Meta-Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(2) 515–527

DOI: 10.1177/0300060518819626
journals.sagepub.com/home/imr
SAGE

Diagnostic application of water exchange colonoscopy: A meta-analysis of randomized controlled trials

Xiufang Xu, Dongqiong Ni, Yuping Lu and Xuan Huang

Abstract

Background: Few well-designed studies have investigated water exchange colonoscopy (WE). We performed a meta-analysis to comprehensively evaluate the clinical utility of WE based on high-quality randomized controlled trials (RCTs) and to compare the impacts of WE, water immersion colonoscopy (WI), and gas-insufflation colonoscopy.

Methods: We searched the Cochrane Library, MEDLINE, Embase, PubMed, Elsevier, CNKI, VIP, and Wan Fang Data for RCTs on WE. We analyzed the results using fixed- or random-effect models according to the presence of heterogeneity. Publication bias was assessed by funnel plots.

Results: Thirteen studies were eligible for this meta-analysis. The colonoscopic techniques included WE as the study group, and WI and air- or CO_2-insufflation colonoscopy as control groups. WE was significantly superior to the control procedures in terms of adenoma detection rate, proportion of painless unsedated colonoscopy procedures, and cecal intubation rate according to odds ratios. WE was also significantly better in terms of maximal pain score and patient satisfaction score according to mean difference.

Conclusions: WE can remarkably improve the adenoma detection rate, proportion of painless unsedated colonoscopy procedures, patient satisfaction, and cecal intubation rate, as well as reducing the maximal pain score in patients undergoing colonoscopy.

Keywords

Water exchange, water immersion, air insufflation, CO_2-insufflation, colonoscopy, randomized controlled trial, meta-analysis

Date received: 28 August 2018; accepted: 22 November 2018

The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

Corresponding author:
Xuan Huang, The First Affiliated Hospital of Zhejiang Chinese Medical University, No. 54 Youdian Road, Hangzhou 310006, China.
Email: huangxuan1976@163.com

Introduction

Colonoscopy plays an important role in the diagnosis and treatment of colorectal diseases, especially in screening for colorectal cancer.[1–3] Conventional air-insufflation colonoscopy (AI) often causes abdominal distension, abdominal pain, and other discomfort during the procedure;[4,5] however, technical developments have led to the introduction of water exchange (WE) and water immersion (WI) techniques.[6] In WE, the cecal intubation process proceeds more slowly with the infused water suctioned during insertion rather than during withdrawal, and the suctioning of any retained gas pockets as they are encountered. WI involves infusing water solely for the purpose of expanding the lumen and intubating the cecum, with suctioning of the water during withdrawal. WE has been reported to be clinically more valuable than WI,[7–9] especially in terms of the adenoma detection rate (ADR) and cecal intubation rate.[10,11] One report showed that the cecal intubation time of WE was longer than either WI and AI,[12] while WI has also been suggested to have better diagnostic and therapeutic performances than AI.[6,10,13] Recent studies of CO_2-insufflation colonoscopy, which uses CO_2 instead of air to achieve minimal distension of the lumen throughout the insertion phase and during withdrawal, demonstrated superiority of CO_2 in reducing postprocedural pain. Three previous meta-analyses have analyzed the use of WE;[14–16] however, Chen et al.[14] only analyzed WE versus WI, Zhang et al.[15] compared any two of AI, CO_2-insufflation colonoscopy, WI, and WE, and did not focus on WE, while Fuccio et al.[16] separately compared WI and/or WE with AI and/or CO_2-insufflation colonoscopy. In contrast, in the current meta-analysis, we set WE as the experimental group and the three other methods (WI, AI, CO_2-insufflation colonoscopy) as the control groups, and compared the subgroups. This meta-analysis thus comprehensively evaluated the clinical utility of WE based on high-quality RCTs.

Methods

Inclusion and exclusion criteria

Inclusion criteria. Studies were included if they met the following criteria: 1) contained case inclusion criteria, and the study design was an RCT with a quality level of A or B (see 'Quality assessment' below); 2) were designed to study WE; 3) had a study group that received WE and a control group that received AI, CO_2-insufflation colonoscopy, or WI; and 4) included one or more of the following indicators for comparing efficacy between WE and other colonoscopic techniques: cecal intubation rate, ADR, proportion of painless unsedated colonoscopy, maximal pain score, and patient satisfaction.

Exclusion criteria. Studies were excluded if they met any of the following criteria: 1) incomplete data; 2) duplicate publications (only those with credible data were included); 3) had a control group that underwent WE combined with other colonoscopic techniques; or 4) were a RCT without WE as one of the methods.

Literature retrieval and data collection

We searched the Cochrane Library, MEDLINE, Embase, PubMed, Elsevier and Technological Periodical Database, and Wanfang Data prior to July 2018. The search excluded studies involving children or pregnant women, and review articles. References in the included articles were checked to identify any study that might have been omitted. The articles

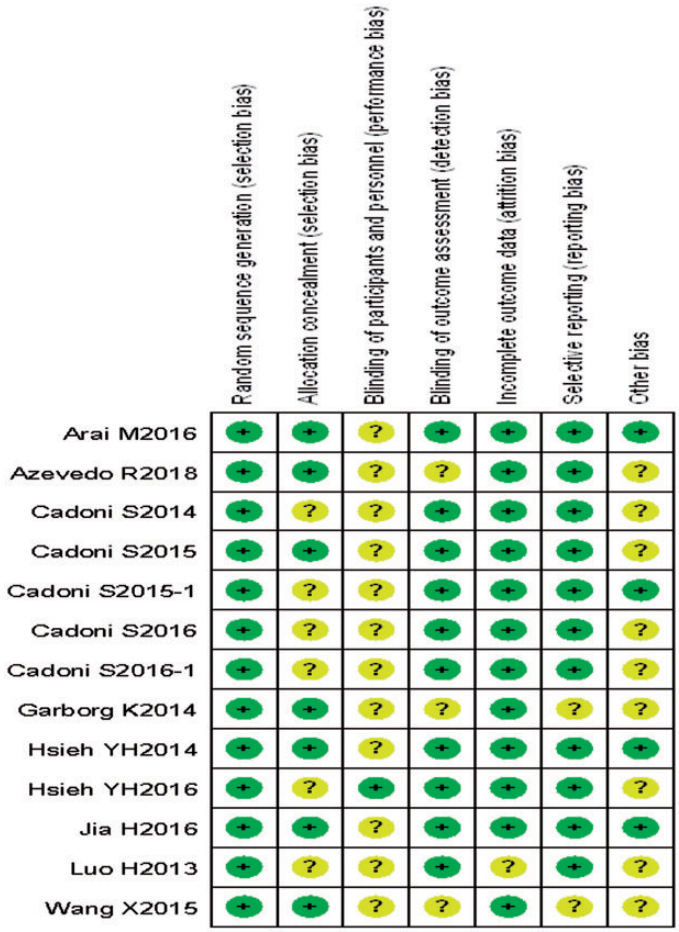

Figure 1. Summary of the risk of bias assessment (1).

were screened by two reviewers independently, according to the steps for preliminary screening and full-text screening, and any disagreements were resolved by discussion or consultation with a third evaluator.

Quality assessment

Study quality was evaluated according to the quality evaluation criteria recommended in the Cochrane Reviewers' Handbook 5.1.0. Briefly, study quality was rated as A, B, or C based on its randomization method, allocation concealment, blinding method, incomplete outcome data, selective outcome data, and other bias sources. The results are shown in Figures 1 and 2. All studies[12,17–28] described the process of randomization, whereas only seven[12,17,18,20,24,26,28] studies described appropriate allocation concealment. Nine studies[18–20,22–25,27,28] did not clearly describe other biases. Reference blinding was similar in all the included studies. The only study[25] with a guaranteed low risk of bias was a study in which the

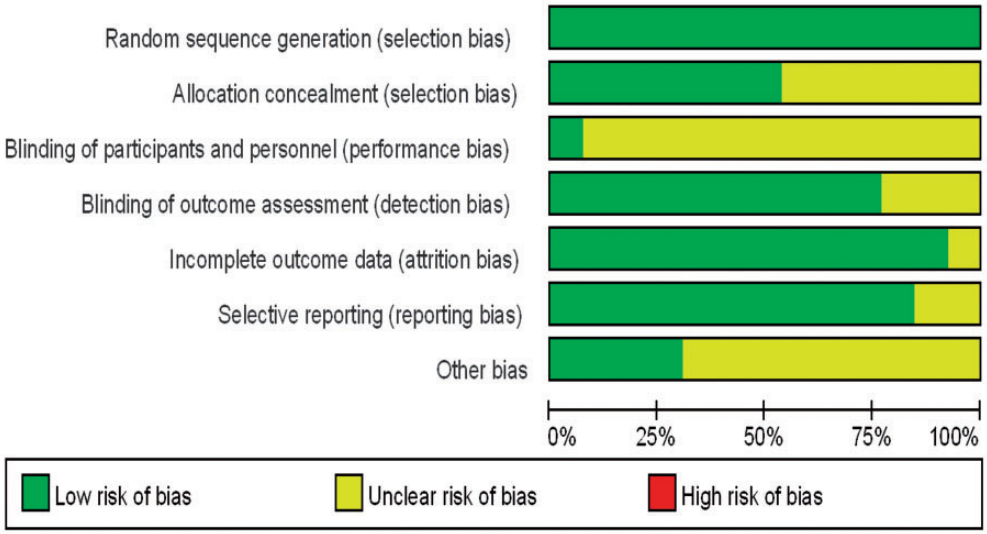

Figure 2. Graph of the risk of bias assessment (2).

colonoscopists were blinded to the insertion method (double-blinded).

Data analysis

The data were analyzed statistically using Review Manager 5.3. Odds ratios (ORs) were used to analyze the heterogeneity of numerical data such as ADR, proportion of painless unsedated colonoscopy, and cecal intubation rate between the two groups in each study. Maximal pain score and patient satisfaction were analyzed by weighted mean difference (MD) and the effect variables were expressed by 95% confidence intervals (CI). Each study was considered to be homogeneous when the P value was >0.1 or the I^2 statistic was $<50\%$; otherwise the study was regarded as non-homogenous. A fixed-effect model was used to estimate the overall effect if the OR was homogenous and a random-effect model if it was non-homogenous. A symmetrical funnel plot that was narrow at the top and wide at the bottom indicated no publication bias in relation to the analyzed index (Figure 3).

Results

Literature search and information retrieval of included studies

A total of 76 articles were extracted, of which 63 were excluded after reading the titles and abstracts and 13 RCTs were eventually included in the final analysis (Figure 4). Of the included articles, 11 were rated as grade A and two as grade B in terms of methodological quality. The included studies contained a total of 8780 patients, and the colonoscopic techniques used in these studies included WE, AI or CO_2-insufflation colonoscopy, and WI (Table 1).

Efficacy indicators

Nine RCTs[17–19,23–26,28] reported the ADR in the WE group, with a non-significant χ^2 value of 3.60 for heterogeneity, indicating

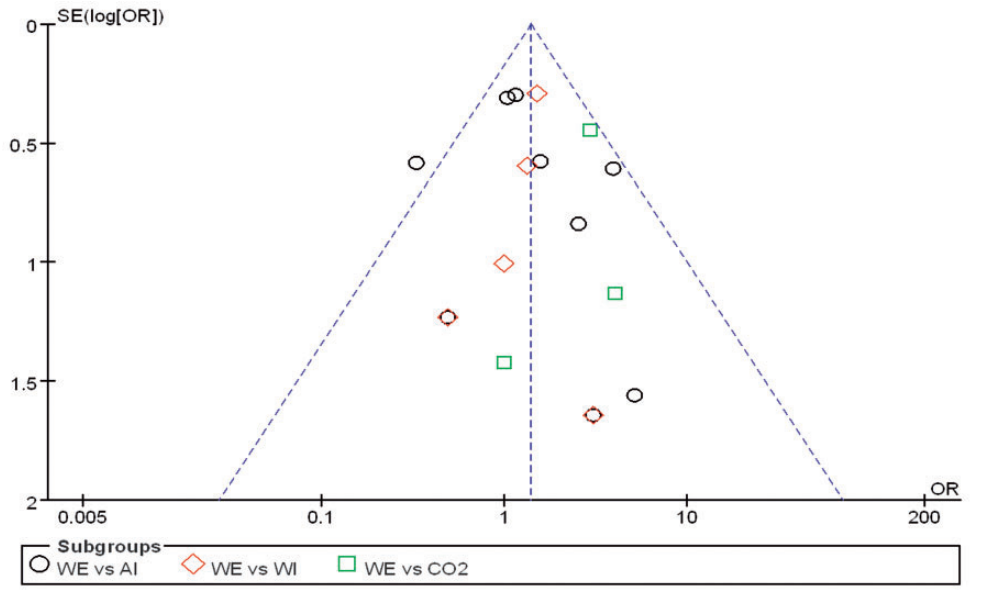

Figure 3. Funnel plots of the risk of publication bias (according to cecal intubation rate). SE: standard error, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy, CO_2: CO_2-insufflation colonoscopy.

homogeneity of effects among the trials. A fixed-effect model was therefore used, and the OR value in the WE group was 1.43 (95%CI: 1.30 to 1.59, $P < 0.001$). The OR values in the AI, WI, and CO_2-insufflation groups were 1.49 (95%CI: 1.32 to 1.68, $P < 0.001$), 1.36 (95%CI: 1.10 to 1.67, $P = 0.004$), and 1.18 (95%CI: 0.80 to 1.73), respectively, indicating that WE could significantly increase ADR (Figure 5).

Three RCTs[19–21] reported the proportion of painless unsedated colonoscopy procedures in the WE group, with a non-significant χ^2 value of 0.97 for heterogeneity, indicating homogeneity of effects among the trials. A fixed-effect model was therefore used. The OR for WE was 2.43 (95%CI: 1.87 to 3.14, $P < 0.001$), and the OR values for the AI and WI groups were 2.52 (95%CI: 1.88 to 3.37, $P < 0.001$) and 2.11 (95%CI: 1.21 to 3.68, $P < 0.001$), respectively, indicating that WE could significantly increase the proportion of painless unsedated colonoscopy procedures (Figure 6).

Maximal pain score during insertion was investigated in the WE group in seven RCTs,[12,20,21,25–28] with a χ^2 value for heterogeneity of 114.86 ($P < 0.001$), indicating significant heterogeneity of effect among the trials. The results were therefore analyzed using a random-effect model. The MD value for WE was −1.48 (95%CI: −1.98 to 0.98, $P < 001$), indicating that the maximal pain score during insertion was remarkably lower in the WE group compared with the AI (MD −1.84 [95%CI: −2.53 to 1.16, $P < 0.001$]) and WI groups (MD −0.62 [95%CI: −1.14 to 0.10, $P = 0.02$) (Figure 7).

Eleven RCTs[12,19–28] reported the cecal intubation rate in the WE group, with a non-significant χ^2 value for

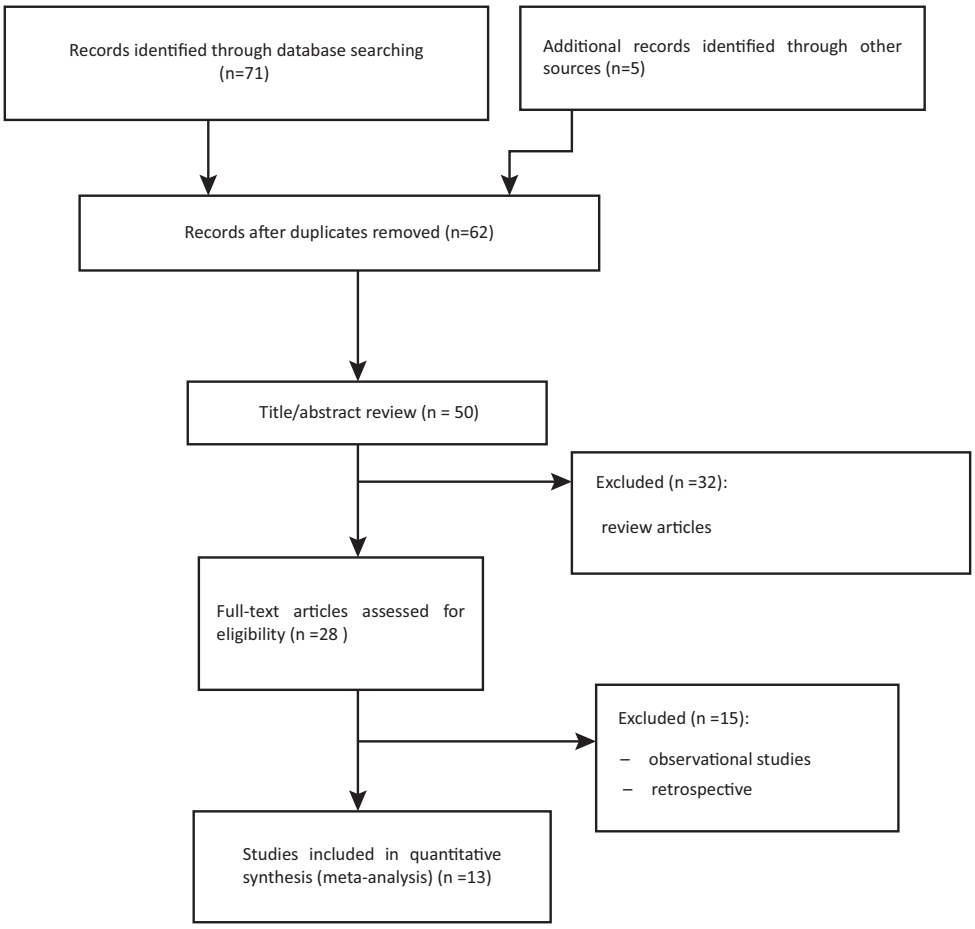

Figure 4. Diagram of article screening and selection. RCT: randomized controlled trial, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy.

heterogeneity of 17.39, indicating homogeneity of effects among the trials. A fixed-effect model was therefore used, and the OR value was 1.39 (95%CI: 1.08 to 1.79, $P = 0.01$). The equivalent ORs in the AI, WI, and CO_2-insufflation groups were 1.20 (95%CI: 0.86 to 1.66), 1.41 (95%CI: 0.87 to 2.26), and 2.85 (95%CI: 1.31 to 6.21, $P = 0.008$), indicating that WE could improve the cecal intubation rate relative to the control groups (Figure 8).

Patient satisfaction score was assessed in the WE group in three RCTs,[12,21,22] and the χ^2 value for heterogeneity was 2.31, indicating homogeneity of effects among the trials. A fixed-effect model was therefore used. The MD value for WE was 0.20 (95%CI: 0.05 to 0.35, $P = 0.01$), indicating that WE could increase patient satisfaction compared with the AI (MD 0.19 [95%CI: 0.02 to 0.35, $P = 0.03$]) and CO_2-insufflation groups (MD0.20 [95%CI: −0.26 to 0.63]) (Figure 9).

Table 1. Clinical characteristics of studies included in the meta-analysis.

	Water-exchange group						Control group					
Reference	Total number (n)	Method	Male/female (n)	Age (years)	BMI	Previous abdominal/ pelvic surgery (%)	Male/female (n)	Age (years)	Method	BMI	Previous abdominal/ pelvic surgery (%)	Quality
Arai M 2016[17]	403	WE	125/81	65.6 ± 12.0	22.9 ± 3.8	24.8%	122/75	63.1 ± 12.6	AI	23.3 ± 4.2	28.8%	A
Azevedo R 2018[18]	141	WE	41/29	61.6 ± 13.4	26.4 ± 5.2	42.9%	40/31	63.6 ± 13.3	AI	25.8 ± 7	39.4%	A
Cadoni S 2014[19]	672	WE	201/137	58 ± 12.4	–	29.9%	204/130	60 ± 12.3	AI	–	21.0%	A
Cadoni S 2015[20]	576	WE	110/76	59 ± 11.3	26.5 ± 4.9	33.3%	112/81	59 ± 11.3	AI	26.0 ± 5.0	30.1%	A
							116/81	60 ± 10.8	WI	25.9 ± 4.2	27.4%	
Cadoni S 2015-1[21]	520	WE-CO_2 WE	–	–	–	–	–	–	CO_2 AI WI	–	–	B
Cadoni S 2016-1[22]	240	WE-CO_2	48/31	58.3 ± 13.6	27.3 ± 4.4	36.7%	50/31	58 ± 13.7	CO_2	26.3 ± 4.1	40.7%	A
Cadoni S 2016[23]	1224	WE	224/184	61.4 ± 6.2	26.4 ± 4.1	36.8%	225/183	60.9 ± 6.2	AI	26.6 ± 4.4	37.7%	A
							223/185	61.0 ± 6.3	WI	26.4 ± 4.4	30.9%	
Garborg K 2014[24]	473	WE-CO_2	49/114	60 ± 4.5	26.9 ± 3.8	25%	49/118	61 ± 3.7	CO_2	26.7 ± 4.1	30%	A
Hsieh YH 2014[12]	270	WE	55/35	58	24.9 ± 2.9	27.8%	59/31	59	AI	25.3 ± 3.2	27.8%	A
							53/37	53	WI	25.0 ± 3.3	23.3%	
Hsieh YH 2016[25]	651	WE	121/96	55.7 ± 10.6	24.1 ± 3.2	38.2%	105/112	54.8 ± 10.5	AI	24.1 ± 4.2	29.5%	B
							110/107	55.9 ± 10.2	WI	24.3 ± 3.3	36.9%	
Jia H 2016[26]	3303	WE	830/823	50.2 ± 13.7	22.8 ± 3.5	23.7%	855/795	50.2 ± 13.9	AI	23.3 ± 3.8	26.1%	A
Luo H 2013[27]	110	WE	18/37	55.8 ± 11.0	22.0 ± 3.4	100%	16/39	56.6 ± 12.0	AI	21.3 ± 3.6	100%	A
Wang X 2015[28]	197	WE	51/48	46.4 ± 11.8	23.0 ± 2.9	28%	46/52	48.6 ± 13.2	AI	22.8 ± 3.1	19%	A

AI: air-insufflation, BMI: body mass index, CO_2: CO_2-insufflation, WE, water exchange, WI: water immersion.

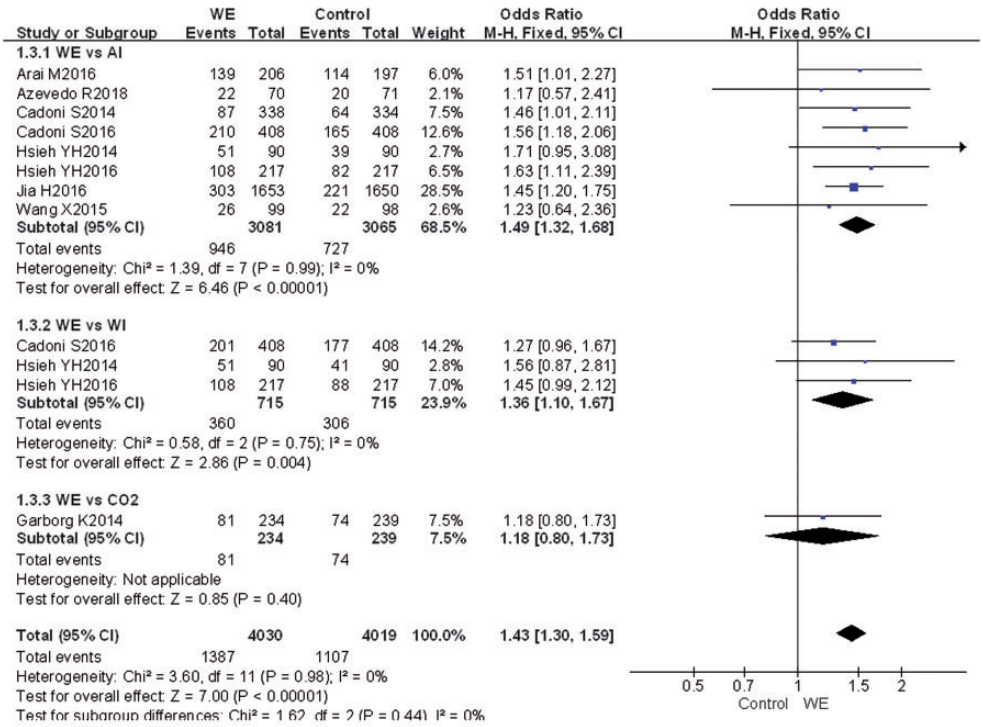

Figure 5. Comparison between WE and control groups in relation to ADR. Forest plot showing odds ratio (OR) with 95% confidence interval (CI). df: degrees of freedom, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy, CO_2: CO_2-insufflation colonoscopy, M-H: Mantel–Haenszel.

Discussion

ADR is known to be an important colonoscopy quality indicator related to the risk of interval cancer. The current meta-analysis showed that WE could significantly increase the ADR compared with other colonoscopy techniques, with a pooled OR of 1.43, in line with the results of previous studies.[12,19] However, only one study compared WE and CO_2-insufflation in relation to ADR,[24] and the result for this comparison was therefore not significant, probably due to the small sample size. Further clinical studies should therefore be conducted to compare the ADRs of these two techniques. We also compared WE with AI, WI, and CO_2-insufflation colonoscopy in terms of cecal intubation rate, and confirmed that WE had a higher cecal intubation rate than all the other insertion techniques. WE has consistently been shown to be the least-painful insertion technique,[29] and we verified that WE could significantly increase the proportion of painless unsedated colonoscopy procedures compared with AI and WI. Unsedated colonoscopy in the clinic could reduce medical costs and ensure post-procedural patient safety,[30,31] and the current analysis indicated that WE could be used to perform unsedated colonoscopy, especially in patients who cannot tolerate pain. Pain limits the cecal intubation rate from 67% to 83% worldwide among

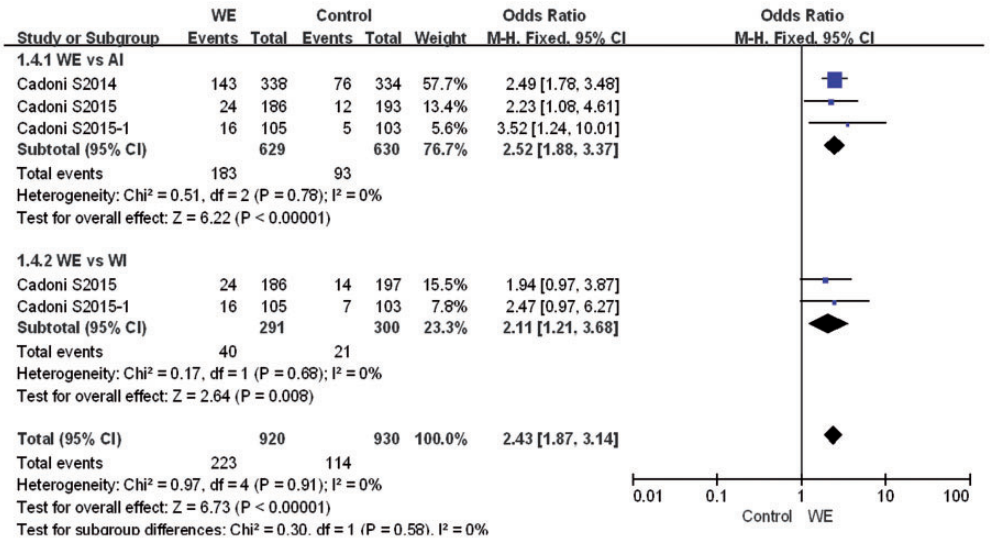

Figure 6. Comparison between WE and control groups in relation to painless unsedated colonoscopy. Forest plot showing odds ratio (OR) with 95% confidence interval (CI). df: degrees of freedom, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy, CO_2: CO_2-insufflation colonoscopy, M-H: Mantel–Haenszel.

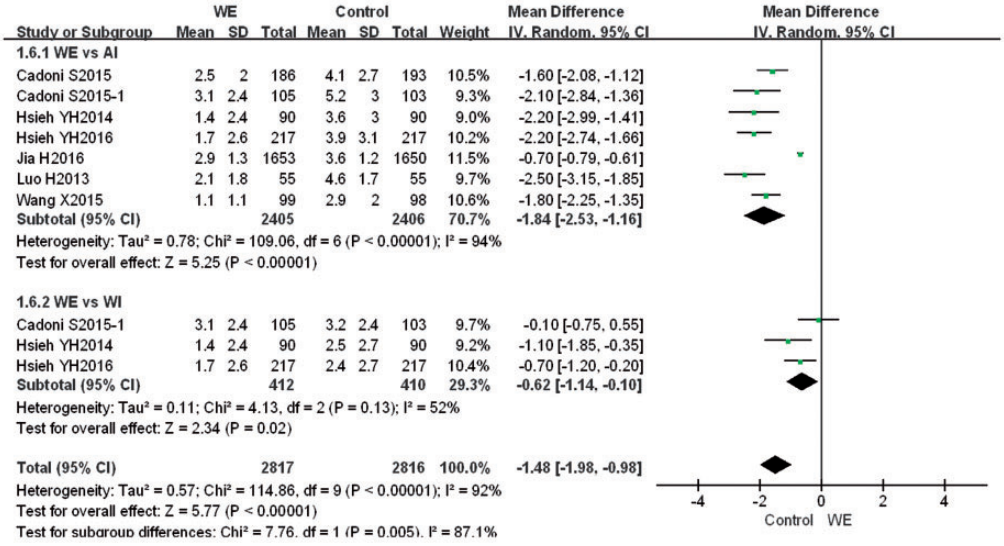

Figure 7. Comparison between WE and control groups in relation to maximal pain score during insertion. Forest plot showing mean difference (MD) with 95% confidence interval (CI). df: degrees of freedom, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy, CO_2: CO_2-insufflation colonoscopy, IV: inverse variance.

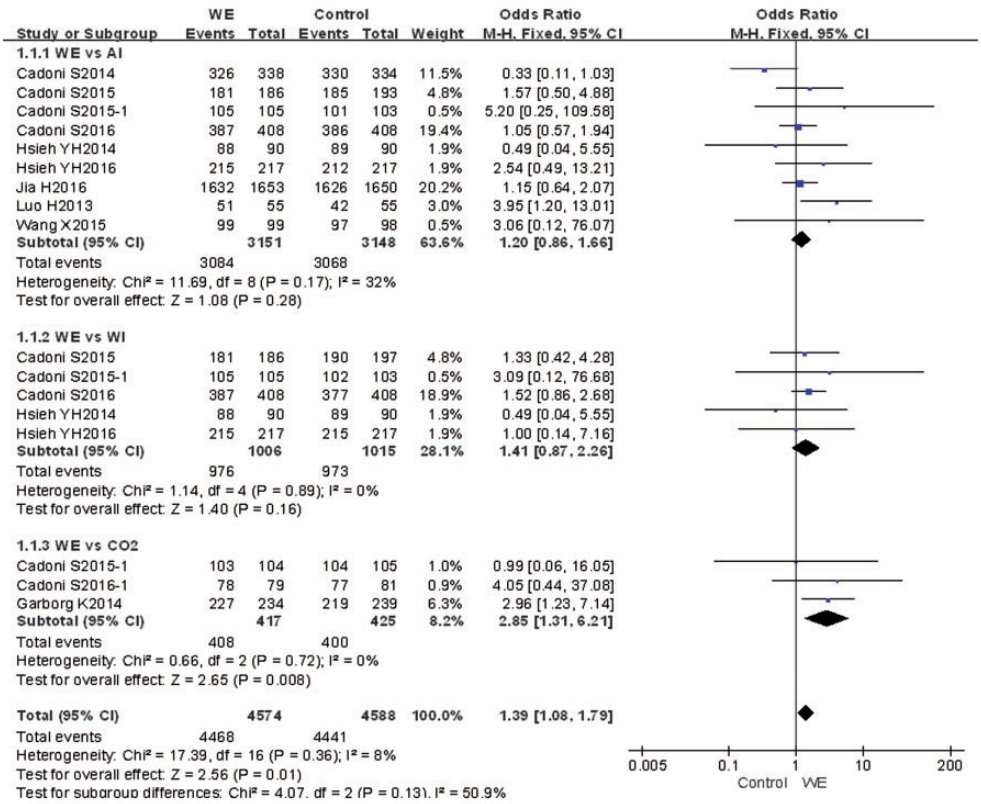

Figure 8. Comparison between WE and control groups in relation to cecal intubation rate. Forest plot showing odds ratio (OR) with 95% confidence interval (CI). df: degrees of freedom, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy, CO_2: CO_2-insufflation colonoscopy, M-H: Mantel–Haenszel.

patients undergoing scheduled, unsedated colonoscopy.[32] Our analysis indicated that WE significantly reduced the maximal pain on insertion, based on visual analog scale (0 = none,10 = maximum) pain scores. WE might thus allow the completion of difficult colonoscopy procedures, e.g., in patients with a history of abdominal surgery and those referred for prior incomplete colonoscopy, and may decrease the maximal discomfort during colonoscopy in these patients. This study thus further confirmed that WE was a relatively comfortable method in unsedated patients.[33] Finally, our meta-analysis also showed that WE was associated with higher patient satisfaction than the control techniques, suggesting that WE might be a popular choice for patients in the future .

All the studies included in this comprehensive meta-analysis were high-quality RCTs with consistent diagnostic criteria. However, there were still some limitations. Notably, the included studies were performed in different races and ethnic groups. Furthermore, differences in experimental design, numbers of patients in the control groups, and outcome measurements led to large heterogeneities among the included studies in terms of maximal pain

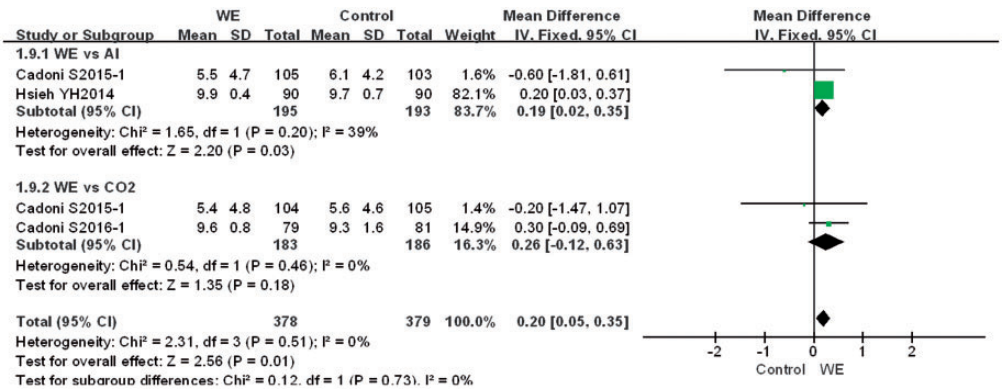

Figure 9. Comparison between WE and control groups in relation to patient satisfaction score. Forest plot showing mean difference (MD) with 95% confidence interval (CI). df: degrees of freedom, WI: water immersion colonoscopy, AI: air-insufflation colonoscopy, WE: water-exchange colonoscopy, CO_2: CO_2-insufflation colonoscopy, IV: inverse variance.

score during insertion, necessitating the use of a random-effect model for this item, which might have affected the results. In addition, colonoscopy was divided into insertion and withdrawal phases, with some differences among studies in terms of withdrawal procedure. Finally, relatively few RCTs compared WE and CO_2-insufflation colonoscopy.

In summary, WE is a promising colonoscopic technique that can remarkably increase the ADR and thus improve the detection rate of interval cancer. WE can also significantly increase the proportion of painless unsedated colonoscopy procedures and cecal intubation rate, and lower the maximal pain score. However, there was some heterogeneity among the included studies, and more high-quality RCTs with consistent outcome measurements are needed to verify the clinical value of WE in terms of maximal pain score during insertion and to compare WE with CO_2-insufflation colonoscopy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Xuan Huang http://orcid.org/0000-0002-4921-8620

References

1. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; 150: 1–8.
2. Bressler B, Paszat LF, Vinden C, et al. Colonoscopic miss rates for right-sided colon cancer: a population-based analysis. *Gastroenterology* 2004; 127: 452–456.
3. Stock C, Pulte D, Haug U, et al. Subsite-specific colorectal cancer risk in the colorectal endoscopy era. *Gastrointest Endosc* 2012; 75: 621–630.
4. Takahashi Y, Tanaka H, Kinjo M, et al. Prospective evaluation of factors predicting difficulty and pain during sedation-free colonoscopy. *Dis Colon Rectum* 2005; 48: 1295–1300.
5. Stevenson GW, Wilson JA, Wilkinson J, et al. Pain following colonoscopy: elimination

with carbon dioxide. *Gastrointest Endosc* 1992; 38: 564–567.
6. Friedland S. The water immersion technique for colonoscopy insertion. *Gastroenterol Hepatol (NY)* 2010; 6: 555–556.
7. Leung FW. Water exchange may be superior to water immersion for colonoscopy. *Clin Gastroenterol Hepatol* 2011; 9: 1012–1014.
8. Anderson JC. Water-aided colonoscopy. *Gastrointest Endosc Clin N Am* 2015; 25: 211–226.
9. Cadoni S and Leung FW. Water-assisted colonoscopy. *Curr Treat Options Gastro* 2017; 15: 135–154.
10. Sugimoto S and Mizukami T. Diagnostic and therapeutic applications of water-immersion colonoscopy. *World J Gastroenterol* 2015; 21: 6451–6459.
11. Leung CW, Kaltenbach T, Soetikno R, et al. Water immersion versus standard colonoscopy insertion technique: randomized trial shows promise for minimal sedation. *Endoscopy* 2010; 42: 557–563.
12. Hsieh YH, Koo M and Leung FW. A patient-blinded randomized, controlled trial comparing air insufflation, water immersion and water exchange during minimally sedated colonoscopy. *Am J Gastroenterol* 2014; 109: 1390–1400.
13. Vemulapalli KC and Rex DK. Water immersion simplifies cecal intubation in patients with redundant colons and previous incomplete colonoscopies. *Gastrointest Endosc* 2012; 76: 812–817.
14. Chen Z, Li Z, Yu X, et al. Is water exchange superior to water immersion for colonoscopy? A systematic review and meta-analysis. *Saudi J Gastroenterol* 2018; 24: 259–267.
15. Zhang Z, Wu Y, Sun G, et al. Bayesian network meta-analysis: efficacy of air insufflation, CO(2) insufflation, water exchange, and water immersion in colonoscopy. *Dig Endosc* 2018; 30: 321–331.
16. Fuccio L, Frazzoni L, Hassan C, et al. Water exchange colonoscopy increases adenoma detection rate: a systematic review with network meta-analysis of randomized controlled studies. *Gastrointest Endosc* 2018; 88: 589–597.e11.
17. Arai M, Okimoto K, Ishigami H, et al. A randomized controlled trial comparing water exchange and air insufflation during colonoscopy without sedation. *Int J Colorectal Dis* 2016; 31: 1217–1223.
18. Azevedo R, Leitão C, Pinto J, et al. Can water exchange improve patient tolerance in unsedated colonoscopy a prospective comparative study. *GE Port J Gastroenterol* 2018; 25: 166–174.
19. Cadoni S, Gallittu P, Sanna S, et al. A two-center randomized controlled trial of water-aided colonoscopy versus air insufflation colonoscopy. *Endoscopy* 2014; 46: 212–218.
20. Cadoni S, Sanna S, Gallittu P, et al. A randomized, controlled trial comparing real-time insertion pain during colonoscopy confirmed water exchange to be superior to water immersion in enhancing patient comfort. *Gastrointest Endosc* 2015; 81: 557–566.
21. Cadoni S, Falt P, Gallittu P, et al. Water exchange is the least-painful colonoscope insertion technique, increasing completion of unsedated colonoscopy. *Clin Gastroenterol Hepatol* 2015; 13: 1972–1980.
22. Cadoni S, Falt P, Gallittu P, et al. Impact of carbon dioxide insufflation and water exchange on postcolonoscopy outcomes in patients receiving on-demand sedation: a randomized controlled trial. *Gastrointest Endosc* 2017; 85: 210–218.
23. Cadoni S, Falt P, Rondonotti E, et al. Water exchange for screening colonoscopy increases adenoma detection rate: a multicenter, double-blinded, randomized controlled trial. *Endoscopy* 2017; 49: 456–467.
24. Garborg K, Kaminski MF, Lindenburger W, et al. Water exchange versus carbon dioxide insufflation in unsedated colonoscopy: a multicenter randomized controlled trial. *Endoscopy* 2015; 47: 192–199.
25. Hsieh YH, Tseng CW, Hu CT, et al. Prospective multicenter randomized controlled trial comparing adenoma detection rate in colonoscopy using water exchange, water immersion, and air insufflation. *Gastrointest Endosc* 2017; 86: 192–201.
26. Jia H, Pan Y, Guo X, et al. Water exchange method significantly improves adenoma detection rate: a multicenter, randomized controlled trial. *Am J Gastroenterol* 2017; 112: 568–576.

27. Luo H, Zhang L, Liu X, et al. Water exchange enhanced cecal intubation in potentially difficult colonoscopy. Unsedated patients with prior abdominal or pelvic surgery: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2013; 77: 767–773.
28. Wang X, Luo H, Xiang Y, et al. Left-colon water exchange preserves the benefits of whole colon water exchange at reduced cecal intubation time conferring significant advantage in diagnostic colonoscopy - a prospective, randomized controlled trial. *Scand J Gastroenterol* 2015; 50: 916–923.
29. Leung JW, Siao-Salera R, Abramyan O, et al. Impact of water exchange colonoscopy on serum sodium and potassium levels: an observational study. *Dig Dis Sci* 2014; 59: 653–657.
30. Leung F, Harker J, Leung J, et al. Removal of infused water predominantly during insertion (water exchange) is consistently associated with a greater reduction of pain score - review of randomized controlled trials (RCTs) of water method colonoscopy. *J Interv Gastroenterol* 2011; 1: 114–120.
31. Hsieh YH, Lin HJ and Tseng KC. Limited water infusion decreases pain during minimally sedated colonoscopy. *World J Gastroenterol* 2011; 17: 2236–2240.
32. Leung FW. Is there a place for sedationless colonoscopy? *J Interv Gastroenterol* 2011; 1: 19–22.
33. Azevedo R, Leitão C, Pinto J, et al. Can water exchange improve patient tolerance in unsedated colonoscopy a prospective comparative study. *GE Port J Gastroenterol* 2018; 25: 166–174.