs search strategy.

Search	Query	Items found
#1	Endoscopia Gastrointestinal [Subject descriptor] and acetilcisteína [Words] or pronasa [Words]	13
#2	Endoscopia Gastrointestinal [Words] and acetilcisteína [Words] or Simethicone [Words]	9
#3	Endoscopia Gastrointestinal [Words] and Premedicación [Words] and Simethicone [Words]	0
#4	Endoscopia Gastrointestinal [Words] and Premedicación [Words] and acetilcisteína [Words]	0
#5	Endoscopia Gastrointestinal [Words] and Premedicación [Words] and pronasa [Words]	0

Measurement of the effect of treatment

The visualization score was estimated based on the McNally scale [14], modified by Kuo [15], reported for the gastric antrum. We decided not to use the global visualization score (given by the sum of the anatomical segments evaluated) owing to an inconsistency in the number of segments evaluated [16]. Furthermore, we used continuous data to calculate the mean difference with a CI of 95% using the random effects model.

The process diagram is described using the PRISMA template (see Figure 1).

Unit of analysis

We investigated the effectiveness of using the gastric antrum visualization score of a single arm trial vs. control (active or placebo). If the active treatment arms cannot be combined, they were raised as a subgroup analysis for common treatment.

Addressing missing data

Measurements reported as proportions in various studies were adjusted prior to meta-analysis whenever possible; otherwise, such studies were excluded from the quantitative analysis (see the summary of quantitative measurements provided in Table 4).

Assessment of heterogeneity

The I^2 statistic was used to measure heterogeneity, and it provides an estimate of variability between studies in terms

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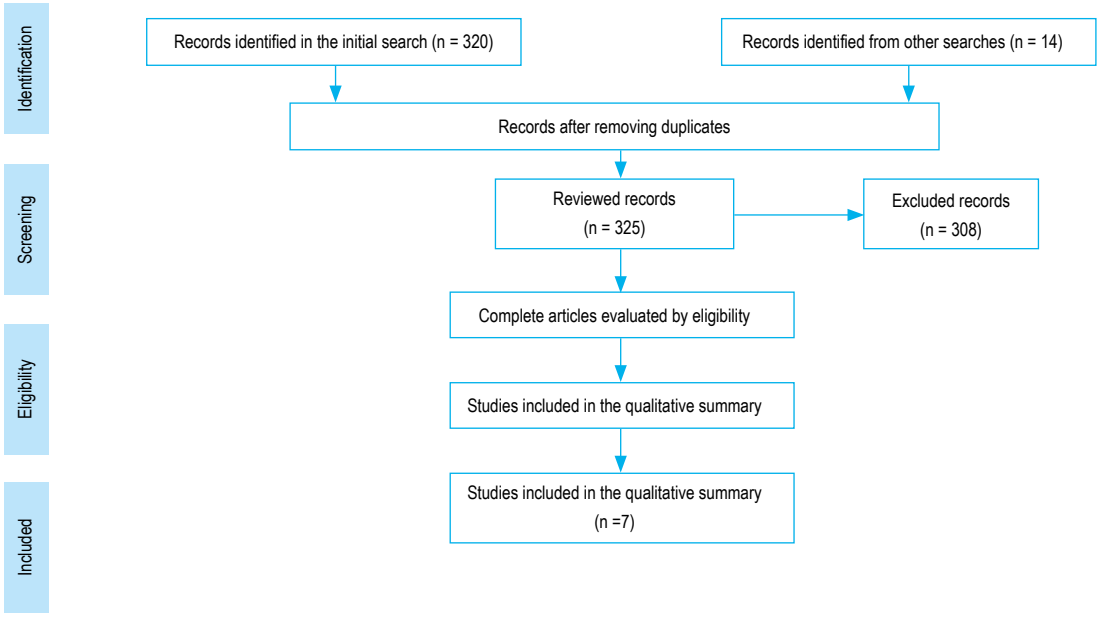

Figure 1. Flow diagram (Prism template).

of total variation. Thus, the proportion of total variation is due to heterogeneity rather than within-study sampling error.

Herein, we treated clinical heterogeneity by combining studies that assessed similar conditions, and assessed statistical heterogeneity when the $I^2 > 50\%$ [13].

Assessment of reporting biases

This review analyzes continuous results of the endoscopic visualization score in upper GI endoscopy for patients in whom elective/scheduled procedure was not contraindicated [16]. This review did not depend on what the authors chose to include or on the non-reporting of the original studies, although studies where no continuous results were reported presented a challenge. Publication bias was assessed using a method designed to detect the amount of unpublished data with a null effect required to render any result clinically irrelevant (generally considered an NNT of 10 or higher) [14].

Data synthesis

A random effects model was used for the meta-analysis considering the expected significant clinical heterogeneity between studies (active and non-active comparators were included together with different doses of the active ingredient in the same test for exploratory purposes).

Statistical aspects or plan of analysis

The studies were extracted from the electronic databases using the Mendeley electronic bibliographic reference software importer (Mendeley Web Importer), and later exported as citations in RIS format and imported into the Cochrane Organization Software Review Manager, Version 5.3, for management in this review.

Table 4. Summary of measurements included in the quantitative analysis.

Arm	Media	SD	n	Study
Water	2.34	0.74	40	Basford, 2016
Simethicone +NAC	1.58	0.62	41	Basford, 2016
Simethicone	1.74	0.91	39	Chang, 2007
Simethicone	1.49	0.82	35	Chang, 2007
Simethicone+Pronasa	1.18	0.63	34	Chang, 2007
Simethicone + NAC	1.21	0.52	39	Chang, 2007
Water	2.39	0.94	38	Hosseini, 2011
NAC	2.05	0.78	37	Hosseini, 2011
Simethicone	1.22	0.53	37	Hosseini, 2011
Simethicone + NAC	1.28	0.51	36	Hosseini, 2011
Water	2.53	1.1	58	Keratichananot, 2010
Simethicone	1.44	0.8	63	Keratichananot, 2010
Simethicone	1.26	0.4	34	Kuo, 2002
Simethicone	1.33	0.44	30	Kuo, 2002
Pronasa	1.28	0.72	31	Kuo, 2002
Pronasa	1.77	0.85	32	Kuo, 2002
Pronasa+Simethicone	1.03	0.12	33	Kuo, 2002
Water	2.56	1.5	27	Song, 2016
Simethicone	1.3	0.54	27	Song, 2016
Simethicone	1.4	0.7	72	Kim, 2015
Pronasa + Simethicone	1.1	0.1	71	Kim, 2015

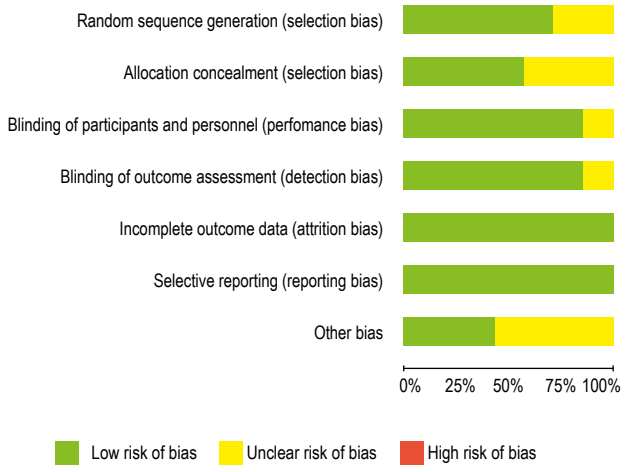

Figure 2. Risk of bias graph.

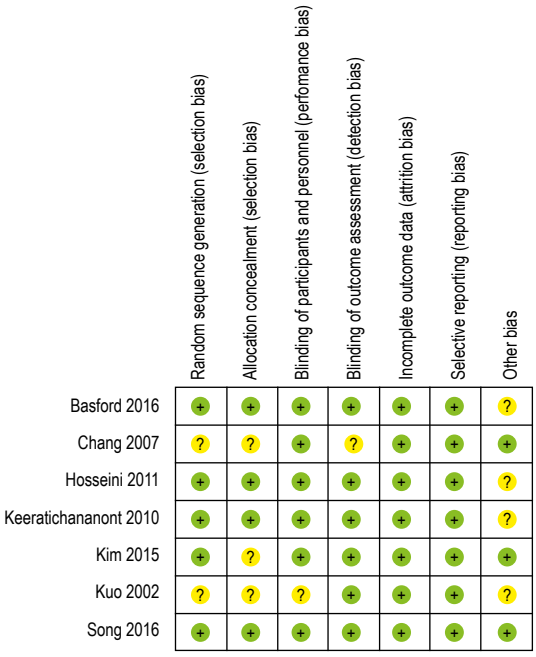

Figure 3. Risk of bias summary.

The IETS guidelines on methodological efficacy and safety in the 2014 manual version were followed (in effect at the time of this review).

Ethical considerations

The study is secondary, therefore it is low risk, it does not require approval by the ethics committee.

RESULTS

Characteristics of the comparators in the studies are shown in Table 4. We obtained 17 studies with 7 studies meeting the inclusion criteria after assessment, with a total of 854 patients. Trials were conducted in 6 countries, UK, Taiwan, South Korea, Singapore, Iran and Thailand. Most of them conducted in primary care, in patients with no major gastrointestinal condition, most of them single center based, with the exception of Kim 2015 which was multicentric.

Most trials compare Simethicone alone or in combination (Chang 2007) [5], (Hosseini 2011) [15], (Keratichananot 2010) [10], (Kuo 2002) [16], (Song 2016) [17], (Kim 2015) [18], the second agent most used was N-Acetylcysteine (Chang 2007) [6], (Hosseini 2011) [15], (Basdford 2016) [19], followed by Pronase (Kuo 2002) [16], (Kim 2015) [18], The dosage most frequently used for Simethicone was 100 mg , with a range between 60 to 133 mg, N-Acetylcysteine was used mostly in a dosage of 600 mg ranging from 200 up to 1000 mg and Pronase use was more standardized since all the studies administrated 2000 U. Most of the studies (4 out of 7) compared the main intervention against other agents, the rest of them used Water as a comparator in a range between 5 ml to 100 ml.

Risk of Bias

The overall risk of bias is presented in Figures 2 and 3, The risk of bias for random sequence generation and allocation concealment was generally low. Incomplete outcome data was not a issue in the studies since primary and secondary outcomes are measured immediately in the endoscopy procedure. Similarly, there was not issues detected on selective reporting. Most of the issues in the risk of bias was due to failing in reporting procedures, several studies did not state clear their methods to generate the random sequence, to conceal the allocation and to declare his sources of funding.

Only one of the trials claimed private sponsorship, the remaining was founded by public sources of national agencies, except by two studies who failed to declare source of founding.

Effects of Interventions

All the studies probed improved mucosal visibility with Simethicone when was compared with water regardless whether it was or not combined with other agents, the aggregate improvement was 1.03 points in a 4-point scale, and it was statistically significant (-1.27, -0.58) in a total of 405 patients, with a 15% of calculated heterogeneity.

Simethicone combined with NAC or Pronase showed an improvement of 0.24 points in a 4-point scale when it was compare with single Simethicone, although high heterogeneity was proved (I^2=59).

The Forest plot graphs of the study analyses show that simethicone used alone or in combination with NAC or Pronase is more effective than the use of water (alone) to improve the endoscopic visualization score of the gastric antrum. The subgroup analysis showed no marginal increase in the use of combinations compared to the use of

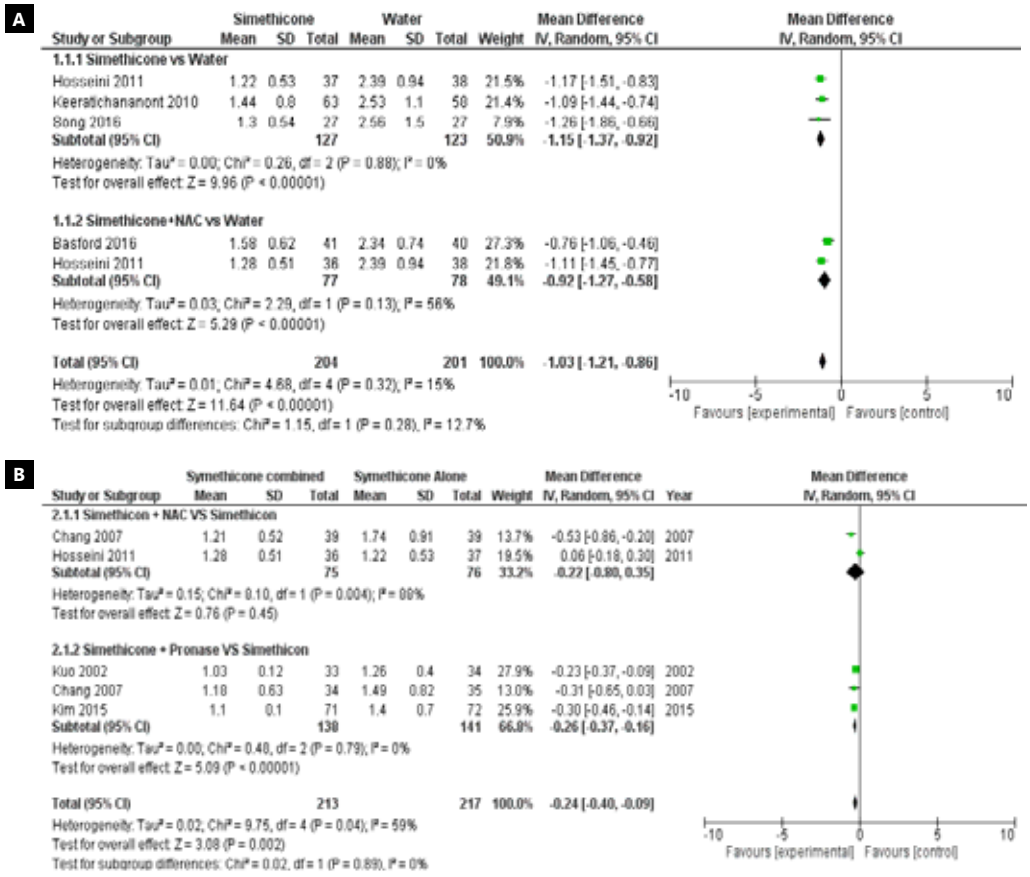

Figure 4. A) Forrest plot. Simethicone vs Water for a 4 scale visualization in Antrum. **B)** Forrest plot. Simethicone Combined vs Simethicone for a 4 scale visualization in Antrum.

simethicone alone. The studies included in the comparisons described above showed good quality of evidence with little heterogeneity between studies for each comparison. Figures 4 and 5.

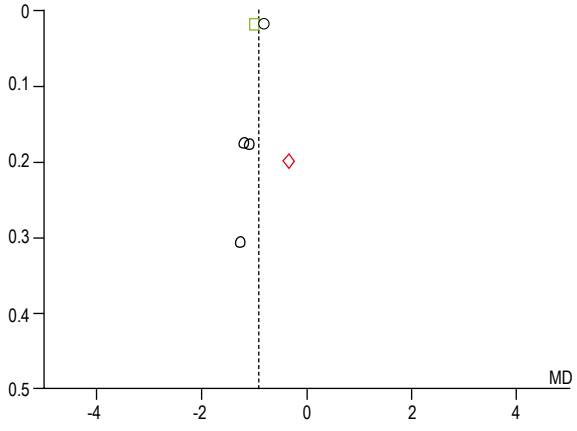

Figure 5. Funnel plot graph for comparison: Simethicone alone or in combination with NAC or Pronase vs. Water.

DISCUSSION

Clinical trials aimed at evaluating the efficacy of mucous clearing agents to improve visualization in upper GI endoscopy have been reported for over 40 years [20-25]. However, disparities in the recommendations and consensus of scientific societies [14,15,26], have been observed because of the considerable variability in trial design in terms of the dosage used, combined use with other drugs, type of procedure (upper GI endoscopy, capsule endoscopy, or colonoscopy) [10,11,16,27], and its association with problems related with the disinfection of endoscopic devices [13,28].

In 1988, the McNally scale [24,27], introduced a standard system for reporting findings regarding endoscopic visualization. Originally, it proposed a simple and reproducible system based on the amount of bubbles detected during the procedure. However, the modification made by Kuo in 2002 [16,27], suggests an aggregation of segments visualized in a measure called total visibility score (TVS). This limits the subsequent modifications in the number of segments included, thereby changing the magnitude in the meta-analysis.

Most of the evidence found from all premedication agents corresponds to simethicone, with less evidence found in studies including NAC and pronase. The

premedication agents showed higher effectiveness against their comparator, which was generally water. Simethicone alone or in combination is the most widely used agent, which correlates with Western clinical practices [24,26,29-31], added to the unavailability of pronase in most regions.

There were no significant differences (additive effect) in the improvement of visualization due to changes in the concentration or combination of premedication agents (evaluated through inter and intra studies). However, this could be due to the limited number of studies aimed at evaluating combinations between agents. All recruited patients were reported in the outcomes, and no major safety events related to the use of any of the premedications studied were reported.

Of the studies included in the quantitative analysis, only seven included some type of information regarding safety outcomes, and only two serious adverse events were reported [32]—a laryngospasm and an unspecified adverse event [19]. There is little recoverable information regarding the safety outcomes from the reviewed articles, making it unclear whether the investigators found no safety events or whether they were not evaluated in the studies.

One of the strengths of the study was that the Cochrane Handbook guidelines were followed [26,33], "If there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect." Therefore, it was the consistency in the direction of the effects and not in their magnitudes that allowed us to make our recommendations for selecting the best premedication. Similarly, inclusion of all available premedication agents is highlighted as a strength; thus, the drugs approved for use in patients with GI disorders were recommended [34,35].

The high heterogeneity between studies on the quantitative analysis with respect to the I^2 coefficient is significant [36]. This is mainly due to the use of ordinal scales as a measurement of comparison [37]. Ordinal scales, particularly those based on images (as in this case), require elements that support their stability and reproducibility from their qualitative origin. Furthermore, using scales with fewer than five items limits the use of averages as a measure of aggregation of effects, which, to a large extent, explains the heterogeneity detected in the statistical instruments [35]. This limited the number of studies included in the quantitative analysis as well as differences in the preparations used as comparators. Use of several agent dosages is also suspected as a source of heterogeneity, as a precaution when using high volumes of preparation that may increase the risk of severe adverse events during upper GI endoscopy.

The applicability of the findings of this review will depend on the degree of adoption of the available defoaming agents available in each country. Based on the above, simethicone is recommended as a premedication agent for improving endoscopic visualization in patients undergoing elective upper GI endoscopy procedures.

Additional studies are required to improve the statistical validity of the visualization scales for the issuance of recommendations based on the magnitude rather than on the direction of the effects. More clinical studies on this topic are recommended according to the results of this systematic review.

In conclusion, the evidence suggests that the use of simethicone is effective and safe for improving the quality of visualization of the gastric mucosa for diagnostic purposes during elective upper GI endoscopy, based on the information available in this review.

The evidence supporting that the addition of NAC, pronase, other mucolytic or defoaming agents, or their combination, further optimizes endoscopic visibility of the gastric mucosa, is not clear.

Additional, well-designed studies are required to improve the quality of the evidence on the effective and safe use of mucolytic and/or defoaming agents during elective upper GI endoscopy.

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