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ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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META-ANALYSIS

Effect of antifoaming agent on benign colorectal tumors in colonoscopy: A meta-analysis

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Abstract

BACKGROUND

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

AIM

To clarify whether adding simethicone to PEG solution could improve the detection of benign colorectal tumors.

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.

RESULT

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 taking simethicone. We also found that simethicone could significantly improve the ADR in the proximal colon but did not affect the colorectal polyp detection rate. Furthermore, the subgroup analyses revealed a beneficial effect of simethicone on the ADR among Asians (P = 0.005) and those with an ADR < 25% (P = 0.003). Moreover, it was a significant finding that the low dose simethicone was as effective as the high dose

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one with respect to the detection of benign colorectal tumors.

CONCLUSION

In summary, the addition of simethicone to PEG might improve the detection of diminutive adenomas in the right colon by colonoscopy in Asia. Low-dose simethicone was recommended for the detection of benign colorectal tumors. However, large clinical trials are necessary to validate our results and determine the ideal dose of simethicone.

Key Words: Antifoaming agent; Simethicone; Polyethylene glycol; Colonoscopy; Meta-analysis

Core Tip: The addition of simethicone to polyethylene glycol might improve the detection of diminutive adenomas in the right colon by colonoscopy in Asia. Low-dose simethicone was recommended for the detection of benign colorectal tumors.

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INTRODUCTION

Colorectal cancer (CRC) is a common cancer 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 for the screening, surveillance, and prevention of colorectal tumors[3,4]. The colorectal adenoma detection rate (ADR) is regarded as the most important indicator of colonoscopy. Polyethylene glycol (PEG) is recommended as the preferred choice for bowel preparation[5]. However, up to a quarter of patients have shown inadequate bowel preparation[6]. Inadequate bowel preparation is related to an increased risk of missed benign colorectal tumors and more discomfort for patients[7-9].

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

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

MATERIALS AND METHODS

Literature search

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

Inclusion criteria

(1) Study design: randomized studies as full manuscripts; (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; and (6) Outcomes: primary endpoints: colorectal ADR and polyp detection rate (PDR) and secondary endpoint: adverse events.

Exclusion criteria

(1) Bowel preparation without PEG or simethicone; (2) Nonhuman studies; (3) Duplicate publications; and (4) Studies without available data.

Data extraction

The data were extracted by 3 investigators (HZ, JG, and LM) independently. Disagreements were resolved by consensus. The data included the author, year, number of patients, country or region, detailed information on interventions and controls (ADR and PDR), and adverse events.

Assessment of study quality

The Cochrane Collaboration's risk of bias tool[10] 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 analysis

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

RESULTS

Study selection

The literature search retrieved 169 citations, 96 of which were excluded due to duplication. Of the 73 eligible studies, 53 studies were excluded, and 20 studies focused on comparing PEG with and without simethicone to evaluate the effects on ADR and PDR. This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[12] (Figure 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, South Korea, Italy, United States, and Netherlands).

Quality assessment

The quality of the randomized studies was evaluated by the Cochrane Collaboration's risk of bias tool. Although all of the studies were single-blind to the examiner, the blinding of outcome assessments was not affected. Therefore, the risk bias of selective reporting of each trial was considered low risk. The quality assessment of the randomized studies is shown in Supplementary Table 1.

Primary endpoints

ADR: For the primary endpoint, nine studies reported data on the ADR, including 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 hetero-

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

Ref.	Groups		*n*	Dose of simethicone in mg	Bubble score	Insertion time in min	Withdraw time in min	Adverse events				
								Bloating	Nausea	Vomiting	Abdominal pain	Sleep disorder
Rishi *et al*[32] (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 *et al*[31] (2019)	NS	4L	139	480	2.10 ± 2.15	6.19 ± 4.62	6.65 ± 1.28	NR	NR	NR	NR	NR
	S	4L + Sim	129		0.10 ± 0.15	6.06 ± 3.71	6.60 ± 1.15	NR	NR	NR	NR	NR
Zhang *et al*[13] (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 *et al*[14] (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 *et al*[15] (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 *et al*[16] (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 *et al*[17] (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 *et al*[18] (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 *et al*[19] (2015)	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 *et al*[20] (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 *et al*[21] (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 *et al*[22] (2013)	NS	4L	51	160	NR	9.5 ± 5.8	7.0 ± 1.8	12	23	NR	2	NR
	S	2L + Sim	50		NR	8.1 ± 3.8	7.6 ± 2.4	4	10	NR	6	NR
Gentile *et al*[23] (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 *et al*[24] (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 *et al*[25] (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 *et al*[26] (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 *et al*[27] (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 *et al*[28] (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 *et al*[29] (1989)	NS	NR	12	160	0.778 ± 0.278	NR	NR	NR	NR	NR	NR	NR
	S	NR	14		0.180 ± 0.054	NR	NR	NR	NR	NR	NR	NR
McNally *et al*[30] (1988)	NS	NR	48	80	0.696 ± 0.112	NR	NR	NR	NR	NR	NR	NR
	S	NR	49		0.114 ± 0.050	NR	NR	NR	NR	NR	NR	NR

N: Total number of patients included; NR: Not reported; NS: Polyethylene glycol group only; S: Polyethylene glycol with simethicone group; Sim: Simethicone.

geneity 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), suggesting that there was no statistically significant difference in the ADR during colonoscopy between the two groups (Figure 2). Begg's funnel plots and Egger's regression test revealed that there was no significant effect of publication bias on the overall ADR (P = 0.307).

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 was higher in the group treated with simethicone during colonoscopy (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 significantly different between the two groups (Figure 3). Egger's regression test revealed that there was no significant effect of publication bias on the overall PDR (P = 0.221).

Table 2 Adenoma detection rate and polyp detection rate of the studies included in the meta-analysis

Ref.	Country	Groups		N	Adenoma						Polyp					
					n	%	Left colon	Right colon	< 10 mm	≥ 10 mm	*n*	%	Left colon	Right colon	< 10 mm	≥ 10 mm
Rishi *et al*[32] (2019)	United States	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 *et al*[31] (2019)	United States	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 *et al*[13] (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 *et al*[14] (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 *et al*[15] (2016)	Korea	NS	2L	130	60	46.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		S	2L + Sim	130	65	50.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zorzi *et al*[16] (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 *et al*[17] (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 *et al*[18] (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 *et al*[19] (2015)	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 *et al*[20] (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 *et al*[21] (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 *et al*[22] (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 *et al*[23] (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 *et al*[24] (2012)	United States	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
Repici *et al*[25] (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 *et al*[26] (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 *et al*[27] (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 *et al*[28] (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 *et al*[29] (1989)	United States	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 *et al*[30] (1988)	United States	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

N: Total number of patients included; NR: Not reported; NS: Polyethylene glycol group only; PEG: Polyethylene glycol; S: Polyethylene glycol with simethicone group; Sim: Simethicone.

Secondary endpoints

Adverse events: Sixteen studies reported data on adverse events, including bloating, vomiting, nausea, abdominal pain, and sleep disturbance. Simethicone significantly reduced the incidence of bloating (15.8% *vs* 25.3%) (OR = 0.52; 95%CI: 0.44-0.63, $P < 0.00001$). There were no statistically significant differences in other adverse events. 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 the ADR in the right colon (heterogeneity $P = 0.09$, $I^2 = 58\%$). When Bai *et al*[14] was excluded, it no longer showed heterogeneity for the ADR (heterogeneity $P = 0.18$, $I^2 = 45\%$). The other two outcomes had significant heterogeneity, including the PDR and adverse events of bloating. When Valiante *et al*[21] was excluded, they no longer showed heterogeneity of the PDR. The studies associated with the heterogeneity of each outcome are 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%CI)	*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%	-
Sleep disturbance	9	1990	0.81 (0.64-1.01)	0.06	25%	-

ADR: Detection rate of colorectal adenoma; MD: Mean difference; NR: Not reported; OR: Odds ratio; 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

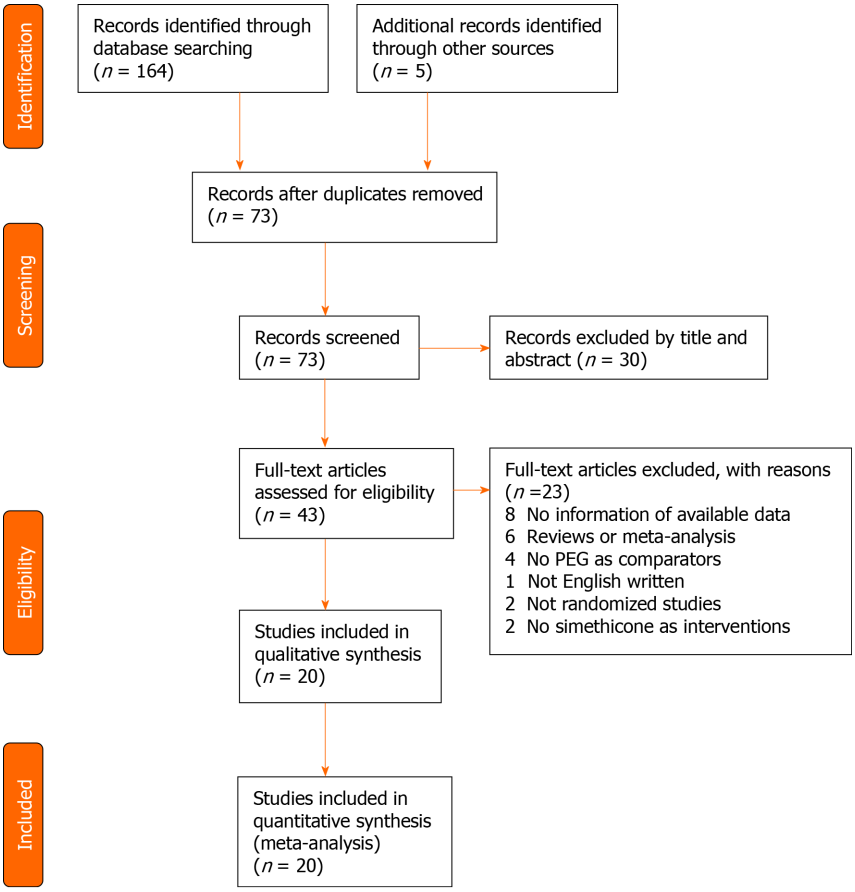


Figure 1 Flowchart of the study selection. PEG: Polyethylene glycol.

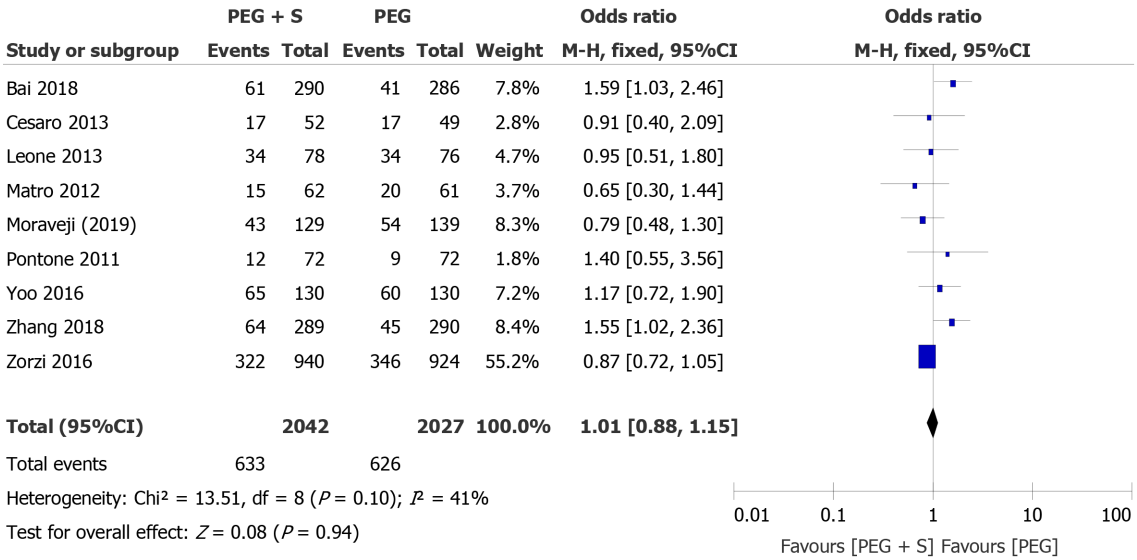


Figure 2 Forest plot of the effect of simethicone on overall adenoma detection rate. CI: Confidence interval; PEG: Polyethylene glycol; PEG+S: Polyethylene glycol plus simethicone.

adenomas or polyps (≥ 10 mm or < 10 mm), populations (Asian or non-Asian), dose of simethicone (≥ 400 mg or < 400 mg and NR), and proportion of ADR (≥ 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) or 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 treated with simethicone

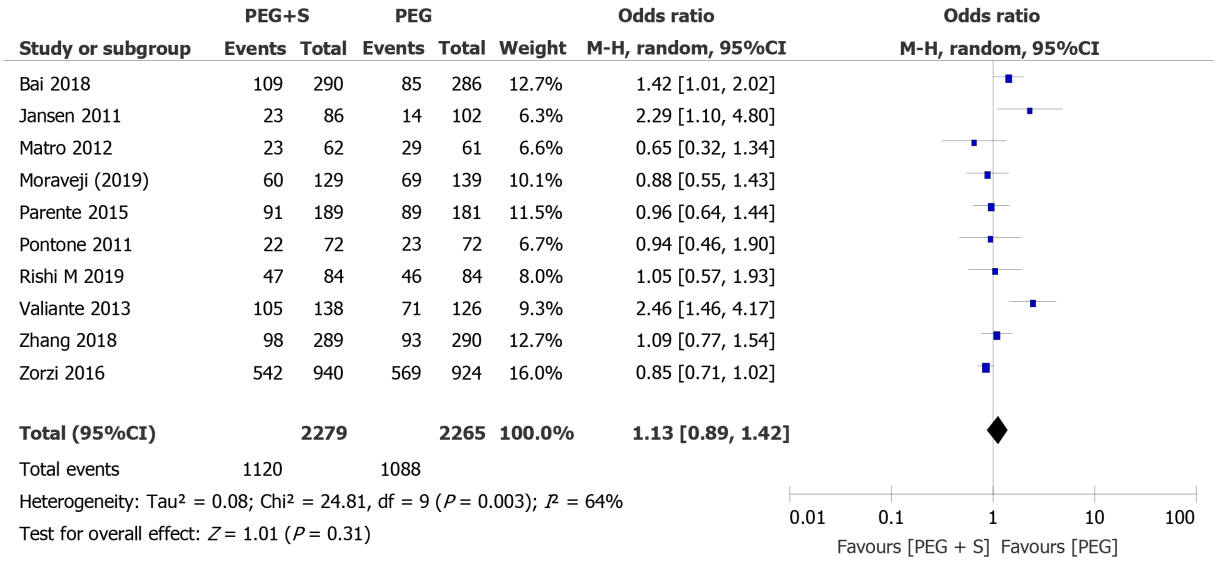


Figure 3 Forest plot of the effect of simethicone on overall polyp detection rate. CI: Confidence interval; PEG: Polyethylene glycol; PEG+S: Polyethylene glycol plus simethicone.

(OR = 2.36; 95%CI: 1.79-3.10; $P < 0.00001$) (Figure 4A).

When analyzed separately, a significantly larger 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, $P = 0.002$) (Figure 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 in the ADR in the studies from Asia in the PEG with simethicone group (26.8% *vs* 20.7%, OR= 1.45, 95%CI: 1.12-1.87, $P = 0.005$) (Figure 4C), and a baseline ADR < 25% of the studies included was associated with a significant benefit of simethicone (OR = 1.55, 95%CI: 1.16-2.07, $P = 0.003$) (Figure 4D). In addition, our analysis revealed that there was no significant difference in ADR between the two groups with respect to the dose of simethicone, suggesting that the low dose of simethicone was as effective as the high dose with respect to the detection of benign colorectal tumors.

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

DISCUSSION

The effectiveness of colonoscopy could significantly reduce the incidence and mortality of CRC[33], depending on adequate bowel preparation and removal of colorectal precancerous lesions[34]. Inadequate bowel preparation increases economic costs, prolongs procedure times, and increases the likelihood of potential lesions being missed, especially those in the proximal colon[35].

Simethicone is an effective antifoaming agent used during endoscopic procedures. The Gastroenterological Society of Australia consensus panel found that the current evidence supported the use of simethicone for improving visibility and that it likely facilitates adenoma detection at colonoscopy[36]. Although simethicone addition to PEG solution could improve bowel cleanness and mucosal visibility[37], our results found that simethicone did not affect the total ADR or PDR. This outcome might be related to the possible explanation that solid stool was unlikely to be cleaned, although simethicone could improve the overall bowel cleanness.

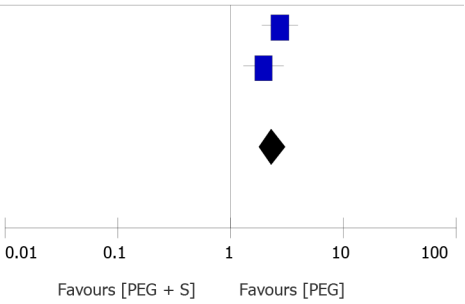
The ADR has been recognized as the most important indicator of colonoscopy quality. The current international guidelines have recommended that the ADR should be ≥ 25% overall as the minimal requirement for surveillance colonoscopy[38]. In the subgroup analysis, we revealed a positive effect of simethicone with statistical significance in the low ADR group (< 25%). An interesting finding in our study was that the population of the low ADR group was Asian. This phenomenon might be related to the genes, diet, and/or microbiota of Asians.

A

Study or subgroup	PEG + S Events	PEG + S Total	PEG Events	PEG Total	Weight	Odds ratio M-H, fixed, 95%CI
Bai 2018	122	290	60	286	51.1%	2.74 [1.89, 3.95]
Zhang 2018	78	289	46	290	48.9%	1.96 [1.30, 2.95]
Total (95%CI)		**579**		**576**	**100.0%**	**2.36 [1.79, 3.10]**
Total events	200		106			

Heterogeneity: Chi² = 1.41, df = 1 (P = 0.24); I^2 = 29%

Test for overall effect: Z = 6.15 (P < 0.00001)

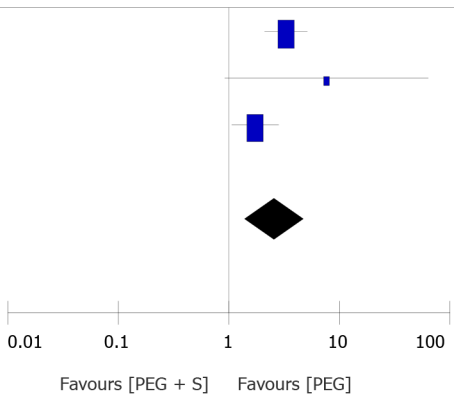


B

Study or subgroup	PEG + S Events	PEG + S Total	PEG Events	PEG Total	Weight	Odds ratio M-H, random, 95%CI
Bai 2018	85	290	32	286	47.6%	3.29 [2.11, 5.14]
Pontone 2011	7	72	1	72	7.1%	7.65 [0.92, 63.84]
Zhang 2018	48	289	30	290	45.2%	1.73 [1.06, 2.81]
Total (95%CI)		**651**		**648**	**100.0%**	**2.61 [1.43, 4.76]**
Total events	140		63			

Heterogeneity: Tau² = 0.15; Chi² = 4.74, df = 2 (P = 0.09); I^2 = 58%

Test for overall effect: Z = 3.13 (P = 0.002)

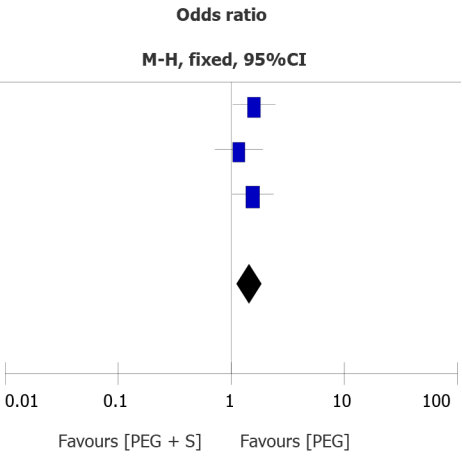


C

Study or subgroup	PEG + S Events	PEG + S Total	PEG Events	PEG Total	Weight	Odds ratio M-H, fixed, 95%CI
Bai 2018	61	290	41	286	33.4%	1.59 [1.03, 2.46]
Yoo 2016	65	130	60	130	30.7%	1.17 [0.72, 1.90]
Zhang 2018	64	289	45	290	35.8%	1.55 [1.02, 2.36]
Total (95%CI)		**709**		**706**	**100.0%**	**1.45 [1.12, 1.87]**
Total events	190		146			

Heterogeneity: Chi² = 1.04, df = 2 (P = 0.60); I^2 = 0%

Test for overall effect: Z = 2.81 (P = 0.005)



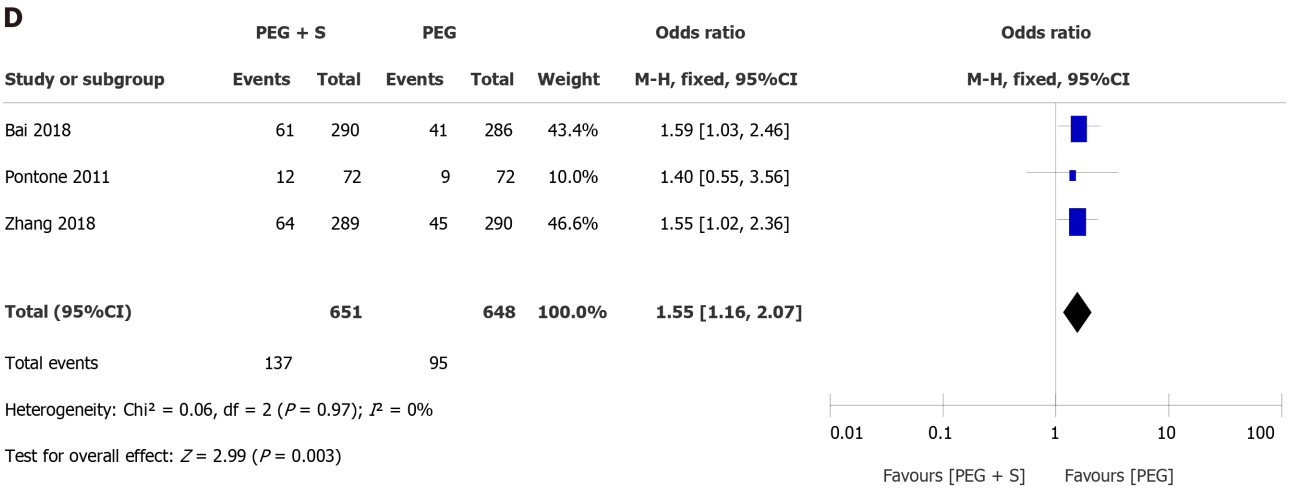


Figure 4 Forest plots of subgroup analysis. A: Forest plot of subgroup analysis of the effect of simethicone on adenoma detection rate (ADR) in trials with small adenomas (< 1 cm); B: Forest plot of subgroup analysis of the effect of simethicone on ADR in trials with right-side adenomas; C: Forest plot of subgroup analysis of the effect of simethicone on ADR in trials of the population from Asia; D: Forest plot of subgroup analysis of the effect of simethicone on ADR in trials with the baseline ADR < 25%. CI: Confidence interval; PEG: Polyethylene glycol; PEG+S: Polyethylene glycol plus simethicone.

The most important finding in our study was that simethicone could significantly improve detection of small adenomas (< 10 mm) of the proximal colon. The main reason is that simethicone can improve bowel preparation, especially in the right colon[39]. Because bubbles usually present in the ascending colon, bubble elimination could enhance the ability to detect smaller proximal adenomas. A previous study revealed that missed cancers in the proximal colon were more often found with poor bowel preparation[40]. A previous study reported that CRC in Eastern China has undergone a rightward change in the site distribution over the past two decades[41]. Therefore, improving the effectiveness of right-sided cleansing plays a key role in improving compliance with screening programs, which is crucial for screening efficiency in CRC prevention. However, simethicone did not significantly affect the ADR in the left colon, which might be associated with the small samples in the studies included. Therefore, further large clinical trials are necessary to confirm our results.

Although a recent study reported a 10% increase in the detection rate of colorectal polyps when simethicone was added to the water pump during colonoscopy[42], residual simethicone in biopsy channels could promote biofilm formation[43]. In addition, endoscopists with higher ADRs likely spent more time cleaning the colon. Simethicone addition to PEG solution could decrease the infection risk from endoscope transmission[31]. However, the optimal dose of simethicone has yet to be ascertained[44]. 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 low-dose simethicone (< 400 mg) to that of high-dose simethicone (≥ 400 mg) for the ADR and PDR. Our results revealed that simethicone at a high or low dose made no significant difference in terms of ADR and PDR, suggesting that the low dose was not inferior to the high dose, similar to the study of Li *et al*[45]. Further research is required to determine the optimal dose of simethicone in clinical practice.

The strengths were as follows in our study. First, subgroup analyses and sensitivity analyses were conducted to seek potential reasons. To reduce possible bias, we conducted sensitivity analyses to assess the impact on the heterogeneity by excluding one or more studies at a time and performing subgroup analyses according to the site and size of colorectal benign tumors, the population included, and the proportion of ADR. There was no significant heterogeneity found in the meta-analysis of the ADR, except for right-side ADR. When Valiante *et al*[21] study was excluded, it no longer showed heterogeneity of the PDR. Second, our results of the subgroup analyses for the ADR and PDR included the population included and the dose of simethicone before colonoscopy. Third, 20 studies were included in our meta-analysis. This large number of 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 potential selection bias. Second, all of the included studies were single blinded for outcome assessment; therefore, further double-blind randomized controlled trials should be

conducted to confirm the positive effects of simethicone. Third, demographic and procedure data, such as race, diet, microbiota, and genes, might have been interesting to evaluate, but these data were not analyzed due to the limited condition. Fourth, although the endoscopists were trained adequately, the effects of observer bias cannot be ignored.

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

The incidence and mortality of colorectal cancer have been rapidly increasing in Asian countries, and inadequate bowel preparation is related to an increased risk of missed benign colorectal tumors and more discomfort for patients.

Research motivation

Simethicone is an effective and safe antifoaming agent for use during endoscopic procedures. A combination of simethicone and polyethylene glycol has been shown to improve the visualization of the bowel for colonoscopy.

Research objectives

We performed a meta-analysis to investigate its effect on the detection of benign colorectal tumors.

Research methods

The PubMed, EMBASE, and Cochrane Library databases were searched for articles published.

Research results

A significant effect of simethicone for diminutive adenomas (< 10 mm) and the adenoma detection rate in the proximal colon were revealed in the group taking simethicone. 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 tumors.

Research conclusions

The addition of simethicone to polyethylene glycol might improve the detection of diminutive adenomas in the right colon by colonoscopy in Asia. Low-dose simethicone was recommended for the detection of benign colorectal tumors.

Research perspectives

We believe that simethicone might improve small adenoma detection rates, especially in the proximal colon for colonoscopy in Asians with low baseline adenoma detection rates.

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