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Simethicone with or without N-acetylcysteine as premedication in esophagogastroduodenoscopy: a systematic review and meta-analysis

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Abstract

Background The impairment of gastrointestinal mucosa visibility during esophagogastroduodenoscopy (EGD), due to the presence of foam and bubbles, may lead to reduced quality in the EGD results. The combination of simethicone, a defoaming agent, along with N-acetylcysteine (NAC), which has mucolytic properties, has been proposed to improve the visibility of the mucosa. This study aimed to evaluate the effectiveness of pre-procedural administration of simethicone and N-acetylcysteine in improving mucosal visibility, procedure time and mucosal cleansing volume needed during EGD.

Methods We conducted a comprehensive literature search from inception to November 23, 2023, in PubMed, CENTRAL, ProQuest, SAGE, and JSTOR. We included randomized clinical trials that investigated the effects of simethicone with or without NAC as premedication in EGD. For the quantitative analysis, standardized mean difference (SMD) was used to assess continuous outcomes and risk ratio for dichotomous outcomes. The Cochrane risk of bias 2 tool was used to evaluate the risk of bias.

Results This meta-analysis comprised a total of 20 studies and found that simethicone with or without NAC improved mucosal visibility compared with control (SMD -1.27, 95% confidence interval [CI] -1.74 to -0.81, P<0.001). The combination of simethicone and NAC was significantly better than simethicone alone (SMD -0.68, 95%CI -1.08 to -0.28, P=0.001). Simethicone with or without NAC also shortened the procedure time compared to control (MD -1.40, 95%CI -2.67 to -0.12, P=0.03). The risk of bias was low with a moderate grade of certainty.

Conclusion The administration of simethicone with or without NAC may improve EGD quality.

Keywords Simethicone, N-acetylcysteine, premedication, esophagogastroduodenoscopy, meta-analysis

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Conflict of Interest: None

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Introduction

Esophagogastroduodenoscopy (EGD) is a diagnostic technique that allows visualization of the oropharynx, esophagus, stomach and proximal duodenum [1]. This procedure is extremely important in discovering multiple pathologies found in the upper gastrointestinal tract. Unfortunately, foam and bubbles may build up along the gastrointestinal tract and obscure its mucosa. This can lead to longer endoscopic duration, lower patient tolerance, and a decline in diagnostic accuracy [2].

Simethicone, an oral agent made of the combination of silica gel and dimethylpolysiloxane, has the ability to

eliminate air bubbles. It is biologically inert and not absorbed by the digestive tract. This agent has been proposed as a premedication that could be useful in eliminating foams and bubbles [3]. N-acetylcysteine (NAC), a mucolytic and antioxidant agent, has also been proposed as a premedication to reduce mucus covering the gastrointestinal mucosa. NAC works by altering the viscoelastic characteristics of gastric mucin, thus eliminating excess mucus in the gastrointestinal tract [4].

The use of defoaming agents such as simethicone, with or without NAC, for improving the viability of gastrointestinal mucosa has already been reported by several studies. However, very few studies provided systematically updated evidence of these agents. The purpose of this study was to conduct a systematic assessment of the current body of evidence on the efficacy of simethicone and NAC prior to EGD in enhancing mucosal visibility.

Materials and methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline 2020 (Supplementary Table 1). The protocol for this study has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023486128.

Literature search

A literature search investigating the efficacy of simethicone alone vs. simethicone with NAC as a premedication in gastroscopy was conducted from inception to November 23, 2023, in CENTRAL, PubMed, ProQuest, SAGE and JSTOR. The following search strategy was used during the literature search: ((((((“Simethicone”[Mesh]) OR “dimethicone” [Supplementary Concept]) OR (Simethicone)) OR (Simethicone)) OR (Dimethicone)) OR ((((((“Acetylcysteine”[Mesh]) OR (Acetylcysteine)) OR (N-acetylcysteine)) OR (N-acetyl-L-cysteine)) OR (NAC)) OR (NALC))) AND ((((((((“Gastroscopy”[Mesh]) OR (Gastroscopy)) OR (Oesophagogastroduodenoscopy)) OR (Oesophago-gastro-duodenoscopy)) OR (Esophagogastroduodenoscopy)) OR (Esophago-gastro-duodenoscopy)) OR (OGD)) OR (EGD)) OR (Upper endoscopy)).

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Study selection

The inclusion criteria for this study were: (1) investigated the effects of simethicone with/without NAC as premedication in gastroscopy; (2) was a human study; (3) was a randomised clinical trial (RCT); (4) was written in English; (5) full text was available. The exclusion criteria were as follows: (1) non-RCT study, case report, case series, review, *in vivo* or *in vitro* study, letter to editor; (2) lack of suitable data; (3) unclear methodology.

Data extraction

Two reviewers independently extracted the data from the included papers. Any disagreements were settled via discussion with a third reviewer. The data extracted in this study were: first author name, country, publication year, population (number of patients, age, sex, race), type of intervention, control, outcome, and adverse events.

Statistical analysis

For continuous variables, standardized mean difference (SMD) was used if the measuring tools varied, whereas mean difference (MD) was used if the measuring tools were the same for all studies. For dichotomous variables, risk ratio (RR) was used. All effect measures used a confidence interval (CI) of 95%. RR <1 indicates a result that favors the intervention group (simethicone with/without acetylcysteine). Heterogeneity was evaluated using I^2 and the χ^2 test. A random-effect model was used if there was substantial heterogeneity (I^2>50% or P<0.1), whereas if there was no substantial heterogeneity (I^2<50% and P>0.1) a fixed-effect model was applied. If more than 10 studies were included, publication bias was investigated using a funnel plot [5]. All statistical analyses were conducted using RevMan 5.4.

Quality assessment

The Cochrane risk of bias 2 (RoB 2) tool was used to assess the risk of bias of each included study. The RoB 2 tool contains 5 domains: (1) bias in the randomization process; (2) deviation from intended intervention; (3) missing outcome data; (4) measurement of outcome; (5) selection bias. If there is an overall low risk of bias, then there is a low risk of bias across all domains. Meanwhile, if there are some concerns about numerous domains or a high risk of bias for at least 1 domain, then the overall risk of bias is high [5]. This process was completed independently by 2 reviewers and any disagreements were handled via discussion with a third reviewer.

Certainty of evidence

The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and

Evaluation (GRADE) scale. GRADE contains 5 domains: (1) risk of bias; (2) indirectness; (3) inconsistency; (4) imprecision; (5) publication bias [6]. Risk of bias was evaluated using the Cochrane RoB 2 tool [5]. A study that had RR=1, MD=0 or SMD=0 was deemed imprecise [7]. Studies with substantial heterogeneity (I^2>50%) were deemed inconsistent. Each outcome can be graded as having a high, moderate, low or very low level of certainty. A high level of certainty means that we are very confident that the true effect lies close to the estimate of effect, whereas a very low level of certainty means that we have very little confidence that the true effect lies close to the estimate of effect [6]. This process was also completed by 2 independent reviewers, with any disagreements handled via discussion with a third reviewer.

Results

After conducting a search through Pubmed, CENTRAL, ProQuest, SAGE and JSTOR, and removing duplicates, we identified 1140 articles. From the articles retrieved, we selected a total of 20 RCTs. The PRISMA flow diagram for the selection process is shown in Fig. 1.

The studies included ranged from the year 1992-2023, and originated from Asia, Europe, the Middle East, and Chile. A total of 20 RCTs with 8893 participants were included in this review [8-27]. Four of these 20 studies were excluded from the meta-analysis as they lacked appropriate data for quantitative analysis [11,16,19,22]. Eighteen studies

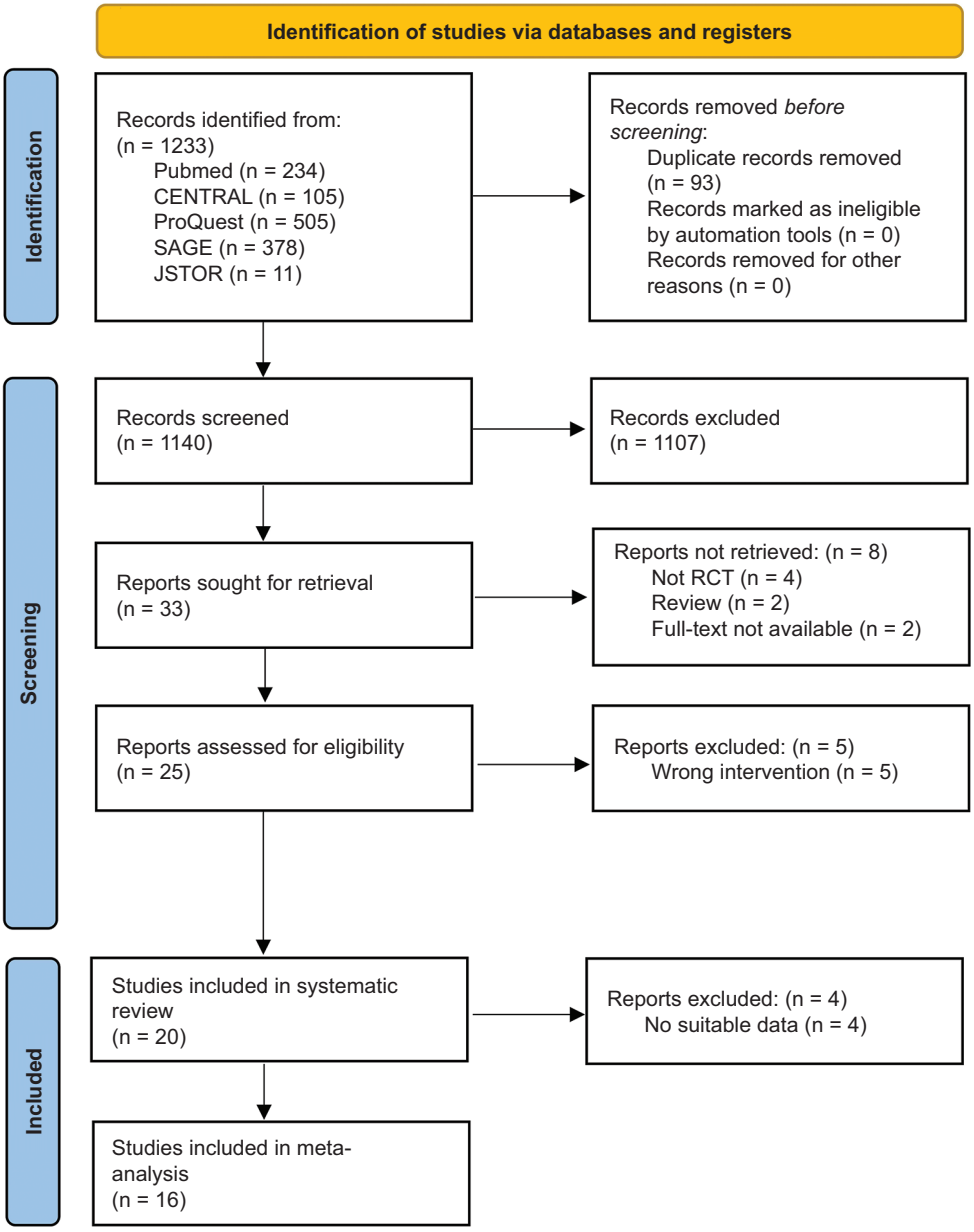

Figure 1 PRISMA flow diagram

investigated the efficacy of simethicone with or without NAC vs. controls [8,10-12,14-27], 7 studies simethicone with NAC against simethicone alone [9,12,13,16,18,20,25], and 2 studies simethicone with NAC against NAC alone [12,25]. The dosage for simethicone ranged from 20 mg to 400 mg, while the NAC dosage ranged from 300-1000 mg. All premedications were given as a single dose 15-30 min before EGD. The characteristics of each included study are summarized in Table 1.

Mucosal visibility

For mucosal visibility, a total of 16 studies were identified [9,12,13,15-27]. Nine of 10 studies reported better mucosal visibility during EGD in those given simethicone compared to control [12,16,17,19-21,24-26]. Only Monrroy *et al* [18] reported no significant difference between groups in mucosal visibility. Similarly, 11 studies that investigated the efficacy of simethicone with or without NAC against controls also reported significantly better mucosal visibility in the simethicone with or without NAC group [12,15-17,19-22,24-26]. Meanwhile, 2 studies reported that simethicone with or without NAC did not significantly improve mucosal visibility compared with controls [23,27]. When compared to the control group, Monrroy *et al* [18] found that simethicone with NAC improved mucosal visibility significantly, but not simethicone alone.

Seven studies compared the efficacy of simethicone with NAC against simethicone alone [9,12,13,16,18,20,25]. Four studies reported significantly better mucosal visibility in the simethicone with NAC group when compared to the simethicone alone group [9,18,20,25]. In contrast, 2 studies reported no significant difference in mucosal visibility between the simethicone with NAC group and the simethicone alone group [12,16]. Chang *et al* [13] found that the group receiving simethicone with NAC had significantly better mucosal visibility when compared to 5 mL simethicone syrup (containing 100 mg simethicone), but not to 100 mg simethicone in 100 mL water. Only 2 studies were identified that compared the efficacy of simethicone with NAC against NAC alone. Both studies had a similar conclusion: that the use of simethicone with NAC resulted in better mucosal visibility compared to NAC alone [12,25].

Table 1 Characteristics of included studies

Study [ref.]	Experimental group	Comparator group	Mucosal visibility score	Procedure time	Cleansing volume	Lesion detection
Bertoni *et al* [8] 1992, Italy	A (n=81): 65 mg simethicone in 90 mL water B (n=80): 65 mg simethicone in 30 mL water C (n=82): 195 mg simethicone in 90 mL water	D (n=87): placebo in 60 mL water	-	ABC: 91.9±30.7 sec D: 119±33.5 sec ABC vs. D: P<0.001	-	-
Chang *et al* [9] 2006, China	A (n=39): 5 mL DMPS B (n=35): 5 mL DMPS in 100 mL water	C (n=39): 5 mL DMPS and 400 mg NAC in 100 mL water	A: 8.2±3.1 B: 7.6±2.6 C: 6.5±2.2 A vs. B: P=0.39 A vs. C: P<0.01 B vs. C: P=0.06	-	-	-
Keeratichananont *et al* [10] 2010, Thailand	A (n=63): 2 mL simethicone liquid (133.3 mg simethicone) in 60 mL water	B (n=58): 2 mL placebo in 60 mL water	-	A: 9.9±4.9 min B: 9.8±4.0 min A vs. B: P=0.895	-	-
Ahsan *et al* [11] 2011, Iran	A (n=90): 40 mg simethicone in 30 mL water	B (n=83): 40 mg placebo tablet+30 mL water	-	A: 308±116.2 sec B: 376±108.1 sec A vs. B: P<0.001	-	-
Asl *et al* [12] 2011, Iran	A (n=37): 100 mg dimethicone in 100 mL water B (n=37): 600 mg NAC in 100 mL water C (n=36): 100 mg dimethicone and 600 mg NAC in 100 mL water	D (n=38): 100 mL water	A: 5.11±1.28 B: 8.41±2.10 C: 5.39±1.71 D: 9.50±2.55 A vs. B: P<0.001 A vs. C: P>0.05 A vs. D: P<0.001 B vs. C: P<0.001 C vs. D: P<0.001	-	-	-

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Table 1 (*Continued*)

Study [ref.]	Experimental group	Comparator group	Mucosal visibility score	Procedure time	Cleansing volume	Lesion detection
Chang *et al* [13] 2013, China	A (n=709): 100 mg simethicone in 5 mL water B (n=723): 100 simethicone in 100 mL water	C (n=657): 100 mg simethicone and 300 mg NAC in 100 mL water	A: 8.34±1.75 B: 7.67±1.06 C: 7.52±0.96 A vs. B: P<0.001 A vs. C: P<0.001 B vs. C: P=0.160	A: 13.7±2.5 min B: 13.7±2.6 C: 13.8±2.4 min P-value across groups=0.354	-	A: esophageal ulcer 6/709, esophageal tumor 6/709, gastric ulcer 88/709, gastric tumor 3/709, duodenal ulcer 76/709 B: esophageal ulcer 5/723, esophageal tumor 5/723, gastric ulcer 86/723, gastric tumor 3/723, duodenal ulcer 61/723 C: esophageal ulcer 8/657, esophageal tumor 3/657, gastric ulcer 74/657, gastric tumor 2/657, duodenal ulcer 67/657 P-value across all groups: esophageal ulcer P=0.646, esophageal tumor P=0.748, gastric ulcer P=0.837, gastric tumor P>0.99, duodenal ulcer P=0.480
Neale *et al* [14] 2013, United Kingdom	A (n=23): 2.5 mL simethicone and 3 mL NAC in 100 mL water	B (n=23): 100 mL water	-	A: 8.5 min (5.0-12.0 min) B: 10.5 min (7.5-13.5 min) A vs. B: P value not significant	A: 12.1 mL (3.5-20.7 mL) B: 61.0 mL (21.0-101.0 mL) A vs. B: P<0.01	-

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Table 1 (*Continued*)

Study [ref.]	Experimental group	Comparator group	Mucosal visibility score	Procedure time	Cleansing volume	Lesion detection
Basford *et al* [15] 2016, Europe	A (n=41): 60 mg simethicone and 1000 mg NAC in 50 mL water	B (n=40): 50 mL water	A: 1.45±0.18 B: 2.10±0.20 A vs. B: P<0.001	A: 309±129 sec B: 352±216 sec A vs. B: P=0.438	A: 2.0±9.13 mL B: 31.5±38.3 mL A vs. B: P=0.001	-
Elvas *et al* [16] 2016, Portugal	A (n=101): 100 mg simethicone in 100 mL water B (n=98): 100 mg simethicone and 600 mg NAC in 100 mL water	C (n=98): 100 mL water	A: esophagus 92/101 "excellent", stomach 77/101 "excellent", duodenum 86/101 "excellent" B: esophagus 85/98 "excellent", stomach 73/98 "excellent", duodenum 80/98 "excellent" C: esophagus 70/98 "excellent", stomach 38/98 "excellent", duodenum 72/98 "excellent" A vs. C: esophagus P<0.001, stomach P<0.001, duodenum P=0.042 B vs. C: esophagus P=0.008, stomach P<0.001, duodenum P=0.171 AB vs. C: esophagus P<0.001, stomach P<0.001, duodenum P=0.11	-	-	A: esophagus 23/101, stomach 61/101, duodenum 4/101 B: esophagus 19/98, stomach 65/98, duodenum 3/98 C: esophagus 13/98, stomach 55/98, duodenum 4/98 A vs. B: esophagus P=0.082, stomach P=0.541, duodenum P=0.255
Song *et al* [17] 2016, Singapore	A (n=27): 100 mg simethicone in 5 mL water	B (n=27): 5 mL water	A: 5.78±1.65 B: 8.89±1.97 A vs. B: P<0.001	A: 154.85±49.07 sec B: 193.67±87.04 sec A vs. B: P=0.049	A: 3.89±11.46 mL B: 84.81±110.18 mL A vs. B: P<0.001	-
Monrroy *et al* [18] 2017, Chile	A (n=46): 200 mg simethicone in 100 mL water B (n=46): 200 mg simethicone and 500 mg NAC in 100 mL water C (n=46): 200 mg simethicone and 1000 mg NAC in 100 mL water	D (n=46): 100 mL water	A: 7 (5-10) B: 6 (5-10) C: 5 (4-11) D: 7 (6-14) A vs. B: P=0.81 A vs. C: P=0.046 A vs. D: P=0.14 B vs. C: P=0.613 C vs. D: P=0.015	A: 10 (8-13) min B: 10 (7-13.5) min C: 9 (7-13) min D: 10 (7-12.5) min P-value across groups=0.818	ABC: 50 (0-330) mL D: 90 (10-200) mL ABC vs. D: P=0.035	A: 13/39 B: 11/36 C: 13/40 D: 6/42 ABC vs. D: P=0.027 BC vs. D: P=0.048

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Table 1 (*Continued*)

Study [ref.]	Experimental group	Comparator group	Mucosal visibility score	Procedure time	Cleansing volume	Lesion detection
Liu *et al* [19] 2018, China	A (n=1777): 80 mg simethicone in 100 mL water	B (n=1772): 100 mL water	A: esophagus (1: 792±44.6; 2: 798±44.9; 3: 187±10.5), cardia (1: 920±51.8; 2: 740±41.6; 3: 117±6.6), fundus (1: 896±50.4; 2: 699±39.3; 3: 182±10.3), gastric body (1: 821±46.2; 2: 786±44.2; 3: 170±9.6), antrum (1: 1271±71.6; 2: 422±23.7; 3: 84±4.7) B: esophagus (1: 120±6.8; 2: 913±51.5; 3: 739±41.7), cardia (1: 88±5.0; 2: 788±44.5; 3: 896±50.5), fundus (1: 103±5.8; 2: 582±32.8; 3: 1087±61.4), gastric body (1: 121±6.8; 2: 705±39.8; 3: 946±53.4), antrum (1: 375±21.2; 2: 721±40.7; 3: 676±38.1) A vs. B: esophagus P<0.001, cardia P<0.001, fundus P<0.001, gastric body P<0.001, antrum P<0.001	-	-	A: pre-cancerous lesion 10.0%, early cancer 1.5% B: pre-cancerous lesion 8.7%, early cancer 1.3% P-value: pre-cancerous lesion P=0.138; early cancer P=0.878
Mahawongkajit *et al* [20] 2020, Thailand	A (n=32): 100 mg simethicone in 100 mL water B (n=32): 100 mg simethicone and 600 mg NAC in 100 mL water	C (n=32): 100 mL water	A: 10.5±1.45 B: 7.17±0.98 C: 13.4±1.86 A vs. B: P<0.001 A vs. C: P<0.001 B vs. C: P<0.001	A: 9.09±1.46 min B: 8.81±1.2 min C: 9.56±1.43 min A vs. B: P=0.201 A vs. C: P=0.027 B vs. C: P=0.404	A: 39.06±30.41 mL B: 14.06±22.84 C: 59.37±26.75 mL A vs. B: P=0.006 A vs. C: P<0.001 B vs. C: P<0.001	-
Zuberi *et al* [21] 2020, Pakistan	A (n=124): 15 mL simethicone syrup in 35 mL water	B (n=124): 50 mL placebo	A: 5.8±1.748 B: 8.14±2.437 A vs. B: P<0.001	-	-	-
Manfredi *et al* [22] 2021, Germany	A (n=97): 2 mL simethicone and 600 mL NAC in 450 mL water	B (n=100): control	A: 7.6±1.5 B: 6.0±0.7 A vs. B: P<0.001	-	-	-
Stepan *et al* [23] 2021, Czech Republic	A (n=44): 20 mg simethicone and 400 mg NAC in 100 mL water	B (n=44): 100 mL water	A: 17.4±1.9 B: 17.6±1.81 A vs. B: P=0.342	A: 7.84±1.46 min B: 7.55±1.74 min A vs. B: P=0.3108	-	-

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Table 1 (*Continued*)

Study [ref.]	Experimental group	Comparator group	Mucosal visibility score	Procedure time	Cleansing volume	Lesion detection
Duez *et al* [24] 2022, Belgia	A (n=52): 5 mL simethicone in 95 mL water	B (n=47): 5-10 drops orange juice syrup in 100 mL water	A: 6.5±1.5 B: 11.0±4.5 A vs. B: P<0.001	A: 7 (4-20) min B: 8 (4-17) min A vs. B: P=0.55	-	-
Krishnamurthy *et al* [25] 2022, India	A (n=192): 150 mg simethicone in 75 mL water B (n=192): 150 mg simethicone and 600 mg NAC in 75 mL water C (n=192): 600 mg NAC in 75 mL water	D (n=192): 75 mL water	A: 9.93±2.19 B: 8.31±1.73 C: 11.46±2.4 D: 12.06±2.3 A vs. B: P<0.05 A vs. C: P<0.05 A vs. D: P<0.05 P-value across all groups: P<0.05	A: 5.28±1.52 min B: 5.27±1.28 min C: 6.05±1.45 D: 6.95±1.85 A vs. B: P>0.05 A vs. BCD: P<0.05	-	A: - B: 72/192 C: - D: - A vs. B: P value not significant B vs. CD: P<0.05
Cao *et al* [26] 2023, China	A (n=64): 10 mL simethicone in 90 mL water	B (n=62): 10 mL normal saline in 90 mL water	A: 12.36±2.93 B: 14.52±2.57 A vs. B: P=0.006	A: 7.8±2.9 B: 7.4±2.6 A vs. B: P=0.261	A: 50±30 mL B: 55±37 mL A vs. B: P<0.001	A: 48/64 B: 37/62 A vs. B: P=0.173
Stepan *et al* [27] 2023, Czech Republic	A (n=30): 400 mg simethicone and 600 mg NAC in 100 mL water B (n=30): 20 mg simethicone and 400 mg NAC in 100 mL water	C (n=30): 100 mL water	A: 18.93±2.886 B: 18.53±3.4 C: 18.6±1.9052 A vs. B: P>0.99 A vs. C: P>0.99 B vs. C: P>0.99	A: 7.84±1.46 min B: 7.87±1.64 min C: 7.55±1.74 min P-value across all groups=0.132	-	-

DMPS, dimethylpolysiloxane; NAC, N-acetylcysteine

We performed a meta-analysis comparing the mucosal visibility in simethicone with or without NAC with control and confirmed that the simethicone with or without NAC group produced significantly better mucosal visibility (SMD -1.27, 95%CI -1.74 to -0.81, P<0.001; Fig. 2). In addition, we found that the combination of simethicone with NAC resulted in significantly better mucosal visibility compared to simethicone alone (SMD -0.68, 95%CI -1.08 to -0.28, P=0.001; Fig. 3). A meta-analysis to compare the mucosal visibility between the groups simethicone with NAC and NAC alone could not be performed because the number of studies was too small.

Procedure time

A total of 13 studies investigated the procedure time [8,10,11,14,15,17,18,20,23-27]. Four out of 9 studies reported significantly shorter procedure times in the simethicone group compared to control [8,11,17,25], whereas the other 5 studies did not find any significant difference between groups [10,18,20,24,26]. Similarly, most of the studies that investigated the procedure time in a simethicone with or without NAC group and a control group reported no significant difference in the procedure time [10,14,15,18,23,24,26,27]. Only 4 studies reported shorter procedure times in the simethicone ± NAC group when compared to control [8,11,17,25]. Mahawongkajit *et al* [20] only found significantly shorter procedure time in the simethicone with NAC group, but not in the simethicone alone group, when compared to control. When comparing the procedure times for simethicone with NAC vs. simethicone alone, all 4 studies found no significant difference between the groups [13,18,20,25]. Only 1 study compared the procedure times for simethicone with NAC vs. NAC alone, and found the procedure time to be similar in both groups [25].

Our meta-analysis suggests that using simethicone with or without NAC might be beneficial in reducing procedure time when compared to control (MD -1.40, 95%CI -2.67 to -0.12, P=0.03; Fig. 4). On the other hand, the combination of simethicone with NAC was not better than simethicone alone in reducing the procedure time (MD -0.00, 95%CI -0.17 to -0.17, P=0.99; Supplementary Fig. 1). A meta-analysis comparing simethicone with NAC against NAC alone could not be performed because the number of studies was too small.

Cleansing volume

Six studies examined the effect of various premedications on the amount of cleansing volume required during EGD [14,15,17,18,20,26]. All 3 studies reported a significantly smaller amount of cleansing volume needed during EGD in the simethicone group compared to control [17,20,26]. This finding was also reported for the simethicone with or without NAC group compared with controls [14,15,17,18,20,26]. Similarly, the amount of volume cleansing used was significantly lower in

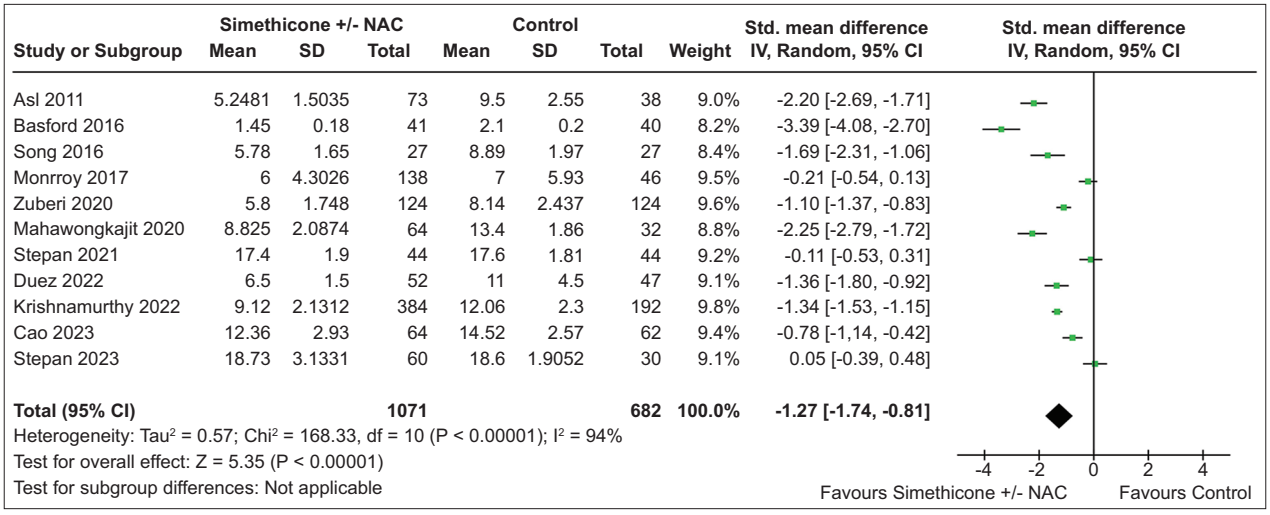

Figure 2 Mucosal visibility in simethicone with or without NAC vs. controls [12,15,17,18,20,21,23-27]. The mucosal visibility in the simethicone with or without NAC group is significantly better than in the control group (SMD -1.27, 95%CI -1.74 to -0.81, P<0.001). A random-effect model was used given the presence of significant heterogeneity (I^2=94%, P<0.001). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; NAC, N-acetylcysteine; SMD, standardized mean difference

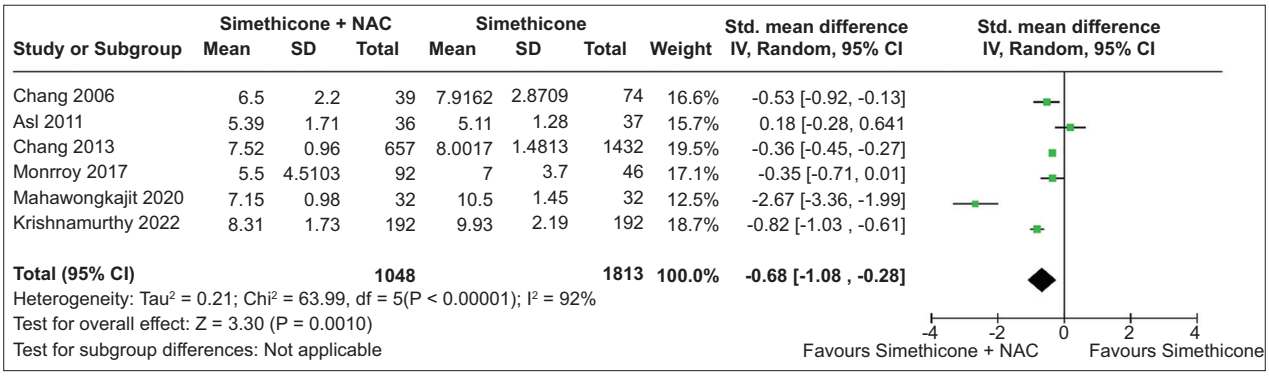

Figure 3 Mucosal visibility in simethicone with NAC vs. simethicone [9,12,13,18,20,25]. The mucosal visibility in the simethicone with NAC group is significantly better than in the simethicone alone group (SMD -0.68, 95%CI -1.08 to -0.28, P=0.001). A random-effect model was used due to the presence of significant heterogeneity (I^2=92%, P<0.001). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; NAC, N-acetylcysteine; SMD, standardized mean difference

the simethicone with NAC group compared to the simethicone alone group [20]. Only Krishnamurthy *et al* [25] compared the amount of volume cleansing between simethicone with NAC and NAC alone. This study found that the combination of simethicone with NAC resulted in a smaller amount of cleansing volume compared to NAC alone.

In our meta-analysis, we found that the amount of cleansing volume was significantly smaller in the simethicone with or without NAC group when compared to control (MD -29.12, 95%CI -50.60 to -7.64], P=0.008; Fig. 5). A meta-analysis comparing the cleansing volume between the simethicone with NAC group and the simethicone alone group was not conducted given the lack of suitable data. We could not perform a meta-analysis comparing the simethicone with NAC group against the NAC alone group because of the small number of studies.

Lesion detection

A total of 5 studies investigated the efficacy of the premedication on lesion detection rate [13,16,18,19,26]. Four of 5 studies found no difference in the lesion detection rate between the simethicone group compared to control, and also no difference between the simethicone with or without NAC group and controls [13,16,19,26]. On the other hand, Monrroy *et al* [18] reported a significantly higher lesion detection rate in the intervention group compared with controls. Both studies that compared the lesion detection rate between simethicone with NAC against simethicone alone concluded no significant difference [9,16] No study compared the lesion detection rate between simethicone with NAC against NAC alone.

Our meta-analysis showed that simethicone with or without NAC did not improve the lesion detection rate when

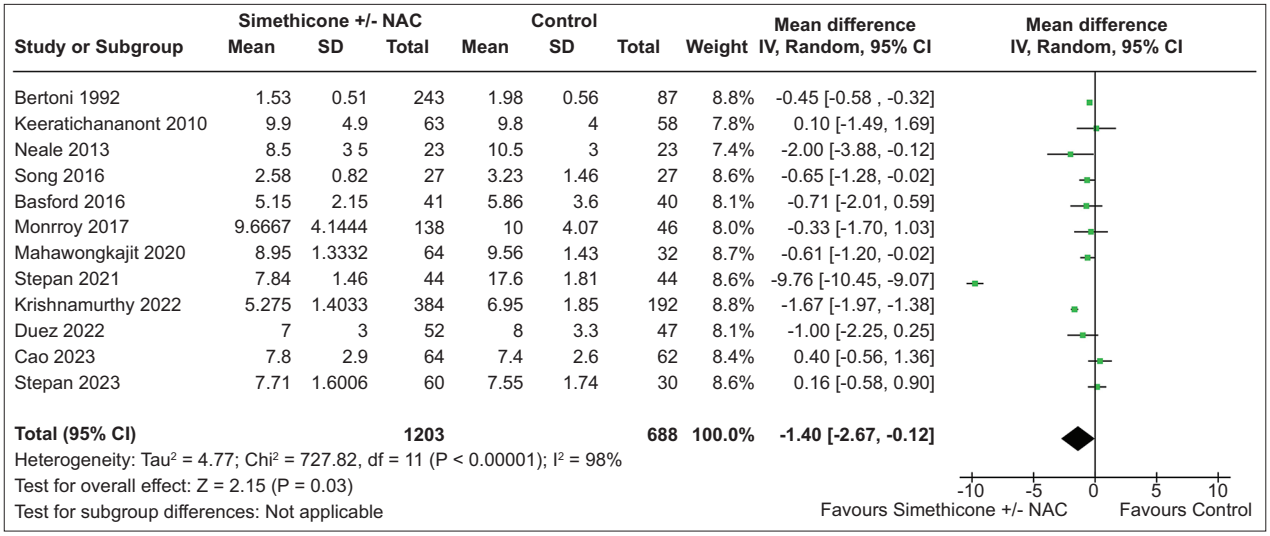

Figure 4 Procedure duration in simethicone with or without NAC vs. controls [8,10,14,15,17,18,20,23-27]. The procedure duration in the simethicone with or without NAC group is significantly shorter than in the control group (MD -1.40, 95%CI -2.67 to -0.12, P=0.03). A random-effect model was used due to the presence of significant heterogeneity (I^2=98%, P<0.001). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; MD, mean difference; NAC, N-acetylcysteine

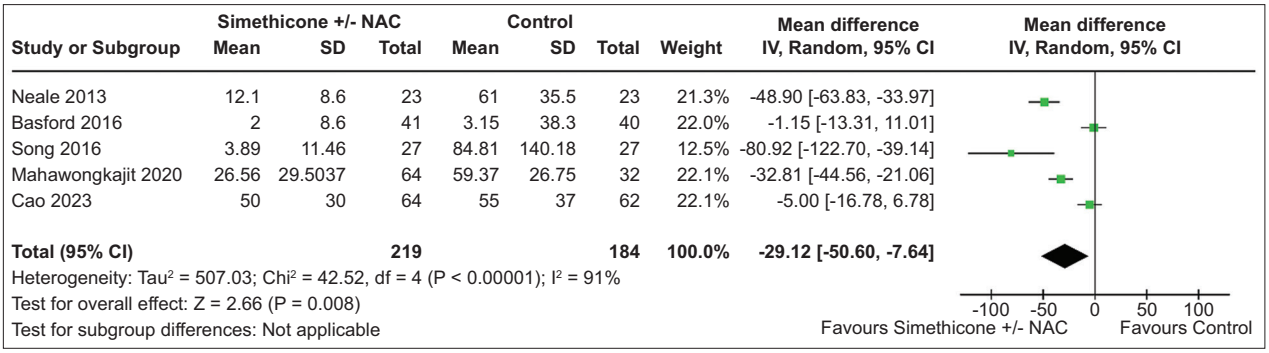

Figure 5 Cleansing volume used in simethicone with or without NAC vs. controls [14,15,17,20,26]. The amount of mucosal cleansing volume used in the simethicone with or without NAC group is significantly lower than in the control group (MD -29.12, 95%CI -50.60 to -7.64, P=0.008). A random-effect model was used due to the presence of significant heterogeneity (I^2=91%, P<0.001). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; MD, mean difference; NAC, N-acetylcysteine

compared to control (RR 1.21, 95%CI 1.07-1.36, P=0.002; Supplementary Fig. 2). In fact, the lesion detection rate was higher in the control group. Similarly, the lesion detection rate did not differ between the simethicone with NAC group and the simethicone alone group (RR 1.00, 95%CI 0.88-1.12, P=0.94; Supplementary Fig. 3).

Side-effects

A total of 13 studies evaluated the safety of simethicone and/or NAC. In general, adverse events were rare in all groups [8,10-12,14-16,18,20,21,24,25,27]. Some of the adverse events reported were nausea (n=10), vomiting (n=10), abdominal pain (n=7), flatulence (n=6), and laryngospasm (n=1) in the control group. In the simethicone group, the reported adverse events were nausea (n=12), vomiting (n=6), abdominal pain (n=2), flatulence (n=2), and regurgitation (n=1). However, there was no statistical difference between the 2 groups [10,16,24]. No studies investigated the safety of simethicone with NAC against NAC alone.

Our meta-analysis validated the safety of simethicone with or without NAC. The simethicone with or without NAC group had considerably fewer adverse events than the control group (RR 0.60, 95%CI 0.38-0.94, P=0.03; Supplementary Fig. 4). As there were zero events in both the simethicone with NAC and simethicone alone group, a meta-analysis was not possible.

Risk of bias

There was an overall moderate risk of bias in the studies included in this review. Among the 20 RCTs assessed, 9

articles [12,13,15-18,20,23,24] were considered at a low risk of bias and 11 articles [8-11,14,19,21,22,25-27] had some concerns about bias. Patients in all included studies were adequately divided into groups using simple randomization procedures. Allocation concealment was achieved using sealed opaque envelopes in 12 studies [8,11-13,15-18,20,23-25], but details about allocation concealment were not provided in 8 studies [9,10,14,21,22,25-27]. Physicians who performed endoscopies were blinded in all included studies and no incomplete outcome data were reported except in 1 study [11]. No selective reporting was found in any of the studies, and no other potential source of bias was present. The risk of bias for each study can be viewed in Supplementary Table 2.

Publication bias

For analyses that had at least 10 studies, we performed a funnel plot to detect the presence of publication bias. We constructed funnel plots for mucosal visibility (Supplementary Fig. 5) and procedure time (Supplementary Fig. 6) in the group simethicone with or without NAC against control. Both funnel plots showed asymmetry, especially the funnel plot for procedure time. This indicated that there could be publishing bias in our study and suggests that newer studies should be performed in order to overcome this bias.

Certainty of evidence

As shown in Supplementary Table 3, the certainty of evidence ranged from moderate to high. The estimated outcomes of procedure duration (simethicone with NAC vs. simethicone group), lesion detection and adverse events showed a high quality of evidence, whereas mucosal visibility, procedure duration (simethicone with or without NAC vs. control group) and cleansing volume showed a moderate quality of evidence. More specifically, we downgraded the quality of the body of evidence by 1 level in view of the significant heterogeneity (I^2>50%). Overall, the certainty of evidence in all included studies was rated moderate.

Discussion

The presence of foam and mucus may impair mucosal visibility and hide lesions during EGD. Thus, a defoaming agent, such as simethicone, and a mucolytic agent, such as NAC, have been proposed to address this issue [25]. This review aimed to determine the efficacy and safety of premedications used for EGD, namely simethicone and NAC.

Three prior meta-analyses have investigated the effectiveness of simethicone with or without NAC. Both Chen *et al* [28] and Sajid *et al* [29] reported improved visibility in the simethicone with or without NAC group. However, these 2 meta-analyses only focused on comparing the efficacy of simethicone with or without NAC vs. controls. Furthermore, these 2 studies only focused on a single outcome, namely mucosal visibility. The meta-analysis by Li *et al* [30] was more comprehensive, and investigated multiple outcomes, including mucosal visibility, procedure time, lesion detection and side-effects. However, this meta-analysis included only 10 studies that compared simethicone with or without NAC against control, and only 3 studies that compared simethicone with NAC against simethicone alone. Hence, the results of this study, especially for the comparison of simethicone with NAC against simethicone alone, might not be valid in view of the small number of studies. In contrast, our review found a total of 20 RCTs, with 6 studies comparing the efficacy of simethicone with NAC against simethicone alone. Furthermore, apart from investigating the mucosal visibility, procedure time, lesion detection and side-effects, we also evaluated the cleansing volume required during EGD. This outcome had not been investigated before, and may provide more comprehensive information regarding the efficacy of simethicone and/or NAC.

In line with previous findings, our review also concluded that the use of simethicone with or without NAC improved mucosal visibility and shortened procedure time compared with controls [28-30]. In line with the findings of Li *et al* [30], we also did not find a higher lesion detection rate in the simethicone with or without NAC group compared to control. Notably, our review found that the combination of simethicone with NAC improved visibility significantly better than simethicone alone. This result differed from the study by Li *et al* [30], in which simethicone with NAC was not better than simethicone alone in improving visibility. The difference in this finding might be due to the larger number of studies included in our review. Furthermore, our review also found that the use of simethicone with or without NAC significantly reduced the amount of cleansing volume required during EGD. This further strengthened the conclusion that simethicone with or without NAC may be beneficial in improving the quality of EGD. Similar to previous findings, our review also found that simethicone and/or NAC have a good safety profile [30].

Some of the limitations of our study include the heterogeneity in the data, such as the dosage for simethicone and NAC, as well as the different measuring tools used for evaluating mucosal visibility. Although our study had an overall low risk of bias, we found a possibility for publication bias, as proven by the presence of asymmetry in the funnel plot. We could not perform a meta-analysis to evaluate the efficacy of simethicone with NAC against NAC alone, or a comparison of simethicone with NAC against simethicone alone, in relation to cleansing volume because of the small number of studies.

In conclusion, this review found that the use of simethicone, either alone or in combination with NAC, can help improve mucosal visibility, shorten procedure time, and reduce the amount of cleansing volume required during EGD. The combination of simethicone with NAC achieved better mucosal visibility when compared to simethicone alone. Simethicone and/or NAC have a satisfactory safety profile, as the use of simethicone with or without NAC did not cause more adverse events when compared to control, supporting its use for premedication in EGD. The studies evaluated in

this review showed a low risk of bias, with a moderate grade of certainty. However, our review detected the possibility of publication bias and thus we recommend that more studies be performed regarding simethicone with/without NAC as premedication for EGD.

Acknowledgment

We would like to acknowledge the Gastrointestinal Cancer Center, MRCCC Siloam Hospital Semanggi, for all its support in conducting this research.

Summary Box

What is already known:

- Simethicone with or without N-acetylcysteine (NAC) is superior to control in improving mucosal visibility, but not superior to simethicone alone
- Simethicone with or without NAC is superior to control as regards procedure time, but not superior to simethicone alone
- Simethicone with or without NAC is not superior to control in improving lesion detection rate

What the new findings are:

- Simethicone with NAC is superior to simethicone alone in improving mucosal visibility
- Simethicone with or without NAC is superior to control in reducing the amount of cleansing volume needed during EGD
- The use of simethicone with or without NAC as premedication for EGD resulted in few or no adverse events

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Supplementary material

Supplementary Table 1 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2 for each meta-analysis.)	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 – 8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Supp Table 1

(contd...)

Supplementary Table 1 *(Continued)*

Section/topic	#	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7 – 12, Figures 2-5, Supp Figures 1-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supp Figures 5 and 6, Supp Tables 1-2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14 – 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

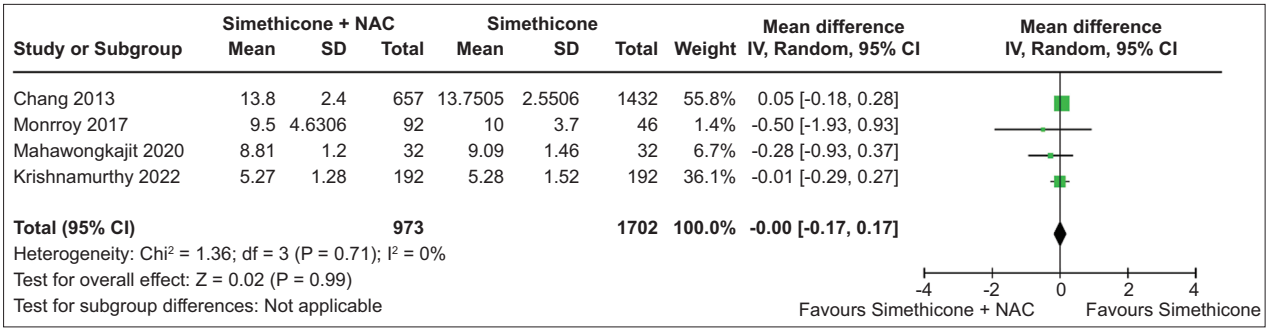
Supplementary Table 2 Risk of bias of included studies

Author, year [ref.]	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other source of bias	Overall bias
Bertoni *et al*, 1992 [8]	Low	Low	Low	Some concerns	Low	Low	Low	Some concerns
Chang *et al*, 2006 [9]	Low	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Keeratichananont *et al*, 2010 [10]	Low	Some concerns	Low	Low	Low	Low	Low	Some concerns
Ahsan *et al*, 2011 [11]	Low	Low	Low	Some concerns	Some concerns	Low	Low	Some concerns
Asl *et al*, 2011 [12]	Low	Low	Low	Low	Low	Low	Low	Low
Chang *et al*, 2013 [13]	Low	Low	Low	Low	Low	Low	Low	Low
Neale *et al*, 2013 [14]	Low	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Basford *et al*, 2016 [15]	Low	Low	Low	Low	Low	Low	Low	Low
Elvas *et al*, 2016 [16]	Low	Low	Low	Low	Low	Low	Low	Low
Song *et al*, 2016 [17]	Low	Low	Low	Low	Low	Low	Low	Low
Monroy *et al*, 2017 [18]	Low	Low	Low	Low	Low	Low	Low	Low
Liu *et al*, 2018 [19]	Low	Some concerns	Low	Low	Low	Low	Low	Some concerns
Mahawongkajit *et al*, 2020 [20]	Low	Low	Low	Low	Low	Low	Low	Low
Zuberi *et al*, 2020 [21]	Low	Some concerns	Low	Low	Low	Low	Low	Some concerns
Manfredi *et al*, 2021 [22]	Low	Some concerns	Low	Low	Low	Low	Low	Some concerns
Stepan *et al*, 2021 [23]	Low	Low	Low	Low	Low	Low	Low	Low
Duez *et al*, 2022 [24]	Low	Low	Low	Low	Low	Low	Low	Low
Krishnamurthy *et al*, 2022 [25]	Low	Low	Low	Some concerns	Low	Low	Low	Some concerns
Cao *et al*, 2023 [26]	Low	Some concerns	Low	Low	Low	Low	Low	Some concerns
Stepan *et al*, 2023 [27]	Low	Some concerns	Low	Low	Low	Low	Low	Some concerns

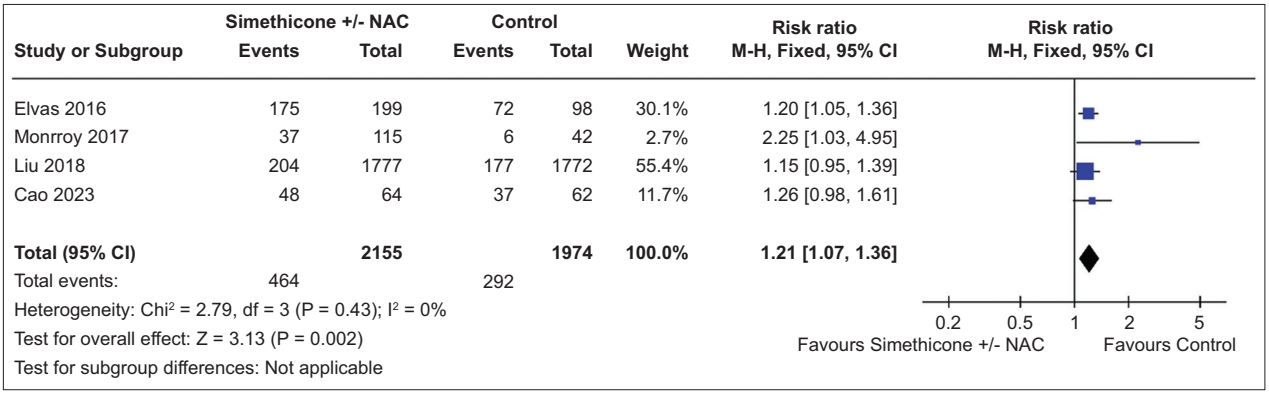
Supplementary Table 3 Certainty of evidence

Certainty Assessment							No. of Patients				Certainty
No. of study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	S only	S+NAC	NAC only	Control	
Mucosal visibility											
Simethicone±NAC vs. controls [12,15,17,18,20,21,23-27]											
11	Randomized trials	Not serious	Serious	Not serious	Not serious	None	574	451	307	682	⊕⊕⊕○ Moderate
Simethicone+NAC vs. Simethicone [9,12,13,18,20,25]											
6	Randomized trials	Not serious	Serious	Not serious	Not serious	None	1813	1048	229	308	⊕⊕⊕○ Moderate
Procedure duration											
Simethicone±NAC vs. controls [8,10,14,15,17,18,20,23-27]											
12	Randomized trials	Not serious	Serious	Not serious	Not serious	None	719	484	192	718	⊕⊕⊕○ Moderate
Simethicone+NAC vs. simethicone [13,18,20,25]											
4	Randomized trials	Not serious	Not Serious	Not serious	Not serious	None	1702	973	192	270	⊕⊕⊕⊕ High
Cleansing volume											
Simethicone±NAC vs. placebo [14,15,17,20,26]											
5	Randomized trials	Not serious	Serious	Not serious	Not serious	None	123	96	0	184	⊕⊕⊕○ Moderate
Lesion detection											
Simethicone±NAC vs. placebo [16,18,19,26]											
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1988	144	46	1978	⊕⊕⊕⊕ High
Simethicone+NAC vs. simethicone [13,16,18]											
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1996	190	0	144	⊕⊕⊕⊕ High
Adverse events											
Simethicone±NAC vs. controls [8,10,11,12,14-16,18,20,21,24,25]											
12	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	980	514	229	868	⊕⊕⊕⊕ High

NAC, N-acetylcysteine; S, simethicone

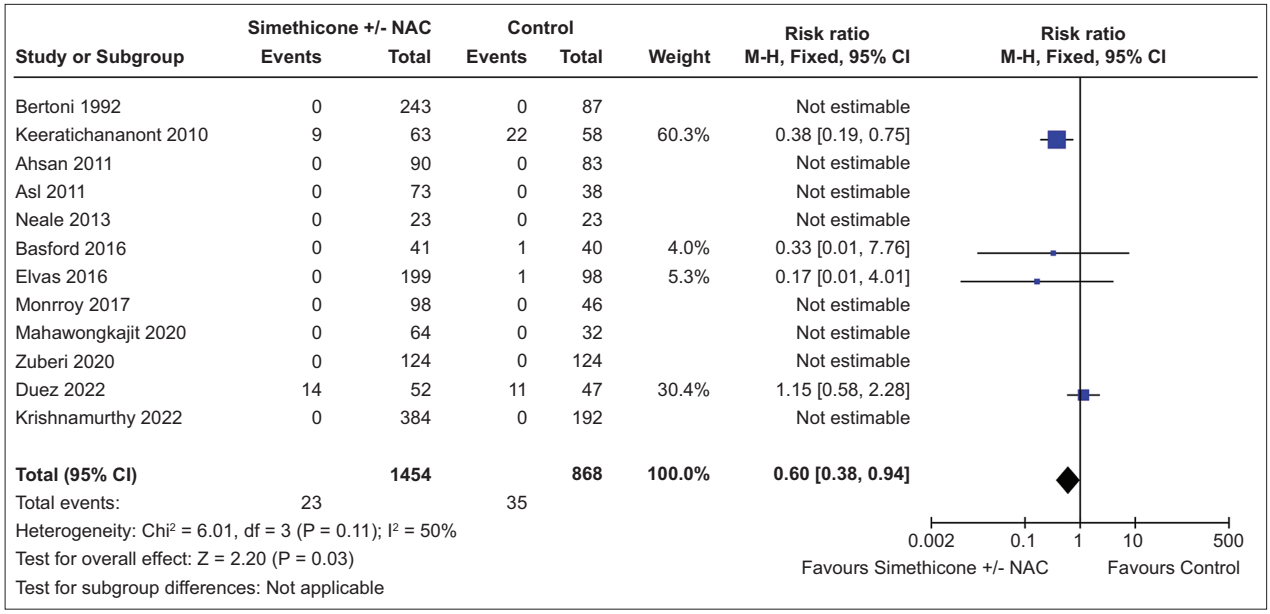


Supplementary Figure 1 Procedure duration in simethicone with NAC vs. simethicone [13,18,20,25]. The procedure duration in the simethicone with NAC group is not significantly different than the simethicone alone group (MD -0.00, 95%CI -0.17 to -0.17, P=0.99). A fixed-effect model was used given the absence of significant heterogeneity (I^2=0%, P=0.71). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; MD, mean difference; NAC, N-acetylcysteine

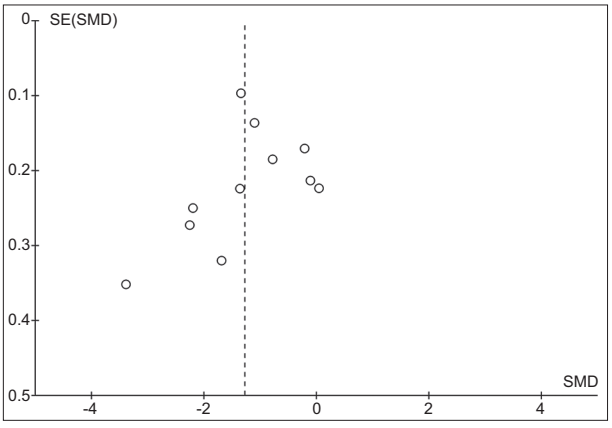


Supplementary Figure 2 Lesion detection in simethicone with or without NAC vs. controls [16,18,19,26]. The amount of lesion detected in the simethicone with or without NAC group is significantly lower than in the control group (RR 1.21, 95%CI 1.07-1.36, P=0.002). Fixed-effect model was used due to the lack of significant heterogeneity (I^2=0%, P=0.43). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; NAC, N-acetylcysteine; RR, risk ratio

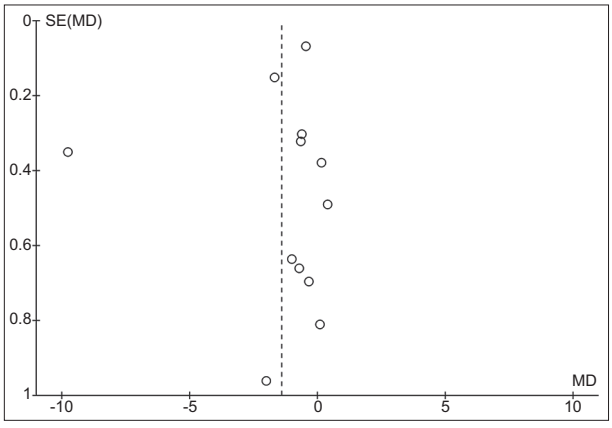
Supplementary Figure 3 Lesion detection in simethicone with NAC vs. simethicone [13,16,18]. The amount of lesion detected in the simethicone with NAC group did not differ from the simethicone alone group (RR 1.00, 95%CI 0.88-1.12, P=0.94). A fixed-effect model was used given the lack of significant heterogeneity (I^2=0%, P=0.89). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; NAC, N-acetylcysteine; RR, risk ratio



Supplementary Figure 4 Adverse events in simethicone with or without NAC vs. controls [8,10,11,12,14-16,18,20,21,24,25]. The number of adverse events in the simethicone with or without NAC group is significantly lower than in the control group (RR 0.60, 95%CI 0.38-0.94, P=0.03). A fixed-effect model was used given the lack of significant heterogeneity (I^2=50%, P=0.11). Each green box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
CI, confidence interval; NAC, N-acetylcysteine; RR, risk ratio



Supplementary Figure 5 Funnel plot of visibility comparing simethicone with or without NAC vs. controls [12,15,17,18,20,21,23-27]. The funnel plot showed slight asymmetry, indicating the possibility of publication bias. The vertical dashed line represents the overall effect of the study, while each circle represents an individual study
NAC, N-acetylcysteine; SMD, standardized mean difference



Supplementary Figure 6 Funnel plot of procedure duration comparing simethicone with or without NAC vs. controls [8,10,14,15,17,18,20,23-27]. The funnel plot showed asymmetry, indicating the possibility of publication bias. The vertical dashed line represents the overall effect of the study, while each circle represents an individual study
NAC, N-acetylcysteine; SMD, standardized mean difference