Systematic Review/Meta-analysis

The effect of using simethicone with or without *N*-acetylcysteine before gastroscopy: A meta-analysis and systemic review

Yuanfa Li, Fangjuan Du[1], Dou Fu[2]

Department of Gastroenterology, [2] Internal Medicine, Xiantao First People's Hospital, [1]Department of Gastroenterology, Liaocheng Second People's Hospital, China

Yuanfa Li and Fangjuan Du contributed equally

Abstract

Background/Aim: To assess the efficacy and safety of simethicone with or without *N*-acetylcysteine (NAC) as premedications before gastroscopy.

Materials and Methods: We searched EMBASE, PubMed, Cochrane library and Web of Science database for randomized clinical controlled trials regarding simethicone ± NAC as oral drinking agents before gastroscopy. Statistical software RevMan5.3 was used for statistical analysis.

Results: Ten randomized clinical trials that fulfilled the inclusion criteria were further pooled into a meta-analysis, which included 5,750 patients. The rate of positive findings in simethicone plus NAC group was higher than that in water group (risk ratio [RR] =1.31, 95%CI: 1.12–1.53, $P = 0.0006$) with high level of evidence. There was no significant difference on the rate of positive findings when comparing simethicone with simethicone plus NAC (RR = 1.02, 95%CI: 0.90–1.16, $P = 0.71$) and with water (RR = 1.13, 95%CI: 0.82–1.55, $P = 0.46$), respectively. Simethicone plus NAC showed better total mucosal visibility score than simethicone alone (MD = −0.14 (−0.25, −0.03), $P = 0.01$) without obvious heterogeneity. Both simethicone plus NAC and simethicone alone offer more benefit than water. The procedure time in simethicone group was shorter than that in water group (MD = −1.23 (−1.51, −0.96), $P < 0.00001$). Regarding adverse events, there was no significant difference in simethicone and water group (RR = 0.45, 95%CI: 0.2–1.0, $P = 0.05$, $I^2 = 0\%$).

Conclusions: As premedication of gastroscopy, simethicone plus NAC offers more benefit on positive findings and total mucosal visibility score.

Keywords: Gastroscopy, meta-analysis, *N*-acetylcysteine, premedication, simethicone

Address for correspondence: Dr. Yuanfa Li, No. 29, Mianzhoudadao Road, Sha Zui District Xiantao City, Hubei Province, China.
E-mail: liyuanfa1985@163.com

INTRODUCTION

Upper gastrointestinal endoscopy (esophagogastroduodenoscopy or EGD) is one of the most common diagnostic and therapeutic methods of assessing upper gastrointestinal diseases.[1,2] Improvements in the detection of premalignant lesions, early esophageal and gastric cancers will enable organ-preserving endoscopic therapy, potentially reduce the number of advanced upper gastrointestinal cancers and offer improved prognosis.[3] Furthermore, endoscopic treatment has now supplanted many surgical procedures.[4] However, the presence of foam, bubbles and mucus can preclude the benefits of endoscopy, as subtle mucosal lesions could be covered.[5]

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_538_18

How to cite this article: Li Y, Du F, Fu D. The effect of using simethicone with or without *N*-acetylcysteine before gastroscopy: A meta-analysis and systemic review. Saudi J Gastroenterol 2019;25:218-28.

Previous studies have showed that >50% of total gastric cancers in Japan were found in an early stage but probably fewer in other countries, and patients with advanced cancer suffer from poor 5-year survival rate.[6,7] Amin *et al*., in a study in UK reported that the diagnosis of 14% patients (18 of 129 patients presenting with gastric adenocarcinoma) was missed at first endoscopy.[8] Detection of the cancer at an early stage is very important to obtain good prognosis. In screening endoscopy, the overall gastric mucosa is thoroughly observed to detect any suspicious findings for neoplasia, whereas only the presence of apparent lesions that may cause symptoms or abnormal image findings are investigated.[9] One limitation of endoscopic procedure is, however, the presence of bubbles and foam in stomach and duodenum, such that it is difficult for an endoscopist to evaluate the mucosa. This will lead to decreased diagnostic accuracy, prolonged endoscopy time and decreased patient's tolerance.[10] Therefore, diagnostic accuracy of early gastric cancer can be improved by effective premedication ingestion with a defoaming agent, before upper gastrointestinal endoscopy, for the removal of bubbles.[11,12]

Many studies have shown that premedication before gastroscopy will improve the total mucosal visibility scores. Simethicone has been reported as an effective defoaming agent in many trials.[13,14] In addition to upper endoscopy, simethicone has also been used in colonoscopy and capsule endoscopy to eliminate bubbles.[15,16] Meanwhile, *N*-acetylcysteine (NAC) is widely used as a mucolytic agent in respiratory diseases previously. Some studies have demonstrated that the combination of a mucolytic such as NAC with a defoaming agent offers further benefit.[17,18]

Although some investigators do use simethicone or NAC before the endoscopic procedure,[17-19] there is a lack of systematic analysis regarding the combination of simethicone and NAC. The aim of this meta-analysis was, therefore, to assess the effectiveness of simethicone and NAC on reduction of bubbles and increasing positive findings in patients undergoing gastroscopy.

MATERIALS AND METHODS

This systematic review and meta-analysis were registered at International Prospective Register of Systematic Reviews (number CRD42018114613).

Data source and search strategy

Studies were identified by a comprehensive search in the following four databases: EMBASE, PubMed, Cochrane library and Web of science database. The search was designed and performed by two authors (Li and Du) and updated until October 1, 2018. Searches were conducted by combining the following terms: ("Simethicone" OR "dimethicone" OR "N-acetylcysteine") and (["Oesophago-gastro-duodenoscopy" and "Simethicone") OR ("gastroscopy" and "Simethicone") OR ("Oesophago-gastro-duodenoscopy" and "dimethicone") OR ("gastroscopy" and "dimethicone") OR ("Oesophago-gastro-duodenoscopy" and "N-acetylcysteine") OR ("gastroscopy" and "N-acetylcysteine"]) and ("premedication" and "Oesophago-gastro-duodenoscopy" OR "gastroscopy").

Inclusion criteria

Type of study

The types of studies included were randomized controlled clinical trials published regardless of whether these were single blind or double blind. We did not apply any date or language restrictions.

Types of participants

Adults who were planned for gastroscopy as part of their management plan were included. Participants who had contraindication to gastroscopy, previous history of surgical resection of the esophagus, stomach, or duodenum or required gastroscopy for urgent indications, such as suspected gastrointestinal bleeding, were all excluded.

Types of intervention studies of simethicone or dimethicone ± NAC for preprocedure of gastroscopy were included

Since simethicone and dimethicone have a similar defoaming mechanism, we included RCTs utilizing dimethicone. Using simethicone or dimethicone alone as an intervention or in combination with NAC could be included. However, other interventions (i.e. pronase) were excluded.

Outcome measures

At least one of the following outcomes was evaluated: (1) positive findings rate: upper gastrointestinal lesion (i.e. peptic ulcer, polyps, early upper gastrointestinal cancer); (2) mucosal visibility score: total mucosal visibility score of upper gastrointestinal tract; (3) procedure time: total time from intubation to withdrawal; and (4) rate of adverse events: frequency of adverse events (i.e., bloating).

Exclusion criteria

Exclusion criteria were as follows: (1) conference abstracts, (2) other methods of treatment as intervention measures, (3) nonrandom or uncontrolled trials, (4) not providing data on the outcome of interest, and (5) not providing adequate information to assess risk of bias (i.e., random sequence generation and allocation concealment)

Data extraction

Two authors (Du and Fu) independently performed data extraction and quality assessment, disagreements were resolved by consensus, and a third senior author (Li) was consulted when necessary. A data extraction form was predefined for data collection [Table 1], including the following entries: first author, year of publication, country, study design information, sample size, drinking time, interventions and outcomes assessed. Owing to the focus of our study, "per protocol" treatment effects were preferred in RCTs.

Assessment for risk of bias

Cochrane collaboration's assessment tool for RCT was used to assess the risk of bias, as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.[20] Summary profile of the resulting evidence was presented by using tool GRADEpro GDT online (http://www.guidelinedevelopment.org/) for every outcome.[21] The level of evidence was classified as high, moderate, low, or very low. Evaluation of the level of evidence was done on the following domains: study design, risk of bias, inconsistency, indirectness, imprecision and publication bias.

Statistical analysis

Cumulative meta-analyses were performed for outcomes reported, in a suitable and consistent format, by more than two studies. Data collected were divided into dichotomous and continuous variables, and risk ratio (RR) and mean difference (MD) were used as effect values, respectively. The effects of treatment on continuous variables were assessed as MD or standardized mean difference, as appropriate. Heterogeneity between studies was evaluated by using χ^2 (chi-squared) test with $P < 0.05$ and I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to correspond to low, medium and high levels of heterogeneity, respectively. A fixed-effect model was used when there was no significant heterogeneity between studies; otherwise a random-effect model was employed and sensitivity analysis was performed to explore heterogeneity.[22] We did sensitivity analysis to analyze the influence of individual trials by omitting included trials one by one. 95% confidence intervals (CI) were calculated, and $P < 0.05$ was regarded as statistically significant.[23,24] Statistically analyses were performed by using Review

Table 1: Baseline characteristics of the included studies

Author	Year	Area	Experimental group	Control group	Drinking time (before procedure) (min)	No. of participants	Outcomes
Keeratichananont[26]	2010	Thailand	A. Sim 133.3 mg in 60-mL water	B. 60-mLwater	15-30	A: 63; B: 58	TMVS, PT, PF, AEs
Ahsan[27]	2011	Iran	A. Sim 40 mg in 30-mL water	B. 30-mL water	15-30	A: 90; B: 83	gastric and duodenal foam/air bubbles, PT
Asl[17]	2011	Iran	A. dimethicone 100 mg in 100 water; B. Dimethicone 100+NAC 600 in 100-mL water	C. 100-mL water	20 min	A: 37; B: 36; C: 38	TMVS
Neale[28]	2013	UK	A. Sim 2.5 mL and NAC 3 mL in 100-mL water	B. 100-mL water	20	A: 23; B: 23	TMVS evaluated as flush volume, PT
Chang[18]	2014	Taiwan	A. Sim 100 mg and NAC 200 mg in 100-mL water	B. Sim 100 mg in 100-mLwater	10-30	A: 583; B: 643	TMVS, PT, AEs
Song[5]	2016	Singapore	A. Sim 100 mg in 5-mL water	B. 5-mL water	30	A: 27; B: 27	TMVS, PT, PF
Elvas[29]	2016	Portugal	A. Sim 100 mg in 100-mL water B. Sim 100 mg and NAC 600 mg in 100-mL water	C.100-mL water	15-30	A: 101; B: 98; C: 98	MVS, PF, AEs
Basford[30]	2016	UK	A. Sim 60 mg and NAC 1,000 mg in 50-mL water	B. 50-mL water	5-10	A: 41; B: 40	TMVS, PT
Liu[32]	2017	China	A. Sim 80 mg in 100-mL water	B. 100-mL water	20	A: 1777; B: 1772	MVS, PT, PF
Monrroy[31]	2017	Chile	A. Sim 200 mg in 100-mL water B. Sim 200 mg and NAC 500 mg in 100-mL water	C. 100-mL water	20	A: 46; B: 46; C: 46	TMVS, PF

Sim: Simethicone; NAC: N-acetylcysteine; TMVS: Total mucosal visibility score; MVS: Mucosal visibility score; PT: Procedure time; PF: Positive findings; AE: Adverse events

Manager (RevMan; Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Search results

Searches in the four databases returned a total of 1,356 papers (EMBASE = 407, PubMed = 238, Cochrane library = 320, and Web of Science database = 391). After removal of duplicates (n = 1142), the titles and abstracts of 214 publications were screened and 200 studies were dropped at this stage for not relevant study design (see Figure 1). Full-text articles were retrieved for 14 studies for further eligibility assessment and four of them failed to meet the inclusion criteria, of which three were excluded due to poor information for methodological quality.[13,14,25] Thus, 10 studies were included in this review.[5,17,18,26-32]

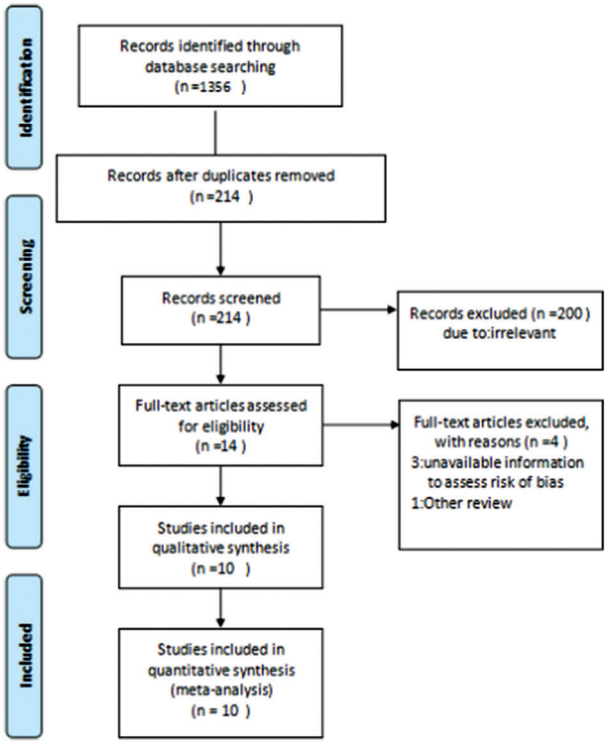

Figure 1: PRISMA: flow diagram

Study characteristics

The characteristics and data extraction of qualified studies included in the meta-analysis are summarized in Table 1. In total, 5,750 participants from 10 RCTs were included. The number of participants varied from 54[5] to 3,549.[32] All but one study[27] reported age, gender, clinical priority and indication in detail. The mean age of patients ranged from 42.2[17] to 63.8 years.[30] Male gender spanned from 33.3%[5] to 69.6%.[28] There was no significant difference in age, gender, clinical priority and indication in all the studies. Among the studies, three[5,26,27] studies compared simethicone with water, six studies[17,18,28-31] assessed simethicone alone or plus NAC versus water, and one[32] compared simethicone alone or plus pronase with water. All interventions were taken orally with water (volume ranged from 5–100 ml) 5–30 min before gastroscopy. Five studies[18,26,29,31,32] reported positive findings. Mucosal visibility scale was adopted in all studies, of which six used four-point scale,[5,17,26,27,31,32] two used three-point scale,[18,32] one used excellent/adequate/inadequate scores,[29] and one used volume of flush used.[28] Five studies[26-28,30,32] focused on procedure time and four[5,26,29,31] mentioned adverse events.

The assessment for risk of bias

Risk of bias of randomized controlled trials is summarized in Table 2. Information on the random sequence generation and allocation concealment was reported in all and nine studies except one,[26] respectively. Eight RCTs were double-blind and two studies were endoscopist-blinded.[18,28] All but three[5,18,28] specifically provided information on blinding of the outcome assessors. All studies reported a sample size calculation. Incomplete outcome data and selective report were not found in all studies. No other potential source of bias was apparently present in the included studies.

Table 2: The risk of bias in included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome data	Incomplete outcome data	Selective report	Other
Keeratichananont[26] 2010	LR	UR	LR	LR	LR	LR	LR
Ahsan[27] 2011	LR	LR	LR	LR	LR	LR	LR
Asl[17] 2011	LR	LR	LR	LR	LR	LR	LR
Neale[28] 2013	LR	LR	LR	UR	LR	LR	LR
Chang[18] 2014	LR	LR	LR	UR	LR	LR	IR
Song[5] 2016	LR	LR	LR	UR	LR	LR	LR
Elvas[29] 2016	LR	LR	LR	LR	LR	LR	LR
Basford[30] 2016	LR	LR	LR	LR	LR	LR	LR
Liu[32] 2017	LR	LR	LR	LR	LR	LR	LR
Monrroy[31] 2017	LR	LR	LR	LR	LR	LR	LR

LR: Low risk of bias; UR: Unclear risk of bias

Outcomes

Positive findings

There were five studies identified.[18,26,29,31,32] Among included studies, Liu *et al*.[32] reported precancerous lesions and early cancer only, and others reported all upper digestive tract diseases. There were no significant differences in the rate of positive findings comparing simethicone with water (RR = 1.13, 95%CI: 0.82–1.55, $P = 0.46$) [Figure 2]. Heterogeneity was significant ($I^2 = 79\%$, $P = 0.008$) and sensitivity analyses were performed. By removing the study by Keeratichananont *et al*.,[26] the heterogeneity reduced to $I^2 = 59\%$. However, we could not find a difference between this study and other two studies. Sensitivity analyses were performed, and meta-analysis did not change significantly. Similar results were observed with simethicone plus NAC versus simethicone (RR = 1.02, 95%CI: 0.90-1.16, $P = 0.71$) [Figure 3], heterogeneity was not significant ($I^2 = 0\%$, $P = 0.52$), and results were stable when sensitivity analyses were performed. We observed significant difference with simethicone plus NAC versus water. The rate of positive findings in simethicone plus NAC group was higher than that in water group (RR = 1.31, 95%CI: 1.12–1.53, $P = 0.0006$) [Figure 4]. Heterogeneity was not significant ($I^2 = 40\%$, $P = 0.2$). The resulting evidence was presented by using tool GRADEpro GDT online for every outcome. The level of evidence for simethicone versus water was moderate, because Liu *et al*.[32] reported only precancerous lesions and early cancer, but not all lesions. The level of evidence of the other two studies was high [Table 3].

Total mucosal visibility score (TMVS)

All studies reported total mucosal visibility score, but only one of the studies presented it as number of excellent/adequate/inadequate scale, and one showed volume of flush used. We could not extract TMVS from either of them. Meanwhile, Monnory *et al*.[31] reported total mucosal visibility score as mean + interquartile range (IQR), and the standard deviation was estimated from number, mean and range.[33] Compared with water, simethicone displayed significant differences on TMVS with substantial heterogeneity (mean difference, MD = −3.62, (−4.65, −2.60), $P < 0.00001$, $I^2 = 67\%$) [Figure 5]. In order to further explore the sources of heterogeneity, we conducted

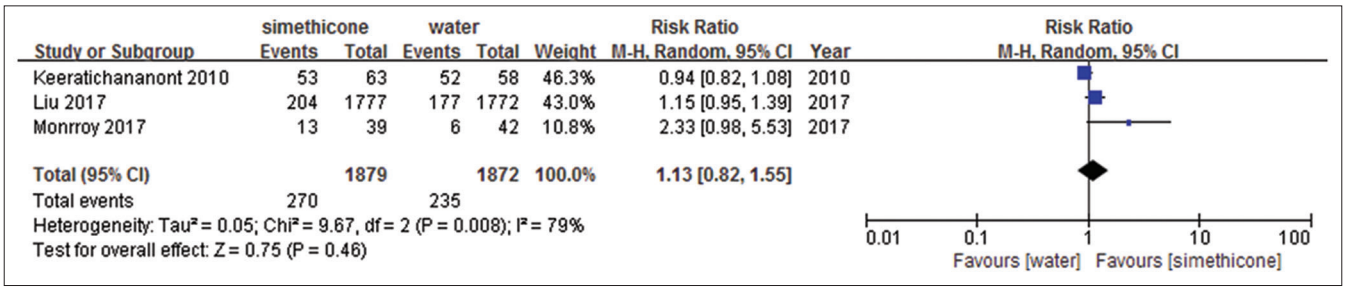

Figure 2: Positive findings (simethicone vs water)

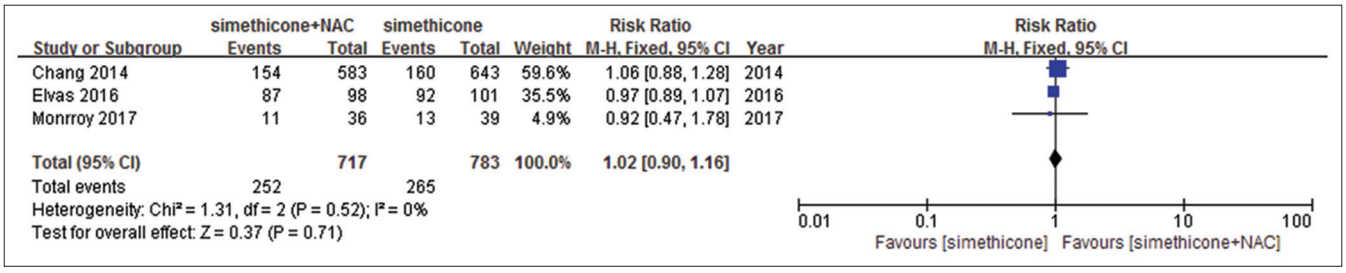

Figure 3: Positive findings (simethicone + NAC vs simethicone). NAC: *N*-acetylcysteine

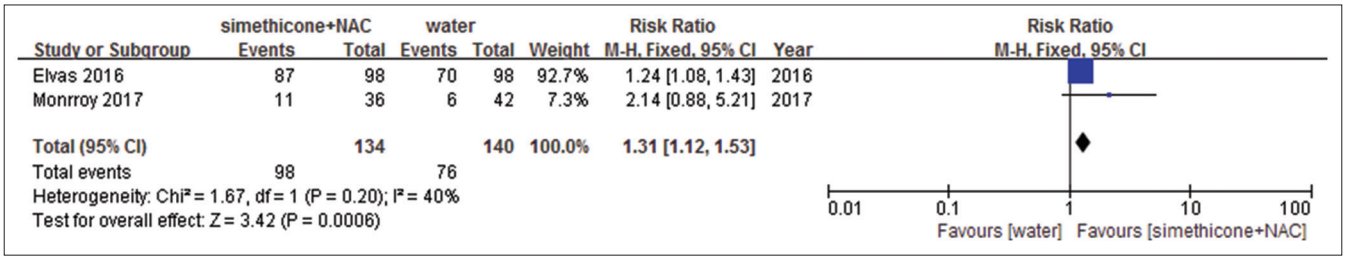

Figure 4: Positive findings (simethicone + NAC vs water). NAC: *N*-acetylcysteine

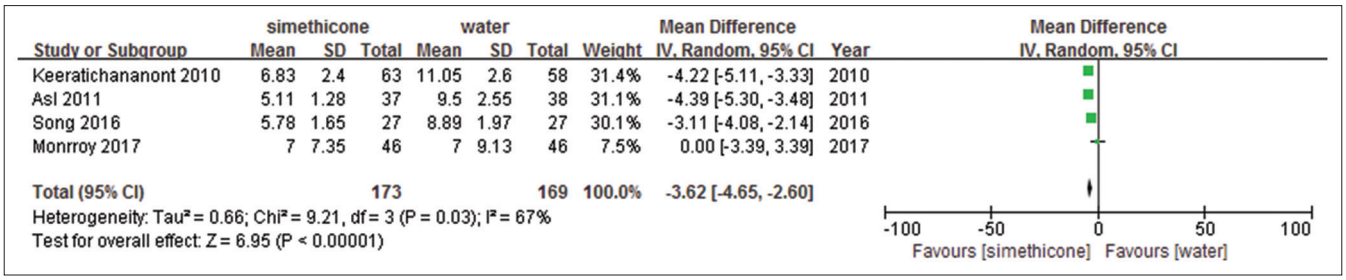

Figure 5: Total mucosal visibility score (simethicone vs water)

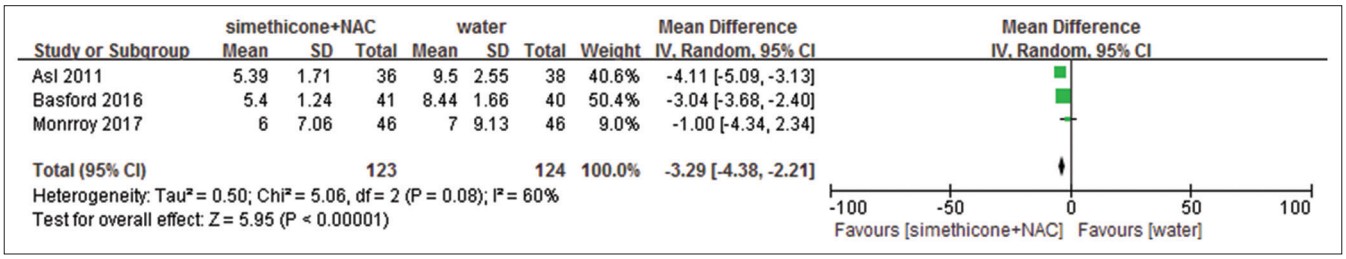

Figure 6: Total mucosal visibility score (simethicone + NAC vs water), NAC: *N*-acetylcysteine

a sensitivity analysis. When removing the study by Monnory *et al*.,[31] the heterogeneity reduced to I^2 = 52%, which potentially accounted for the source of heterogeneity. We speculated that the cause of high heterogeneity was estimated standard deviation, whereas the other three studies provided primary standard deviation. Though the heterogeneity was still high, the outcome was relatively robust. Simethicone plus NAC showed similar effect than water (MD = −3.29 (−4.38, −2.21), P < 0.00001, I^2 = 60%) [Figure 6]. We conducted a sensitivity analysis to look for heterogeneity. Removing the study by Asl *et al*.[17] the heterogeneity reduced to low (I^2 = 28%), the meta-analysis result changed to: MD = −2.7 (−4.19, −1.22, P = 0.0004). It is assumed that the source of heterogeneity might be because the Asl[17] study used dimethicone as an intervention while the other two studies used simethicone. Simethicone plus NAC showed better TMVS than simethicone alone (MD = −0.14 (−0.25, −0.03), P = 0.01, I^2 = 0%) without significant heterogeneity [Figure 7]. GRADEpro GDT showed that the level of evidence was moderate for TMVS for the three outcomes [Table 4].

Procedure time

Five studies[26,27,28,30,32] presented procedure time. For the included studies, one[28] presented time as mean + 95%CI. The standard deviation was estimated from number, mean and 95%CI.[33] Two of them[27,30] used seconds as unit, so we switched it into minutes. The procedure time in simethicone was shorter than that in water group (MD = −1.23 (−1.51, −0.96), P < 0.00001, I^2 = 31%) [Figure 8] without obvious heterogeneity. Compared with water, simethicone plus NAC showed no significant difference (MD = −0.81 (−2.06, −0.44), P = 0.21, I^2 = 0%) [Figure 9] without obvious heterogeneity. GRADEpro GDT showed level of evidence was high on procedure time [Table 5].

Adverse events

Four studies[5,26,29,31] reported adverse events (AEs). Main AEs were nausea, vomiting and bloating. There was no significant difference in simethicone and water group (RR = 0.45, 95%CI: 0.2–1.0, P = 0.05, I^2 = 0%) [Figure 10]. Heterogeneity was not significant. GRADEpro GDT showed level of evidence was high on AEs [Table 6].

DISCUSSION

Simethicone, dimethicone and NAC are widely used as anti-bubble premedication before gastroscopy, colonoscopy and capsule endoscopy.[34,35] The aim of this review was to summarize and evaluate the effect and safety of simethicone or dimethicone ± NAC as preprocedural preparation of gastroscopy. By synthesizing all extractable data from previous trials, this meta-analysis provides a better basis that we can depend on for choosing premedication. We included 10 studies comprising of 5,750 participants into the meta-analysis. Though allocation concealment and blinding of outcome data were unclear in three studies, quality assessment showed that the quality of included articles achieved the "high-quality study." Some data showed significant heterogeneity. We speculated that in the meta-analysis was due to different interventions, and in another that estimated standard deviation from mean + IQR. Unfortunately, we could not ascertain the cause of substantial heterogeneity of positive

Table 3: Grade evidence profile of positive findings

Certainty assessment							No. of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simethicone +-NAC	water	Relative (95% CI)	Absolute (95% CI)		
Simethicone vs water for positive findings (follow-up: range 1-7 days)												
3	Randomized trials	Not serious	Serious*	Not serious	Not serious	None	270/1879 (14.4%)	235/1872 (12.6%)	RR 1.13 (0.82 to 1.55)	16 more per 1,000 (from 23 fewer to 69 more)	⊕⊕⊕◯ Moderate	Critical
Simethicone + NAC VS simethicone for positive findings (follow-up: range 1-7 days)												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	252/717 (35.1%)	265/783 (33.8%)	RR 1.02 (0.90 to 1.16)	7 more per 1,000 (from 34 fewer to 54 more)	⊕⊕⊕⊕ High	Critical
Simethicone + NAC vs water for positive findings (follow-up: range 1-7 days)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	98/134 (73.1%)	76/140 (54.3%)	RR 1.31 (1.12 to 1.53)	168 more per 1,000 (from 65 more to 288 more)	⊕⊕⊕⊕ High	Critical

CI: Confidence interval; RR: Risk ratio, *Liu (2017) reported only precancerous lesions and early cancer, not all lesions

Table 4: Grade evidence profile of total mucosal visibility score

Certainty assessment							No. of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simethicone±NAC	water	Relative (95% CI)	Absolute (95% CI)		
Simethicone vs water for mucosal visibility score (follow-up: mean 1 days)												
4	Randomized trials	Not serious	Serious[a]	Not serious	NOT SERIOUS	None	173	169	-	MD 3.62 lower (4.65 lower to 2.6 lower)	⊕⊕⊕◯ Moderate	Critical
Simethicone + NAC vs water for mucosal visibility score (follow-up: mean 1 days)												
3	Randomized trials	Not serious	Serious*	Not serious	Not serious	None	123	124	-	MD 3.29 lower (4.38 lower to 2.21 lower)	⊕⊕⊕◯ Moderate	Critical
Simethicone + NAC vs simethicone for mucosal visibility score (follow up: mean 1 days)												
3	Randomized trials	Not serious	Serious*	Not serious	Not serious	None	665	726	-	MD 0.14 lower (0.25 lower to 0.03 lower)	⊕⊕⊕◯ Moderate	Critical

[a]Keeratichananont 2010[26] designed 133.3 mg as dose of simethicone, Asl 2011[17] designed 100 mg as dose of dimethicone, Song 2016[5] designed 100 mg as dose of simethicone, Monrroy 2017[31] designed 200 mg as dose of simethicone. CI: Confidence interval; RR: Risk ratio. *Mucosa visibility scores were slightly different, dose of simethicone, and NAC were also different

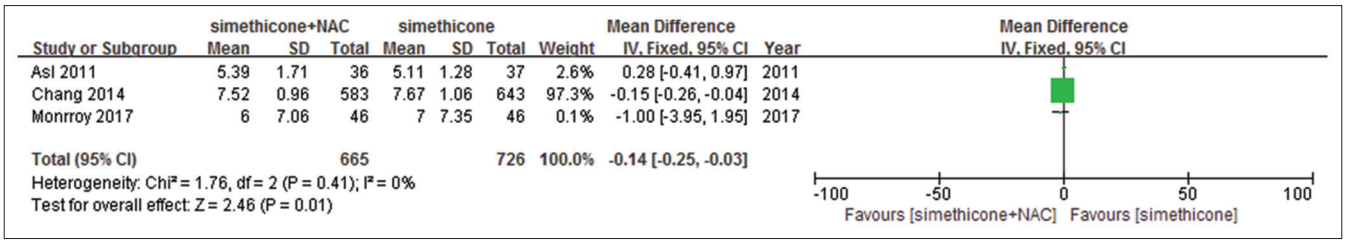

Figure 7: Total mucosal visibility score (simethicone + NAC vs simethicone), NAC = *N*-acetylcysteine

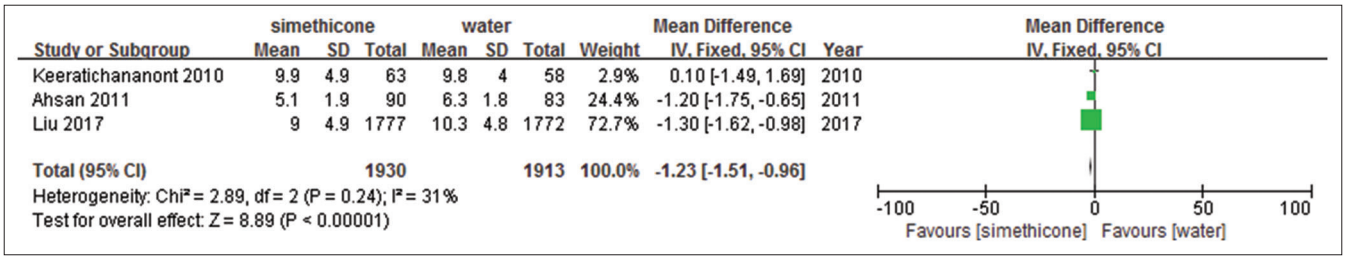

Figure 8: Procedure time (simethicone vs water)

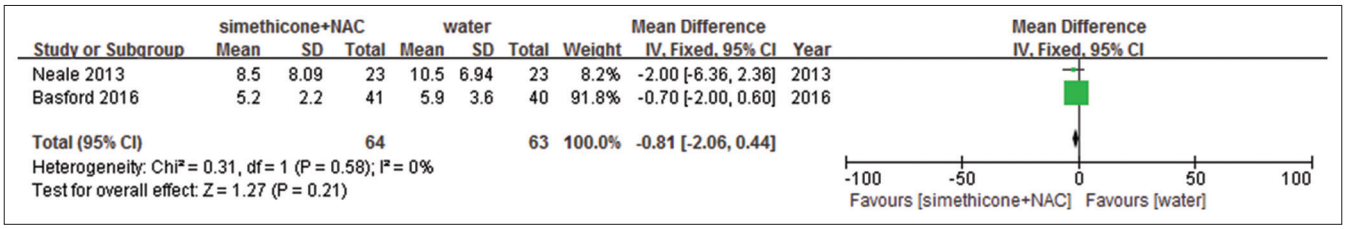

Figure 9: Procedure time (simethicone + NAC vs water). NAC = *N*-acetylcysteine

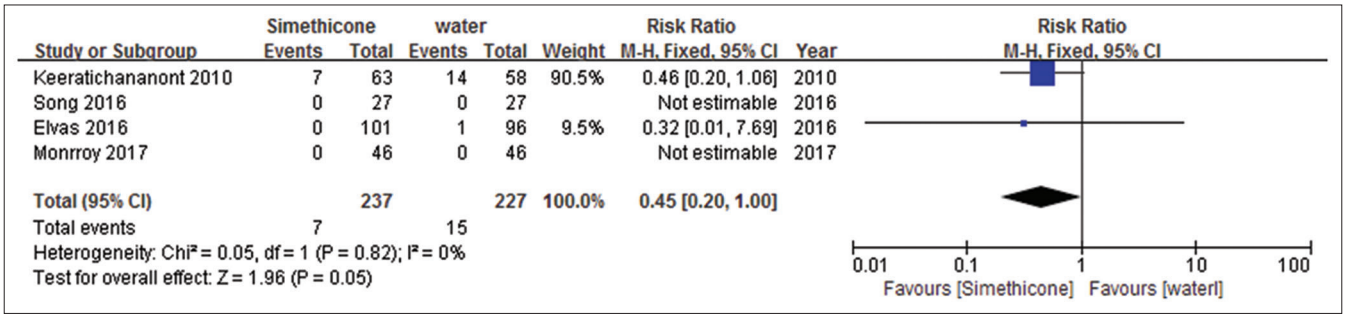

Figure 10: Adverse events (simethicone vs water)

findings (simethicone vs water). However, sensitivity analysis showed that all outcomes remained robust.

Regarding our primary outcome of preprocedural effect of simethicone ± NAC, the result showed that simethicone plus NAC premedication as comparison with water had a significantly higher positive findings rate. Medium level of heterogeneity existed; the level of evidence was high, supporting our confidence of simethicone plus NAC as premedication. Simethicone plus NAC showed no superior effect compared with simethicone alone, accompanying with considerable heterogeneity and high level of evidence. Not only simethicone plus NAC, but also simethicone alone was statistically more effective than water for mucosal visibility, with substantial heterogeneity, whereas the evidence quality was moderate. Mucosal visibility by simethicone plus NAC was significantly better, than simethicone alone, with moderate level of evidence. However, the result did not maintain consistency when sensitivity analysis was performed. Mucosal visibility is one of the important elements for gastroscopy, especially for screening for early upper gastrointestinal cancer. Since early upper gastrointestinal neoplasia is superficial, detection of minor elevations or depressions in the mucosal surface and subtle changes in color is difficult when bubbles and foam exist in esophagus and stomach. Bubbles and foam

Table 5: Grade evidence profile of procedure time

Certainty assessment							No.of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	simethicone±NAC	water	Relative (95% CI)	Absolute (95% CI)		
Simethicone vs water												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1,930	1,913	-	MD 1.23 lower (1.51 lower to 0.96 lower)	⊕⊕⊕⊕ High	Important
Simethicone + NAC vs water												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	64	63	-	MD 0.81 lower (2.06 lower to 0.44 higher)	⊕⊕⊕⊕ High	Important

CI: Confidence interval; MD: Mean difference

Table 6: Grade evidence profile of adverse events

Certainty assessment							No. of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	simethicone	water	Relative (95% CI)	Absolute (95% CI)		
Adverse events (follow-up: mean 1 day)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	7/237 (3.0%)	15/227 (6.6%)	RR 0.45 (0.20 to 1.00)	36 fewer per 1,000 (from 0 fewer to 53 fewer)	⊕⊕⊕⊕High	Important

CI: Confidence interval; RR: Risk ratio

may cover superficial and minor lesions, which can easily be missed during gastroscopic procedure. Simethicone plus NAC, as anti-bubble and mucolytic agents, is an appropriate option before gastroscopy. These defoamers and mucolytic agents are used widely in Japan and China. In our experience, adequate endoscopic visualization helps us screen entire upper gastrointestinal mucosa and increase the rate of positive findings. Procedure time in simethicone group was shorter than water without substantial heterogeneity. Mean procedure time in the included studies ranged from 5.1 to 10.5 min. The main cause for prolonged time is flushing time and aspiration. Actually, for patients without sedation, tolerability of the procedure might influence overall mucosal screening. Shorter procedure time may be suitable for patients with poor tolerance without sedation. However, there is considerable debate about procedure time. The study by Teh *et al*.[36] in 2015 showed a threefold increase in findings for a with procedure time of >7 min compared with those who were spending less time on their examination. A minimum 7-min procedure time for diagnostic EGD was recommended by European Society of Gastrointestinal Endoscopy in 2016.[37] In our opinion, if the patient prefers unsedated procedure, we suggest taking oral simethicone ± NAC before gastroscopy in order to decrease flushing times and provide enough time to screen. If the patient prefers sedation, procedure time of at least 7 min will be better for first diagnostic EGD. Additionally, adverse events were also reported. The most common adverse events were nausea, vomiting and bloating, which were within the acceptable range. Simethicone did not result in more adverse events than water.

There are two meta-analyses published previously evaluating simethicone ± NAC with water within the past 5 years, as follows: Chen *et al*.[38] and Sajid *et al*.[39] TMVS of the meta-analysis is similar to both of them. Neither of them summarized and evaluated positive findings rate, procedure time and adverse events frequency. Chen *et al*.[38] included 10 studies in 2014, 7 of which were excluded by us due to either poor information of design or simethicone combination with pronase. Sajid *et al*.[39] included seven studies in 2018. But the data synthesis and analysis were performed on all included trials regardless of whether simethicone alone or simethicone plus NAC were used. All these items above may lead to a biased. We did not perform subgroup analyses of trials because of fewer number of included studies. In effect, compared with former studies,[38,39] TMVS was similar in this meta-analysis except for positive findings rate, procedure time and adverse events frequency, which are being reported in this meta-analysis.

Nevertheless, there are several limitations in this study. Like previous reviews, the main limitation of our meta-analysis is the number of included studies. Although 10 studies were included, no more than five studies could be combined together evaluated each outcome. We did not evaluate publication bias due to the small number of included studies. Potential publication bias might exist. Otherwise, very few negative results might cause bias as well. Secondly, four mucosal visibility scales and different dose of interventions were adopted in the included studies. Standard deviation was estimated in two studies which did not provide standard deviation. Because of these reasons, heterogeneity and inconsistency existed.

Interestingly, though simethicone is used in many procedures, its safety is a cause of concern is an issue. Fluid containing simethicone may remain inside an despite reprocessing.[40] This could potentially foster result in microbial growth.[41] Its potential harmful effect needs further investigation.

In conclusion, data from currently available RCTs provide a clear rationale for suggesting the use of simethicone plus NAC as premedication before gastroscopy. However, an agreed mucosal visibility scoring tool is needed, along with the flush volume to be used and notwithstanding assessment of safety that remains to be clarified.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cohen J, Safdi MA, Deal SE, Baron TH, Chak A, Hoffman B, *et al*. Quality indicators for esophagogastroduodenoscopy. Gastrointest Endosc 2006;63(4 Suppl):S10-5.
2. Park WG, Shaheen NJ, Cohen J, Pike IM, Adler DG, Inadomi JM, *et al*. Quality indicators for EGD. Gastrointest Endosc 2015;81:17-30.
3. Veitch AM, Uedo N, Yao K, East JE. Optimizing early uppergastrointestinal cancer detection at endoscopy. Nat Rev Gastroenterol Hepatol 2015;12:660-7.
4. ASGE Standards of Practice Committee, Early DS, Ben-Menachem T, Decker GA, Evans JA, Fanelli RD, *et al*. Appropriateuse of GI endoscopy. Gastrointest Endosc 2012;75:1127-31.
5. Song M, Kwek ABE, Law NM, Ong JPL, Tan JY-L, Thurairajah PH, *et al*. Efficacy of small-volume simethicone given at least 30 min before gastroscopy. World J Gastrointest Pharmacol Ther 2016;7:572-8.
6. Marques-Lespier JM, Gonzalez-Pons M, Cruz-Correa M. Current perspectives on gastric cancer. Gastroenterol Clin North Am 2016;45:413-28.
7. Sumiyama K. Past and current trends in endoscopic diagnosis for early stage gastric cancer in Japan. Gastric Cancer 2017;20:20-7.
8. Amin A, Gilmour H, Graham L, Paterson-Brown S, Terrace J, Crofts TJ. Gastric adenocarcinoma missed at endoscopy. J R Coll Surg

Edinb. 2002;47:681-4.
9. Gotoda T, Uedo N, Yoshinaga S, Tanuma T, Morita Y, Doyama H, *et al*. Basic principles and practice of gastric cancer screening using high-definition white-light gastroscopy: Eyes can only see what the brain knows. Dig Endosc 2016;28(Suppl 1):2-15.
10. Kwan V, Devière J. Endoscopy essentials: Preparation, sedation, and surveillance. Endoscopy 2008;40:65-70.
11. Chang CC, Chen SH, Lin CP, Hsieh CR, Lou HY, Suk FM, *et al*. Premedication with pronase or N-acetylcysteine improves visibility during gastroendoscopy: An endoscopist-blinded, prospective, randomized study. World J Gastroenterol 2007;13:444-7.
12. Wu L, Cao Y, Liao C, Huang J, Gao F. Systematic review and meta-analysis of randomized controlled trials of Simethicone for gastrointestinal endoscopic visibility. Scand J Gastroenterol 2011;46:227-35.
13. Banerjee B, Parker J, Waits W, Davis B. Effectiveness of preprocedure simethicone drink in improving visibility during esophagogastroduodenoscopy: A double-blind, randomized study. J Clin Gastroenterol 1992;15:264-5.
14. McDonald GB, O'Leary R, Stratton C. Pre-endoscopic use of oral simethicone. Gastrointest Endosc 1978;24:283.
15. Yoo IK, Jeen YT, Kang SH, Lee JH, Kim SH, Lee JM, *et al*. Improving of bowel cleansing effect for polyethylene glycol with ascorbic acid using simethicone: A randomized controlled trial. Medicine (Baltimore) 2016;95:e4163.
16. Chen HB, Lian-Xiang P, Yue H, Chun H, Shu-Ping X, Rong-Pang L, *et al*. Randomized controlled trial of 3 days fasting and oral senna, combined with mannitol and simethicone, before capsule endoscopy. Medicine (Baltimore) 2017;96:e832.
17. Asl SM, Sivandzadeh GR. Efficacy of premedication with activated Dimethicone or N-acetylcysteine in improving visibility during upper endoscopy. World J Gastroenterol 2011;17:4213-7.
18. Chang WK, Yeh MK, Hsu HC, Chen HW, Hu MK. Efficacy of simethicone and N-acetylcysteine as premedication in improving visibility during upper endoscopy. J Gastroenterol Hepatol 2014;29:769-74.
19. Chen MJ, Wang HY, Chang CW, Hu KC, Hung CY, Chen CJ, *et al*. The add-on N-acetylcysteine is more effective than dimethiconealone to eliminate mucus during narrow-band imaging endoscopy: A double-blind, randomized controlled trial. Scand J Gastroenterol 2013;48:241-5.
20. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
21. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, *et al*. A GRADE Working Group approach for rating the quality of treatment effect estimatesfrom network meta-analysis. BMJ 2014; 349:g5630.
22. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley Sons; 2011.
23. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, editor. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, 2011.
24. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
25. Bertoni G, Gumina C, Conigliaro R, Ricci E, Staffetti J, Mortilla MG, *et al*. Randomizedplacebo-controlled trial of oral liquid simethicone prior to upper gastrointestinal endoscopy. Endoscopy 1992;24:268-70.
26. Keeratichananont S, Sobhonslidsuk A, Kitiyakara T, Achalanan N, Soonthornpun S. The role of liquid simethicone in enhancing endoscopicvisibility prior to esophagogastroduodenoscopy (EGD): A prospective, randomized, double-blinded, placebo-controlled trial. J Med Assoc Thai 2010;93:892-7.
27. Ahsan M, Babaei L, Gholamrezaei A, Emami MH. Simethicone for the Preparation before Esophagogastroduodenoscopy. Diagn Ther Endosc 2011;2011:484532.
28. Neale JR, James S, Callaghan J, Patel P. Premedication with N-acetylcysteine and simethicone improves mucosal visualization during gastroscopy: A randomized, controlled, endoscopist-blinded study. Eur J Gastroenterol Hepatol 2013;25:778-83.
29. Elvas L, Areia M, Brito D, Alves S, Saraiva S, Cadime AT. Premedication with simethicone and N-acetylcysteine in improving visibility during upper endoscopy: A double-blind randomized trial. Endoscopy 2017;49:139-45.
30. Basford PJ, Brown J, Gadeke L, Fogg C, Haysom-Newport B, Ogollah R. A randomized controlled trial of pre-procedure simethicone and N-acetylcysteine to improve mucosal visibility during gastroscopy-NICEVIS. Endosc Int Open 2016;4:E1197-202.
31. Monrroy H, Vargas JI, Glasinovic E, Candia R, Azúa E, Gálvez C, *et al*. Use of N-acetylcysteine plus simethicone to improve mucosal visibility during upper GI endoscopy: A double-blind, randomized controlled trial. Gastrointest Endosc 2018;87:986-93.
32. Liu X, Guan CT, He S, He S, Zhang YM, Zhao DL, *et al*. Effect of premedication on lesion detection rate and visualization of the mucosa during upper gastrointestinal endoscopy: A multicenter large sample randomized controlled double-blind study. Surg Endosc 2018;88:3548-56.
33. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
34. Zhang S, Zheng D, Wang J, Wu J, Lei P, Luo Q, *et al*. Simethicone improves bowel cleansing with low-volume polyethylene glycol: A multicenter randomized trial. Endoscopy 2018;50:412-22.
35. Chen HB, Huang Y, Chen SY, Song HW, Li XL, Dai DL, *et al*. Small bowel preparations for capsule endoscopy with mannitol and simethicone: A prospective, randomized, clinical trial. J Clin Gastroenterol 2011;45:337-41.
36. Teh JL, Tan JR, Lau LJ, Saxena N, Salim A, Tay A, *et al*. Longer examination time improves detection of gastric cancer during diagnostic uppergastrointestinal end-oscopy. Clin Gastroenterol Hepatol 2015;13:480-7.
37. Bisschops R, Areia M, Coron E, Dobru D, Kaskas B, Kuvaev R, *et al*. Performance measures for upper gastrointestinal endoscopy: A European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. Endoscopy 2016;48:843-64.
38. Chen HW, Hsu HC, Hsieh TY, Yeh MK, Chang WK. Pre-medication to improve esophagogastroduodenoscopic visibility: A meta-analysis and systemic review. Hepatogastroenterology 2014;61:1642-8.
39. Sajid MS, Rehman S, Chedgy F, Singh KK. Improving the mucosal visualization at gastroscopy: A systematic review and meta-analysis of randomized, controlled trials reporting the role of Simethicone±N-acetylcysteine. Transl Gastroenterol Hepatol 2018;3:29.
40. Ofstead CL, Wetzler HP, Johnson EA, Heymann OL, Maust TJ, Shaw MJ. Simethicone residue remains inside gastrointestinal endoscopes despite reprocessing. Am J Infect Contr 2016;44:1237-40.
41. Sutton S, Jimeniz L. A review of reported recalls involving microbiological control 2004-2011 with emphasis on FDA consideration of "objectionable organisms." Microbiology 2012;15:42-57.