Effect of Antifoaming Agent on Colorectal Benign Tumours in Colonoscopy: A Meta-Analysis

Hu Zhang

central hospital of wuhan

Jing Liu

central hospital of wuhan

Lin Song Ma

central hospital of wuhan

Heng Zhang (✉ 497697662@qq.com)

Research article

Keywords: Antifoaming agent, Simethicone, Polyethylene glycol, Colonoscopy, Meta-analysis, Systematic review

Posted Date: June 24th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-30593/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Although several trials have showed that addition of antifoaming agent to polyethylene glycol (PEG) can improve bowel preparation, whether PEG plus antifoaming agent has a beneficial role in detection of benign tumours during colonoscopy has yet to be confirmed. Our aim was to clarify whether adding simethicone to PEG solution could improve the effect of detection of colorectal benign tumours.

Methods: The PubMed, EMBASE, and Cochrane Library databases were searched for articles published prior to September 2019. The outcomes included the detection rates of colorectal adenomas and polyps.

Results: Twenty studies were eligible. Although there was no difference in the colorectal adenoma detection rate (ADR), a significant effect of simethicone for diminutive adenomas (< 10 mm) was revealed in the group with simethicone. We also found that simethicone could significantly improve the ADR in proximal colon, but did not affect the colorectal polyp detection rate (PDR). Furthermore, the subgroup analyses revealed that the beneficial effect of simethicone in the ADR among Asian ($P=0.005$) and $ADR < 25\%$ ($P=0.003$). Moreover, it was a significant finding that the low dose simethicone was as effective as the high dose one with respect to the detection of colorectal benign tumours.

Conclusions: In summary, the addition of simethicone to PEG might benefit to improve diminutive adenomas in the right colon for colonoscopy in Asia. The low-dose simethicone was recommend to the detection of colorectal benign tumours. However, large clinical trials are necessary to validate our results and determine the ideal dose of simethicone.

Background

Colorectal cancer (CRC) is one of the most common cancers worldwide. The incidence and mortality of CRC have been rapidly increasing in Asian countries [1, 2]. Early diagnosis is associated with better survival and quality of life. Currently, colonoscopy is a standard first line tool in screening, surveillance, and prevention of colorectal tumours [3, 4]. The colorectal adenoma detection rate (ADR) has been recognized as the most indicator of the quality of colonoscopy. In the consensus statement, polyethylene glycol (PEG) is recommended as the first choice for bowel preparation [5]. However, up to 24% of patients have been shown to have a poor quality of bowel preparation [6]. Inadequate bowel preparation is associated with an increased risk of missed colorectal benign tumours and greater discomfort for the patient [7–9].

Simethicone, preventing bubble formation and gas retention to alleviate bloating, is an effective and safe antifoaming agent during endoscopic procedures. A combination of simethicone and PEG has been shown to improve the visualization of the bowel for colonoscopy. Thus, simethicone may have a theoretical benefit in the detection of benign tumours in colonoscopy, especially diminutive lesions.

A large number of previous studies have evaluated the effect of simethicone in ADR during colonoscopy, but the results are inconsistent. Hence, a recently meta-analysis would be necessary. However, whether simethicone plus PEG has a beneficial role in detection of benign tumours during colonoscopy has yet to be confirmed. Therefore, we performed a meta-analysis to investigate the effect of detection of colorectal benign tumours.

Methods

Literature search

The literature was searched in PubMed, EMBASE, and Cochrane Central databases (up to September 1, 2019) using the keywords ‘colonoscopy’, ‘antifoaming agent’ or ‘simethicone’, and ‘randomized’. We also performed a manual search of the reference list of published articles.

Inclusion criteria

- (1) Study design: randomized studies as a full manuscript;
- (2) Language: limited to English;
- (3) Population: patients who underwent a colonoscopy;
- (4) Controls: PEG without simethicone for bowel preparation;
- (5) Intervention: PEG with simethicone for bowel preparation;
- (6) Outcomes: 1) primary endpoints: colorectal adenoma and polyp detection rate (ADR and PDR), 2) secondary endpoints: adverse events.

Exclusion criteria

- (1) Bowel preparation without PEG or simethicone;
- (2) Non-human studies;
- (3) Duplicate publications;

(4) Studies without available data.

Data Extraction

The three investigators (HZ, JL and LM) were independently assigned to extract the data from each primary manuscript. Discrepancies or disagreements were resolved by consensus. The extracted data included the first author, year of publication, country or region, number of patients, study design, detailed information of interventions and controls (ADR and PDR), and adverse events.

Assessment of Study Quality

The Cochrane Collaboration's risk of bias tool [10], in which the description of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data and selective outcome reporting assessed, was used to evaluate the quality of the randomized studies. The quality scale was assessed as 'low risk of bias', 'unclear risk of bias' and 'high risk of bias'.

Data Syntheses and Statistical Analyses

The odds ratio (OR) was used for discrete variables, and the mean difference (MD) and standardized difference in mean (SDM) were used for continuous variables. The pooled OR and 95% confidence intervals (CIs) were calculated from each study using either a fixed-effects model (Mantel-Haenszel method) or a random-effects model (Der Simonian and Laird method). When the heterogeneity was significant, the random-effects model was used in the pooled data; otherwise, the fixed-effects model was used. Heterogeneity among the studies was assessed using I^2 statistic or χ^2 test. $I^2 > 50\%$ or $P < 0.10$ were considered to represent significant heterogeneity. The publication bias was evaluated by the Egger's test, where $P < 0.1$ in a two-tailed test was considered to be positive. In the subgroup analyses, $P < 0.05$ for the χ^2 test indicated statistically a significant heterogeneity. For all the pooled results, a sensitivity analysis was conducted to examine the robustness by excluding one or more studies each time [11]. All the statistical analyses and plots were performed using the Review Manager statistical software version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 12.0 (Stata Corp LLC, Texas, USA).

Results

Study Selection

The literature search retrieved 169 citations, 96 of which were excluded because they were duplicates. Of the 73 potentially eligible studies, 53 publications were excluded, and 20 studies focused on comparing PEG with and without simethicone evaluated the effect of ADR and PDR. This meta-analysis was conducted in accordance with the standard guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12] (Fig. 1).

Study characteristics

The 20 studies [13–32] included 6306 patients, of whom 3162 and 3144 patients were assigned to the PEG plus simethicone group and PEG group, respectively (Tables 1 and 2). These studies were performed in five countries (China, Korean, Italy, the USA, and the Netherlands).

Table 1
Characteristics of the studies included in the meta-analysis

Author (year)	Groups		N	Dose of simethicone (mg)	Bubble score	Insertion time (min)	Withdraw time (min)	Adverse events				
								bloating	nausea	vomiting	abdominal pain	sleep disorder
Rishi (2019)	NS	2L	84	200	1.77 ± 1.00	5.48 ± 2.82	11.23 ± 3.99	NR	20	6	12	NR
	S	2L + Sim	84		1.20 ± 0.60	6.06 ± 3.55	11.73 ± 5.52	NR	13	4	10	NR
Morave (2019)	NS	4L	139	480	2.1 ± 2.15	6.19 ± 4.62	6.65 ± 1.28	NR	NR	NR	NR	NR
	S	4L + Sim	129		0.1 ± 0.15	6.06 ± 3.71	6.60 ± 1.15	NR	NR	NR	NR	NR
Zhang (2018)	NS	2L	290	1200	2.5 ± 0.7	7.5 ± 5.1	NR	59	57	20	24	57
	S	2L + Sim	289		2.8 ± 0.5	6.3 ± 3.1	NR	34	61	24	21	53
Bai (2018)	NS	2L	286	1200	3.98 ± 2.50	7.55 ± 4.19	6.87 ± 2.03	57	38	27	9	NR
	S	2L + Sim	290		1.00 ± 1.26	7.84 ± 5.12	6.47 ± 1.80	23	39	30	11	NR
Yoo (2016)	NS	2L	130	400	NR	6.75 ± 5.13	17.29 ± 13.17	71	51	15	31	39
	S	2L + Sim	130		NR	6.78 ± 3.78	13.35 ± 7.86	31	54	8	7	36
Zorzi (2016)	NS	2L	924	NR	NR	NR	10.4 ± 29.9	NR	NR	NR	NR	NR
	S	2L + Sim	940		NR	NR	10.6 ± 30.0	NR	NR	NR	NR	NR
Kump (2018)	NS	2L	193	NR	NR	NR	NR	28	26	3	37	NR
	S	2L + Sim	194		NR	NR	NR	26	26	1	34	NR
Parente (2015)	NS	4L	189	NR	NR	12 ± 7	10 ± 3	NR	NR	NR	NR	43
	S	2L + Sim	193		NR	13 ± 7	11 ± 6	NR	NR	NR	NR	37
Mussetto (2014)	NS	4L	60	NR	NR	7.8 ± 5.1	13.8 ± 9.6	21	20	NR	6	26
	S	2L + Sim	60		NR	6.5 ± 3.5	11.4 ± 9.4	15	23	NR	9	17
Leone (2013)	NS	4L	79	NR	NR	9.8 ± 3.6	NR	1	7	2	2	3
	S	2L + Sim	78		NR	10.9 ± 6.1	NR	1	5	6	5	7
Valiante (2013)	NS	4L	126	160	NR	NR	NR	33	26	NR	5	NR
	S	2L + Sim	138		NR	NR	NR	11	27	NR	13	NR
Cesaro (2013)	NS	4L	51	160	NR	9.5 ± 5.8	7.0 ± 1.8	12	23	NR	2	NR

S: PEG with simethicone group; NS: PEG group only; Sim: simethicone; N: total number of patients included; NR: not report; BBPS: Boston Bowel Preparation Scale;

	S	2L + Sim	50		NR	8.1 ± 3.8	7.6 ± 2.4	4	10	NR	6	NR
Gentile (2013)	NS	2L	60	160	NR	NR	NR	NR	6	3	1	0
	S	4L + Sim	60		NR	NR	NR	NR	12	4	1	0
Matro (2012)	NS	2L	61	400	NR	NR	NR	32	18	3	21	16
	S	2L + Sim	62		NR	NR	NR	25	22	3	17	16
Repici (2012)	NS	2L	190	160	NR	7.3 ± 3.5	NR	43	57	NR	30	NR
	S	2L + Sim	187		NR	7.9 ± 3.7	NR	47	60	NR	34	NR
Jansen (2011)	NS	2L	102	NR	NR	NR	NR	NR	NR	NR	12	NR
	S	2L + Sim	86		NR	NR	NR	NR	NR	NR	9	NR
Pontone (2011)	NS	2L	72	160	NR	NR	NR	NR	7	4	2	1
	S	4L + Sim	72		NR	NR	NR	NR	16	5	1	1
Lazzaroni (1993)	NS	4L	48	120	NR	NR	NR	26	23	NR	15	21
	S	4L + Sim	57		NR	NR	NR	26	20	NR	13	11
McNally (1989)	NS	NR	12	160	0.778 ± 0.278	NR	NR	NR	NR	NR	NR	NR
	S	NR	14		0.18 ± 0.054	NR	NR	NR	NR	NR	NR	NR
McNally (1988)	NS	NR	48	80	0.696 ± 0.112	NR	NR	NR	NR	NR	NR	NR
	S	NR	49		0.114 ± 0.05	NR	NR	NR	NR	NR	NR	NR
S: PEG with simethicone group; NS: PEG group only; Sim: simethicone; N: total number of patients included; NR: not report; BBPS: Boston Bowel Preparation Scale;												

Table 2
ADR and PDR of the studies included in the meta-analysis

Author (year)	Country	Groups		N	Adenoma					Polyp						
					N	%	Left colon	Right colon	< 10 mm	≥ 10 mm	N	%	Left colon	Right colon	< 10 mm	≥ 10 mm
Rishi (2019)	USA	NS	2L	84	NR	NR	NR	NR	NR	NR	46	54.8	NR	NR	NR	NR
		S	2L + Sim	84	NR	NR	NR	NR	NR	NR	47	56.0	NR	NR	NR	NR
Morave (2019)	USA	NS	4L	139	54	38.8	NR	NR	NR	NR	69	49.6	NR	NR	NR	NR
		S	4L + Sim	129	43	33.3	NR	NR	NR	NR	60	46.5	NR	NR	NR	NR
Zhang (2018)	China	NS	2L	290	45	15.5	22	30	46	6	93	32.1	64	46	NR	NR
		S	2L + Sim	289	64	22.1	36	48	78	6	98	33.9	67	62	NR	NR
Bai (2018)	China	NS	2L	286	41	14.3	35	32	60	7	85	29.7	NR	NR	NR	NR
		S	2L + Sim	290	61	21.0	49	85	122	12	109	37.6	NR	NR	NR	NR
Yoo (2016)	Korea	NS	2L	130	60	46.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	130	65	50	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zorzi (2016)	Italy	NS	2L	924	346	37.4	NR	NR	NR	NR	569	61.6	NR	NR	403	166
		S	2L + Sim	940	322	34.3	NR	NR	NR	NR	542	57.7	NR	NR	380	162
Kump (2018)	Austria	NS	2L	193	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	194	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Parente (2015)	Italy	NS	4L	189	NR	NR	NR	NR	NR	NR	89	49.2	NR	NR	61	NR
		S	2L + Sim	193	NR	NR	NR	NR	NR	NR	91	48.1	NR	NR	59	NR
Mussetto (2014)	Italy	NS	4L	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Leone (2013)	Italy	NS	4L	79	34	44.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	78	34	43.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Valiante (2013)	Italy	NS	4L	126	NR	NR	NR	NR	NR	NR	71	56.3	NR	NR	55	16
		S	2L + Sim	138	NR	NR	NR	NR	NR	NR	105	76.1	NR	NR	84	21
Cesaro (2013)	Italy	NS	4L	51	17	34.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	50	17	32.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gentile (2013)	Italy	NS	2L	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	4L + Sim	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Matro (2012)	USA	NS	2L	61	20	32.8	NR	NR	NR	NR	29	47.5	NR	NR	NR	NR
		S	2L + Sim	62	15	24.2	NR	NR	NR	NR	23	37.1	NR	NR	NR	NR

S:PEG with simethicone group; NS: PEG group only; PEG: polyethylene glycol; Sim: simethicone; N: total number of patients included; NR: not reported; ADR: detection rate of colorectal adenoma; PDR: detection rate of colorectal polyp.

Repici (2012)	Italy	NS	2L	190	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	187	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jansen (2011)	Netherlands	NS	2L	102	NR	NR	NR	NR	NR	NR	14	13.7	NR	NR	NR	NR
		S	2L + Sim	86	NR	NR	NR	NR	NR	NR	23	26.7	NR	NR	NR	NR
Pontone (2011)	Italy	NS	2L	72	9	12.5	8	1	NR	NR	13	18.1	NR	NR	NR	NR
		S	4L + Sim	72	12	16.7	5	7	NR	NR	22	30.6	NR	NR	NR	NR
Lazzaroni (1993)	Italy	NS	4L	48	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	4L + Sim	57	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
McNally (1989)	USA	NS	PEG	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	PEG + Sim	14	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
McNally (1988)	USA	NS	PEG	48	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	PEG + Sim	49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
S:PEG with simethicone group; NS: PEG group only; PEG: polyethylene glycol; Sim: simethicone; N: total number of patients included; NR: not reported; ADR: detection rate of colorectal adenoma; PDR: detection rate of colorectal polyp.																

Quality assessment

The Cochrane Collaboration's risk of bias tool was used to evaluate the quality of the randomized studies. Although all studies were single-blind to the examiner, the participants and the blinding of outcome assessment were not influence. Thereby the risk bias of selective reporting of each trial was considered low risk. The quality assessment of randomized studies is shown in supplementary table.

Outcomes

Primary endpoints

Colorectal adenoma detection rate (ADR)

For the primary endpoint, 9 studies reported data on the ADR, included 4069 patients (2042 patients treated with PEG plus simethicone and 2027 patients treated with PEG). The overall ADR during colonoscopy was similar in both groups: 30.9% in the PEG group and 31.0% in the PEG plus simethicone group. The heterogeneity among the studies was not significant ($I^2 = 41\%$; $P = 0.10$). According to the fixed-effects model, the pooled OR was not significant (OR = 1.01; 95% CI, 0.88–1.15; $P = 0.94$), which suggested that there was a not statistically significant difference in the ADR during colonoscopy between the two groups (Fig. 2). The Begg's funnel plots and Egger's regression test revealed that there was no significant effect of publication bias on the overall adenoma detection rate ($P = 0.307$).

Colorectal polyp detection rate (PDR)

Overall, the PDR was available in 10 studies, including 4544 patients (2279 patients treated with PEG plus simethicone and 2265 patients treated with PEG). The overall PDR during colonoscopy was higher in the group with simethicone (49.1% vs 48.0%). The heterogeneity among the studies was significant ($I^2 = 64\%$; $P = 0.003$). The pooled OR, according to a random-effects model for PDR (OR = 1.13; 95% CI, 0.89–1.42; $P = 0.31$), was not statistically significant difference between the two groups (Fig. 3). The Egger's regression test revealed that there was no significant effect of publication bias on the overall PDR ($P = 0.221$).

Secondary endpoints

Adverse events

16 studies reported data on adverse events, included bloating, vomiting, nausea, abdominal pain and sleep disturbance. Simethicone significantly reduced the incidence of bloating (15.8% vs. 25.3%). Except for bloating (OR = 0.52; 95% CI, 0.44–0.63, $P < 0.00001$), there were no statistically significant difference in other adverse events. The Egger's regression test revealed that there was no significant effect of publication bias.

Sensitivity analyses

We performed further sensitivity analyses to assess the impact on the heterogeneity by the exclusion of one or more studies at a time. There was statistically significant heterogeneity for ADR in the right colon (heterogeneity $P = 0.09$, $I^2 = 58\%$). When Bai's study was excluded, it no longer showed heterogeneity of ADR (heterogeneity $P = 0.18$, $I^2 = 45\%$). The other two outcomes had significant heterogeneity, included PDR and the adverse event of bloating. When Valiante's study was excluded, it no longer showed heterogeneity of PDR. The studies associated with the heterogeneity of each outcome were listed in Table 3.

Table 3
Sensitivity analyses and subgroup analyses of the studies included in the meta-analysis

	Number of trials	Number of patients	OR/MD (95%CL)	P value	I^2	Study associated with heterogeneity
Primary outcome						
ADR	9	4069	1.01(0.88–1.15)	0.94	41%	-
Proportion of ADR						
< 25%	3	1299	1.55(1.16–2.07)	0.003	0%	-
≥ 25%	6	2770	0.88(0.76–1.03)	0.12	0%	-
Dose of simethicone						
≥ 400 mg	5	1806	1.21(0.97–1.50)	0.09	50%	-
< 400 mg and NR	4	2263	0.89(0.75–1.06)	0.20	0%	-
Size of adenoma						
< 10 mm	2	1155	2.36(1.79–3.10)	< 0.00001	29%	-
≥ 10 mm	2	1155	1.39(0.67–2.86)	0.38	0%	-
Location of adenoma						
Right colon	3	1299	2.61 (1.43–4.76)	0.002	58%	Bai 2018 ($I^2 = 45\%$)
Left colon	3	1299	1.44(1.02–2.02)	0.04	23%	-
Regions of the populations						
Asia	3	1415	1.45(1.12–1.87)	0.005	0%	-
Not-Asia	5	2386	0.88(0.74–1.04)	0.14	0%	-
PDR	10	4544	1.13(0.89–1.42)	0.31	64%	Valiante 2013 ($I^2 = 41\%$)
Dose of simethicone						
≥ 400 mg	4	1546	1.06(0.80–1.41)	0.67	40%	-
< 400 mg and NR	6	2998	1.23(0.85–1.79)	0.28	74%	Valiante 2013 ($I^2 = 41\%$)
Size of adenoma						
< 10 mm	3	2498	0.93(0.79–1.09)	0.37	46%	-
≥ 10 mm	2	2128	0.98(0.78–1.22)	0.84	0%	-
Proportion of PDR						
< 40%	4	1487	1.29(0.97–1.72)	0.08	31%	-
≥ 40%	6	3057	1.03(0.75–1.41)	0.86	67%	Valiante 2013 ($I^2 = 0\%$)
Regions of the populations						
Asia	2	1155	1.24(0.95–1.62)	0.11	14%	-
Not-Asia	8	3389	1.10(0.82–1.47)	0.53	66%	Valiante 2013 ($I^2 = 22\%$)
Secondary outcome						
Adverse events						
bloating	11	3049	0.51(0.36–0.73)	0.0002	67%	Repici 2012 ($I^2 = 49\%$)
nausea	14	3397	1.03(0.87–1.22)	0.69	33%	-
vomiting	9	2514	1.02(0.75–1.40)	0.89	0%	-
abdominal pain	15	3669	0.89(0.72–1.10)	0.29	42%	-

OR, odds ratio; MD, mean difference; CIs, confidence intervals; ADR, detection rate of colorectal adenoma; PDR, detection rate of colorectal polyp.

	Number of trials	Number of patients	OR/MD (95%CL)	P value	I^2	Study associated with heterogeneity
sleep disturbance	9	1990	0.81(0.64–1.01)	0.06	25%	-

OR, odds ratio; MD, mean difference; CLs, confidence intervals; ADR, detection rate of colorectal adenoma; PDR, detection rate of colorectal polyp.

Subgroup analyses

The results of the subgroup analyses for the ADR and PDR in relation to sites of colorectal adenomas or polyps (right or left colon), sizes of adenomas or polyps (≥ 10 mm or < 10 mm), populations (Asia or non-Asia), dose of simethicone (≥ 400 mg or < 400 mg and NR), and proportion of ADR ($\geq 25\%$ or $< 25\%$) are shown in Table 3.

The analysis separately revealed that there was no significant difference (OR = 1.39, 95% CI: 0.67–2.86, $P = 0.38$) and heterogeneity ($P = 0.48$, $I^2 = 0\%$) between the two groups for ADR ≥ 10 mm. However, our study displayed a significant increase in the ADR for small adenomas (< 10 mm) during colonoscopy in the group with simethicone (OR = 2.36; 95% CI, 1.79–3.10; $P < 0.00001$) (Fig. 4a).

When analyzed separately, a significantly higher proportion of ADR in the right colon was present in the PEG plus simethicone group (21.5% vs 9.7%, OR = 2.61, 95% CI 1.43–4.76, $P = 0.002$) (Fig. 4b). In addition, the ADR in the left colon was also higher than that in the PEG group with borderline statistical significance (13.8% vs 10.0%, $P = 0.04$).

The subgroup analysis revealed a significant increase of ADR in the studies from Asian in the PEG with simethicone group (26.8% vs. 20.7%, OR = 1.45, 95% CI 1.12–1.87, $P = 0.005$) (Fig. 4c), and the baseline ADR $< 25\%$ of the studies included was associated with the significant benefit of simethicone (OR = 1.55, 95% CI 1.16–2.07, $P = 0.003$) (Fig. 4d). In addition, our analysis revealed that there was no significant difference of ADR between the two groups with respect to the dose of simethicone, suggesting that the low-dose simethicone was as effective as the high-dose one with respect to the detection of colorectal benign tumours.

The comparison of PDR between the two groups showed no differences for proportion of PDR, dose of simethicone, size of polyps, and the populations, when simethicone was added.

Conclusions

Simethicone is an effective antifoaming agent during endoscopic procedures. The Gastroenterological Society of Australia consensus panel found that the current evidence supported the use of simethicone for improving visibility and likely facilitates adenoma detection at colonoscopy [33]. In addition, a recently study reported that a 10% increase in the detection rate of colorectal polyp when simethicone is added to the water pump during colonoscopy [34].

Although simethicone adding to PEG solution could improve bowel cleanness and mucosal visibility [35], our results found that simethicone did not affect the total ADR and PDR. It may be related to the possible explanation that solid stool was unlikely to be cleaned, despite simethicone could improve the overall bowel cleanness. ADR has been recognized as the most indicator for quality of the colonoscopy. The current international guidelines have recommended the ADR should be $\geq 25\%$ overall as the minimal requirement of the surveillance colonoscopy [36]. In our subgroup analysis, we revealed a positive effect of simethicone with statistical significance in the low ADR group ($< 25\%$) and the studies from Asia. An interesting finding in our study was that the population of the low ADR group were all from Asian. This phenomenon might be related to the gene, diet and microbiota of Asian.

Furthermore, our subgroup analysis revealed that simethicone could significantly improve the small ADR (< 10 mm) of the proximal colon. The main reason is that simethicone can improve the bowel preparation, especially in the right colon [37]. As bubbles are more commonly present in the proximal colon, especially the ascending colon, the bubble elimination could enhance the ability to detect smaller proximal adenomas. Previous study revealed that missed cancers of the proximal colon were more often found in the poor bowel preparation [38]. But simethicone did not affect the ADR in the left colon significantly, which may be associated with the small sample of studies included. Therefore, further large clinical trials are necessary to confirm our results.

The addition of 2–3 mL of 120 mg/mL simethicone to lavage fluid was recommended [33]. In the subgroup analysis, we compared the effect of the low dose simethicone (< 400 mg) versus that of high dose simethicone (≥ 400 mg) for ADR and PDR. Our results also revealed that simethicone with high or low dose had no significant difference of ADR and PDR, suggesting that the low-dose simethicone was not inferior to the high-dose one in terms of ADR and PDR, which is similar to the study of Li et al [39]. Although residual simethicone in biopsy channels could promote biofilm formation [40], simethicone adding to PEG solution could decrease the infection risk of endoscope-transmission [31]. However, the optimal dose of SIM is yet to be ascertained [41]. Further research is required to determine the optimal dose of simethicone in clinical practice.

The strengths of our study were as follows. First, the subgroup analyses and sensitivity analyses were performed to explore the potential causes. To minimize potential bias, we performed sensitivity analyses to assess the impact on the heterogeneity by excluding one or more studies at a time and performed subgroup analyses according to the site and size of colorectal benign tumours, the population included, and the proportion of ADR. There was no significant heterogeneity found in the meta-analysis of ADR, except for the right-side ADR. When Valiente's study was excluded, it no longer showed heterogeneity of PDR. Second, our results of the subgroup analyses for ADR and PDR included the population included and the dose of simethicone

before colonoscopy. Thirdly, 20 studies were eligible for our meta-analysis. A large number of included studies allowed for firm conclusions and adequate subgroup analyses. Therefore, the results of our study are convincing.

There are several limitations to our meta-analysis. First, our meta-analysis was restricted to publications written in English, which might have produced a potential selection bias. Second, all included studies were single-blinded for outcome assessment; therefore, further double-blind RCTs should be conducted to confirm the positive effects of simethicone. Third, demographic and procedure data, such as race, diet, microbiota, and genes, may have been interesting to evaluate, but those data were not analyzed due to the limited condition. Fourth, although endoscopists were trained adequately, the effect of observer bias cannot be ignored.

In conclusion, we believe that simethicone might benefit to improve small ADR, especially in the proximal colon, for colonoscopy in Asian with low baseline ADR. The simethicone with low dose was not inferior to that with high dose with respect to the detection of colorectal benign tumours. Additional large clinical trials are necessary to validate our results and to evaluate the ideal dose of simethicone.

Abbreviations

PEG

Polyethylene glycol; ADR:Colorectal adenoma detection rate; PDR:Colorectal polyp detection rate; CRC:Colorectal cancer; OR:Odds ratio; MD:Mean difference; SDM:Standardized difference in mean; CIs:Confidence intervals; PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analysis; S:PEG with simethicone group; NS:PEG group only; Sim:Simethicone; N:Total number of patients included; NR:Not report; BBPS:Boston Bowel Preparation Scale;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

A dataset including the data analyzed may be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflicts of interest.

Funding

This project was supported by the Natural Science Foundation of Wuhan (grant number: WX18Y04). The funders had no role in the study design, data collection, and data analysis, interpretation of data and writing of the manuscript.

Authors' contributions

HZ (Heng Z) designed this study and critically revised the manuscript; HZ (Hu Z) and JL were responsible for data acquisition and extraction; HZ (Hu Z) drafted the manuscript, analyzed the data, and interpreted the results; HZ (Hu Z), LM, and JL were involved in editing the manuscript; all authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Author details

¹Department of Gastroenterology, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, Hubei Province, China

² Department of Gastroenterology, the Eighth Hospital of Wuhan, Wuhan 430014, Hubei Province, China

References

1. Ng SC, Wong SH. Colorectal cancer screening in Asia. Br Med Bull. 2013;105:29–42. DOI:10.1093/bmb/lds040]. [PMID: 23299409.

2. Shin A, Kim KZ, Jung KW, Park S, Won YJ, Kim J, Kim DY, Oh JH. Increasing trend of colorectal cancer incidence in Korea, 1999–2009. *Cancer Res Treat* 2012; 44(4): 219 – 26 [PMID:23341785 DOI:10.4143/crt.2012.44.4.219].
3. Meester RG, Doubeni CA, Lansdorp-Vogelaar I, Jensen CD, van der Meulen MP, Levin TR, Quinn VP, Schottinger JE, Zauber AG, Corley DA, van Ballegooijen M. Variation in Adenoma Detection Rate and the Lifetime Benefits and Cost of Colorectal Cancer Screening: A Microsimulation Model. *JAMA*. 2015;313(23):2349–58. DOI:10.1001/jama.2015.6251. [PMID:26080339].
4. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; 370 (14): 1298 – 306 [PMID:24693890 DOI:10.1056/NEJMoa1309086].
5. Wexner SD, Beck DE, Baron TH, Fanelli, Robert D, Hyman N, Shen B, Wasco KE. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). *Gastrointest Endosc*. 2006;63(7):894–909. DOI:10.1016/j.gie.2006.03.918. [PMID:16733101].
6. Lebowitz B, Kastrinos F, Glick M, et al. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest Endosc*. 2011;73:1207–14.
7. Clark BT, Protiva P, Nagar A, Imaeda A, Ciarleglio MM, Deng Y, et al. Quantification of Adequate Bowel Preparation for Screening or Surveillance Colonoscopy in Men. *Gastroenterology*. 2016;150(2):396–405; quiz e14-5. Epub 2015/10/07. doi:10.1053/j.gastro.2015.09.041. PubMed PMID: 26439436; PubMed Central PMCID: PMC4728019.
8. Bugajski M, Wieszarczy P, Hoff G, Rupinski M, Regula J, Kaminski MF. Modifiable factors associated with patient-reported pain during and after screening colonoscopy. *Gut*. 2018;67(11):1958–64. doi:10.1136/gutjnl-2017-313905. PubMed PMID: 28970289. Epub 2017/10/04.
9. Horton N, Garber A, Hasson H, Lopez R, Burke CA. Impact of Single-vs. Split-Dose Low-Volume Bowel Preparations on Bowel Movement Kinetics, Patient Inconvenience, and Polyp Detection: A Prospective Trial. *Am J Gastroenterol*. 2016;111(9):1330–7. doi:10.1038/ajg.2016.273. PubMed PMID: 27377521. Epub 2016/07/06.
10. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. DOI:10.1136/bmj.d5928. [PMID:22008217].
11. Higgins JP. Commentary. Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol*. 2008;37(5):1158–60. DOI:10.1093/ije/dyn204. [PMID:18832388].
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. DOI:10.1186/2046-4053-4-1. [PMID:25554246].
13. Zhang S, Zheng DP, Wang JP, Wu J, Lei P, Luo Q, Wang L, Zhang B, Wang H, Cui Y, Chen M. Simethicone improves bowel cleansing with low-volume polyethylene glycol: a multicenter randomized trial. *Endoscopy*. 2018;50(4):412–22. DOI:10.1055/s-0043-121337. [PMID:29132175].
14. Bai Y, Fang J, Zhao SB, Wang D, Li YQ, Shi RH, Sun ZQ, Sun MJ, Ji F, Si JM, Li ZS. Impact of preprocedure simethicone on adenoma detection rate during colonoscopy: a multicenter endoscopist-blinded randomized controlled trial. *Endoscopy*. 2018;50(2):128–36. DOI:10.1055/s-0043-119213. [PMID: 28985630].
15. Yoo IK, Jeon YT, Kang SH, Lee JH, Kim SH, Lee JM, Choi HS, Kim ES, Keum B, Chun HJ, Lee HS, Kim CD. Improving of bowel cleansing effect for polyethylene glycol with ascorbic acid using simethicone: A randomized controlled trial. *Medicine(Baltimore)* 2016; 95(28): e4163 [PMID:27428209 DOI:10.1097/MD.0000000000004163].
16. Zorzi M, Valiante F, Germanà B, Baldassarre G, Coria B, Rinaldi M, Heras Salvat H, Carta A, Bortoluzzi F, Cervellin E, Polo ML, Bulighin G, Azzurro M, Di Piramo D, Turrin A, Monica F. Comparison between different colon cleansing products for screening colonoscopy. A noninferiority trial in population-based screening programs in Italy. *Endoscopy* 2016; 48(3): 223 – 31 [PMID:26760605 DOI:10.1055/s-0035-1569574].
17. Kump P, Hassan C, Spada C, Brownstone E, Datz C, Haefner M, Renner F, Schoefl R, Schreiber F. Efficacy and safety of a new low-volume PEG with citrate and simethicone bowel preparation for colonoscopy (Clensia): a multicenter randomized observer-blind clinical trial vs. a low-volume PEG with ascorbic acid (PEG-ASC). *Endosc Int Open*. 2018;6(8):E907-E. DOI:10.1055/a-0624-2266. PMID:30083580.
18. Parente F, Vailati C, Bargiggia S, Manes G, Fontana P, Masci E, Arena M, Spinzi G, Baccarin A, Mazzoleni G, Testoni PA. 2-Litre polyethylene glycol-citrate- simethicone plus bisacodyl versus 4-litre polyethylene glycol as preparation for colonoscopy in chronic constipation. *Dig Liver Dis* 2015; 47(10): 857 – 63 [PMID:26232311 DOI:10.1016/j.dld.2015.06.008].
19. Mussetto A, Frazzoni L, Paggi S, Dari S, Laterza L, Radaelli F, Hassan C, Triossi O, Fuccio L. Split dosing with a low-volume preparation is not inferior to split dosing with a high-volume preparation for bowel cleansing in patients with a history of colorectal resection: a randomized trial. *Endoscopy* 2015; 47(10): 917 – 24 [PMID: 25910064 DOI:10.1055/s-0034-1391987].
20. de Leone A, Tamayo D, Fiori G, Ravizza D, Trovato C, De Roberto G, Fazzini L, Dal Fante M, Crosta C. Same-day 2-L PEG-citrate- simethicone plus bisacodyl vs split 4-L PEG: Bowel cleansing for late-morning colonoscopy. *World J Gastrointest Endosc* 2013; 5(9): 433–9 [PMID:24044042 DOI:10.4253/wjge.v5.i9.433].
21. 10.3748/wjg.v19.i33.5493] Valiante F, Bellumat A, De Bona M, De Boni M. Bisacodyl plus split 2-L polyethylene glycol-citrate- simethicone improves quality of bowel preparation before screening colonoscopy. *World J Gastroenterol* 2013;19(33): p. 5493-9 [PMID: 24023492 DOI: 10.3748/wjg.v19.i33.5493].
22. 10.1016/j.dld.2012.07.011]

- Cesaro P, Hassan C, Spada C, Petruzzello L, Vitale G, Costamagna G. A new low-volume isosmotic polyethylene glycol solution plus bisacodyl versus split-dose 4 L polyethylene glycol for bowel cleansing prior to colonoscopy: a randomised controlled trial. *Dig Liver Dis* 2013; 45(1): p. 23 – 7 [PMID: 22917636 DOI: 10.1016/j.dld.2012.07.011].
23. 10.1097/SLE.0b013e31828e389d]
Gentile M, De Rosa M, Cestaro G, Forestieri P. 2 L PEG plus ascorbic acid versus 4 L PEG plus simethicone for colonoscopy preparation: a randomized single-blind clinical trial. *Surg Laparosc Endosc Percutan Tech* 2013; 23(3): p. 276 – 80 [PMID: 23751992 DOI: 10.1097/SLE.0b013e31828e389d].
 24. 10.1038/ctg.2012.16]
Matro R, Tupchong K, Daskalakis C, Gordon V, Katz L, Kastenber D. The effect on colon visualization during colonoscopy of the addition of simethicone to polyethylene glycol-electrolyte solution: a randomized single-blind study. *Clin Transl Gastroenterol* 2012; 3: p. e26 [PMID: 23238113 DOI: 10.1038/ctg.2012.16].
 25. Repici A, Cestari R, Annese V, Biscaglia G, Vitetta E, Minelli L, Trallori G, Orselli S, Andriulli A, Hassan C. Randomised clinical trial: low-volume bowel preparation for colonoscopy – a comparison between two different PEG-based formulations. *Aliment Pharmacol Ther* 2012; 36(8): p. 717 – 24 [PMID: 22924336 DOI:10.1111/apt.12026].
 26. Jansen SV, Goedhard JG, Winkens B, van Deursen CT. Preparation before colonoscopy: a randomized controlled trial comparing different regimes. *Eur J Gastroenterol Hepatol*. 2011;23(10):897–902. DOI:10.1097/MEG.0b013e32834a3444. [PMID: 21900786.
 27. 10.3748/wjg.v17.i42.4689]
Pontone S, Angelini R, Standoli M, Patrizi G, Culasso F, Pontone P, Redler A. Low-volume plus ascorbic acid vs high-volume plus simethicone bowel preparation before colonoscopy. *World J Gastroenterol* 2011; 17(42): p. 4689-95 [PMID:22180711 DOI:10.3748/wjg.v17.i42.4689].
 28. Lazzaroni M, Petrillo M, Desideri S, Bianchi PG. Efficacy and tolerability of polyethylene glycol-electrolyte lavage solution with and without simethicone in the preparation of patients with inflammatory bowel disease for colonoscopy. *Aliment Pharmacol Ther*. 1993;7(6):655–9. DOI:10.1111/j.1365-2036.1993.tb00148.x]. [PMID:8161673.
 29. McNally PR, Maydonovitch CL, Wong RK. The effect of simethicone on colonic visibility after night-prior colonic lavage. A double-blind randomized study. *J Clin Gastroenterol*. 1989;11(6):650–2. DOI:10.1097/00004836-198912000-00010]. [PMID:2584664.
 30. McNally PR, Maydonovitch CL, Wong RK. The effectiveness of simethicone in improving visibility during colonoscopy: a double-blind randomized study. *Gastrointest Endosc*. 1988;34(3):255–8. DOI:10.1016/s0016-5107(88)71324-3]. [PMID:3292345.
 31. Moraveji S, Casner N, Bashashati M, Garcia C, Dwivedi A, Zuckerman MJ, Carrion A, Ladd AM. The role of oral simethicone on the adenoma detection rate and other quality indicators of screening colonoscopy: a randomized, controlled, observer-blinded clinical trial. *Gastrointest Endosc*. 2019;90:141–9. DOI:10.1016/j.gie.2019.03.018]. [PMID:30926430.
 32. Rishi M, Kaur J, Ulanja M, Manasewitsch N, Svendsen M, Abdalla A, Vemala S, Kewanyama J, Singh K, Singh N, Gullapalli N, Osgard E. Randomized, double-blinded, placebo-controlled trial evaluating simethicone pretreatment with bowel preparation during colonoscopy. *World J Gastrointest Endosc*. 2019;11(6):413–23. DOI:10.4253/wjge.v11.i6.413]. [PMID:31236194.
 33. Devereaux BM, Taylor AC, Athan E, Wallis DJ, Brown RR, Greig SM, Bailey FK, Vickery K, Wardle E, Jones DM. Simethicone use during gastrointestinal endoscopy: Position statement of the Gastroenterological Society of Australia. *J Gastroenterol Hepatol* 2019; 1440–746 [PMID: 31242327 DOI:10.1111/jgh.14757].
 34. Kutyla M, O'Connor S, Gurusamy AR, Gururatsakul M, Gould K, Whaley A, Kendall BJ, Hourigan L, Holtmann GJ. Influence of simethicone added to the rinse water during colonoscopies on polyp detection rates: Results of an unintended cohort study. *Digestion*. 2018;98:217–21. [PMID: 30045043 DOI: 10.1159/000489304].
 35. Pan P, Zhao SB, Li BH, Meng QQ, Yao J, Wang D, et al. Effect of supplemental simethicone for bowel preparation on adenoma detection during colonoscopy: A meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol*. 2019;34(2):314–20. doi:10.1111/jgh.14401. PubMed PMID: 30069899. Epub 2018/08/03.
 36. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D, Robertson DJ. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2017;153(1):307–23. DOI:10.1053/j.gastro.2017.05.013]. [PMID: 28600072.
 37. Benmassaoud A, Parent J. Canadian Association of Gastroenterology position statement on the impact of simethicone on endoscope reprocessing. *J Can Assoc Gastroenterol*. 2018;1(1):40–2. DOI:10.1093/jcag/gwx002]. [PMID: 31294395.
 38. Doubeni CA, Corley DA, Quinn VP, Jensen CD, Zauber AG, Goodman M, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. *Gut*. 2018;67(2):291–8. doi:10.1136/gutjnl-2016-312712. PubMed PMID: 27733426; PubMed Central PMCID: PMC5868294. Epub 2016/11/02.
 39. Li DF, Luo MH, Du QQ, et al. Efficacy of Low-vs. High-Dose Simethicone with Polyethylene Glycol for Bowel Preparation: A Prospective Randomized Controlled Trial. *J Gastroenterol Hepatol*. 2020: 1440–746 DOI:10.1111/jgh.15022.
 40. Barakat MT, Huang RJ, Banerjee S. Simethicone is retained in endoscopes despite reprocessing: impact of its use on working channel fluid retention and adenosine triphosphate bioluminescence values (with video). *Gastrointest Endosc*. 2019;89:115–23. DOI:10.1016/j.gie.2018.08.012]. [PMID: 30125574.

Figures

Figure 1

flowchart of the study selection

Figure 2

Fig 2

Figure 3

Fig 3

Figure 4

Fig 4

Figure 5

Fig 5

Figure 6

Fig 6

Figure 7

Fig 7

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SMSupplementarytable.docx](#)
- [PRISMA2009checklist.doc](#)