

Comparison of Water Immersion Versus Air Insufflation Colonoscopy Under Various Bowel Preparation Conditions

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ABSTRACT

Background: To investigate the differences between water immersion (WI) and air insufflation (AI) for colonoscopy under various bowel preparation conditions.

Methods: In this study, 526 outpatients were randomly assigned to two groups, namely a WI group ($n = 263$) and an AI group ($n = 263$). During the procedure, the quality of bowel preparation, abdominal pain score, cecal intubation rate (CIR), adenoma detection rate (ADR), the intubation times, and other indicators were recorded. After reaching the cecum, each group of patients was subdivided into one of four grades (excellent, good, fair, and poor) according to the quality of bowel preparation.

Results: Under various bowel preparation conditions, the pain scores of the AI group were higher than those of the WI group ($P < .05$), but there was no significant difference between the two groups in CIR ($P > .05$). For the WI group compared with the AI group, the cecal intubation time (CIT) was prolonged under good bowel preparation ($P = .045$) and fair bowel preparation ($P < .001$). No significant differences were observed between the two groups on ADR in all patients ($P = .476$).

Conclusion: Compared with AI colonoscopy, WI colonoscopy can decrease colonoscopy-related pain in patients for unsedated colonoscopy under various bowel preparation conditions, but there is no significant difference in CIR. WI colonoscopy requires longer CIT in patients with good and fair bowel preparation conditions. WI colonoscopy does not significantly increase ADR.

Keywords: Water immersion colonoscopy, air insufflation colonoscopy, bowel preparation, abdominal pain score, cecal intubation rate, adenoma detection rate

INTRODUCTION

Colorectal cancer (CRC) is considered a serious disease because of its high morbidity and mortality.¹ Recently, the incidence of CRC has increased rapidly in China, and CRC is now the third leading disease that causes cancer-related death.² Early detection and removal of adenomatous polyps can reduce the risk of developing CRC.³ Colonoscopy is widely considered as the most important method for diagnosing adenomatous polyps and CRC because of its high rate of detection and ability to biopsy or resect some intestinal lesions.⁴ Traditional colonoscopy is performed with air insufflation (AI), which is operated by insufflating air into the large bowel to distend the bowel lumen. However, excessive infusion of air could cause discomfort such as abdominal pain. Among patients who underwent traditional colonoscopy, 34% reported moderate or severe abdominal pain, and approximately 14% might have severe abdominal pain.⁵ Pain could cause some patients to suspend the examination or refuse to review,

leading to hindering the popularity of colonoscopy.⁶ So many patients in the United States expressed willingness to receive conscious sedation.^{1-4,7} But the use of conscious sedation for colonoscopy is associated with a risk of cardiopulmonary complications.^{5,7} Recently, Leung et al. proposed a technique of using water immersion (WI) without AI during insertion for colonoscopy. Their results demonstrated that the WI method could decrease patients' discomfort or pain without compromising the quality of colonoscopy.⁸ Other researchers also reported that WI played a possible role in relieving colonic spasms,⁹⁻¹¹ thereby minimizing colonoscopy discomfort.¹²⁻¹⁵

Although some researchers have considered that there are many advantages to WI colonoscopy, others have believed that bowel preparation conditions can seriously affect the quality of WI colonoscopy in comparison with AI colonoscopy.¹⁶ We hypothesize that there are significant differences between WI colonoscopy and AI

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colonoscopy under various bowel preparation conditions. So we designed a clinical trial to evaluate the differences between WI and AI colonoscopy under various bowel preparation conditions.

MATERIALS AND METHODS

We designed a randomized controlled trial. All patients gave written informed consent.

Study Population

The study included a total of 600 consecutive outpatients aged 18-80 years who were willing to undergo screening or diagnosis colonoscopy between January 2018 and April 2019. Exclusion criteria were (1) patients who refused to participate in the study, (2) patients who had undergone partial or complete colectomy, (3) patients with poor bowel preparation after colonoscopy, (4) patients who requested to undergo colonoscopy with sedation, and (5) patients with other abdominal pain known before the procedure.

Quality of Bowel Preparation

All patients underwent a bowel preparation with 1 L of polyethylene glycol electrolyte lavage solution (PEG-ELP; WanHe Pharmaceutical Co, Shenzhen, China) the day before the examination, and 2 L of PEG-ELP at 4:00-5:00 AM within 2 h on the morning of the examination.

In our study, the quality of bowel preparation for both the water method and the air method was graded and categorized by the endoscopist independently as excellent (adequate visualization of the lumen, the entire colon requires no flushing or suction), good (adequate visualization of the lumen, the entire colon (>90%) has a little clear fluid, which needs minimal suction and no or very minimal flushing), fair (unsatisfactory visualization of the lumen, all or part of the colon has colored fluid and liquid feces, which require suction and flushing), and poor (unsatisfactory visualization of the lumen, all or part of the colon has colored fluid and feces, which require suction and flushing, and the colon needs to be re-examined), based on the Aronchik bowel preparation scale,¹⁷ as shown in Figure 1.

Colonoscopy Procedure

Colonoscopies for the two groups were performed by one experienced endoscopist who had performed independently more than 1000 WI colonoscopies and more than 1000 AI colonoscopies. All patients who underwent colonoscopy were without sedation.

Before the procedure, the pulse, oximetry, and respiratory rate, body temperature, blood pressure, and electrocardiography were monitored. At the beginning of colonoscopy, the patients were in the left lateral position. The shaft of the colonoscope was smeared with oil and

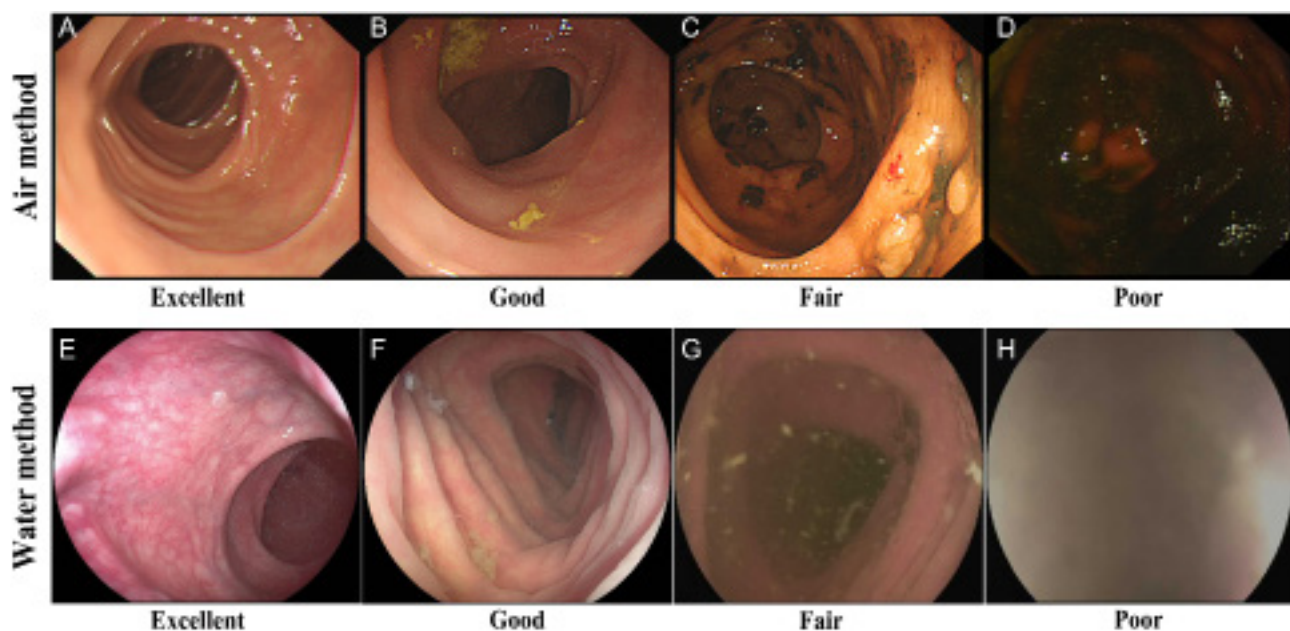


Figure 1. Endoscopic images of the colon in the air insufflation (AI) group (A-D) and water immersion (WI) group (E-H) under four bowel preparation conditions: (A, E) excellent; (B, F) good; (C, G) fair; and (D, H) poor.

inserted into the lumen from the anus. After that, the colonoscope could be advanced through the lumen until it reached the cecum, even to the terminal ileum. The time of withdrawing the colonoscope was not less than 6 min. During colonoscopy, the basic characteristics of the patient, abdominal pain score, cecal intubation rate (CIR), adenoma detection rate (ADR), intubation times, etc., were recorded. The visual analogue scale pain scoring system was used to assess each patient's abdominal pain degree (0 means no pain and 10 means extremely painful). This assessment was carried out immediately after the procedure at a face-to-face interview with an independent nurse, who was blinded to the group allocation.

AI method: For patients who were assigned randomly to the AI group, colonoscopy was operated by the traditional method, with minimal insufflation required to aid insertion. In order to wash residual stool, a little warm water was used.¹⁸

WI method: In order to avoid inadvertent insufflation, the nurse turned off the air pump before starting the procedure. During the insertion of the colonoscope, for patients who underwent the WI method and had a lot of feces, this was mixed with the water present in the colon and aspirated, and then the lumen was infused with clean water. The volume of water that was infused into the colon in order to improve the visibility of the intestinal lumen was not restricted. The water was infused mainly in order to open the lumen, rather than in order to maximize colon cleanliness.

Study Endpoints

Abdominal pain score, CIR, and ADR were the primary outcomes. Secondary outcome measures were the intubation times (splenic flexure intubation time, hepatic flexure intubation time, and cecal intubation time [CIT]), changes in patient position, and manual pressure used.

Sample Size

All sample sizes were performed with PASS 11.0. The required sample size was calculated from preliminary data (unpublished) that showed that the mean of the pain score in the WI group was 2.43, and the mean of the pain score in the AI group was 4.93 under excellent bowel preparation conditions. For the study to have 80% power at a significance level of 0.05, at least 13 pairs of patients were required. Finally, we have enrolled 28 patients in the WI group and 38 patients in the AI group under excellent bowel preparation conditions in our study.

The required sample size was calculated from preliminary data (unpublished) that showed that the mean of the pain score in the WI group was 3.87, and the mean of the pain score in the AI group was 5.00 under good bowel preparation conditions. For the study to have 80% power at a significance level of 0.05, at least 95 pairs of patients were required. Finally, we have enrolled 186 patients in the WI group and 171 patients in the AI group under good bowel preparation conditions in our study.

The required sample size was calculated from preliminary data (unpublished) that showed that the mean of the pain score in the WI group was 3.22, and the mean of the pain score in the AI group was 4.82 under fair bowel preparation conditions. For the study to have 80% power at a significance level of 0.05, at least 39 pairs of patients were required. Finally, we have enrolled 40 patients in the WI group and 43 patients in the AI group under fair bowel preparation conditions in our study.

Statistical Analysis

We analyzed the data of the study using SPSS 13.0 statistical analysis software. Normally distributed data are represented as means \pm standard deviation. Non-normally distributed data are represented as medians \pm interquartile ranges. All of the measurement data were compared using the Student's *t*-test, Wilcoxon rank sum test, Chi-square (χ^2) test, or Fisher's exact test, as appropriate. For all tests, all *P*-values are two-tailed, and a *P*-value of less than .05 was considered to indicate statistical significance.

RESULTS

Baseline Characteristics of the Patients

A total of 600 consecutive outpatients who were willing to undergo screening or diagnostic colonoscopy were included in the study. Of these, 74 inappropriate cases (colectomy, *n* = 19; requested sedation, *n* = 38; refused to participate in this study, *n* = 17) were excluded. Before starting the examination, remaining outpatients were randomized to either the AI group or WI group by opening a sealed opaque envelope. The envelopes were randomized by using a computer-generated random list. Finally, 526 patients enrolled in the study were randomly allocated to one of the two groups (AI group and WI group) at a 1:1 ratio: the WI group (*n* = 263) or the AI group (*n* = 263). Data analyses were carried out based on stratification by the level of colon cleanliness. In the WI group, a total of 263 outpatients were divided on the basis of excellent bowel preparation (*n* = 28), good bowel

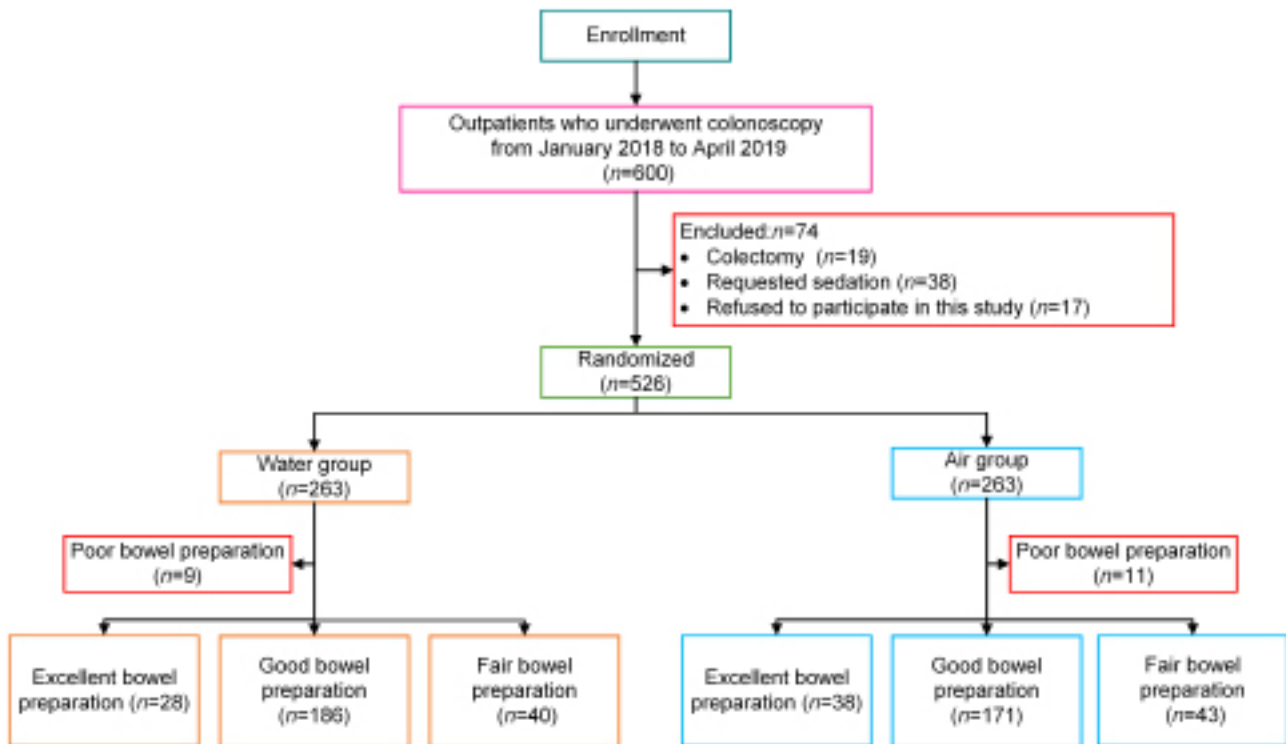


Figure 2. Study flow chart.

preparation ($n = 186$), fair bowel preparation ($n = 40$), and poor bowel preparation ($n = 9$). In the AI group, a total of 263 outpatients were divided on the basis of excellent bowel preparation ($n = 38$), good bowel preparation ($n = 171$), fair bowel preparation ($n = 43$), and poor bowel preparation ($n = 11$). Outpatients who had poor bowel preparation were not analyzed (see Figure 2). There were no significant differences between the WI group and the AI group in terms of age, gender, BMI, and previous major abdominal or pelvic surgery under the various bowel preparation conditions (Tables 1, 2, 3, and 4).

All Patients

In all patients, the rate of reaching the cecum was 96.9% in the WI group and 94.7% in the AI group ($P = .191$). The splenic flexure intubation time (94.0 ± 58.0 s vs. 83.0 ± 50.5 s; $P = .011$), the hepatic flexure intubation time (175.0 ± 112.0 s vs. 160.0 ± 94.5 s; $P = .017$), and the CIT (223.0 ± 165.0 s vs. 206.0 ± 158.5 s; $P = .049$) showed significant differences between the AI group and the WI group. The ADR in the WI group was 25.5% and that in the AI was 22.8% ($P = .476$) in all patients. The median of the pain score was 4 in the WI group and 5 in the AI group ($P < .001$). The frequency of position changes showed statistically significant differences between the WI group

and the AI group ($P < .05$). However, the frequency of manual pressure showed no statistically significant differences between the two groups ($P > .05$) (Table 1).

Under Excellent Bowel Preparation Conditions

Under excellent bowel preparation conditions, the cecum was achieved in 100.0% in the WI group, and 97.4% in the AI group ($P = .387$). No significant difference was observed between the two groups in the splenic flexure intubation time (69.5 ± 27.3 s vs. 74.0 ± 26.5 s; $P = .884$), the hepatic flexure intubation time (103.5 ± 33.8 s vs. 107.0 ± 28.5 s; $P = .928$), and the CIT (128.0 ± 29.5 s vs. 127.0 ± 30.0 s; $P = .509$). The median of the pain score was 2 and 5 for the WI group and the AI group ($P < .001$). The frequency of position changes and manual pressure showed no statistically significant differences between the WI group and the AI group ($P > .05$) (Table 2).

Under Good Bowel Preparation Conditions

The rate of reaching the cecum was 98.4% in the WI group and 97.1% in the AI group ($P = .487$) under good bowel preparation conditions. The splenic flexure intubation times were 96.0 ± 52.0 s and 80.5 ± 45.0 s ($P = .001$), the

Table 1. Comparison of WI Group Versus AI Group in All Patients

	WI (n = 263)	AI (n = 263)	P
Baseline characteristics			
Age (years), mean ± SD	51.7 ± 11.2	51.6 ± 12.3	.909 [†]
Female, n (%)	128 (48.7)	138 (52.5)	.383 [‡]
BMI (kg/m ²), median ± IQR	22.5 ± 2.7	22.8 ± 2.4	.644 [§]
Previous major abdominal or pelvic surgery, n (%)	80 (30.4)	101 (38.4)	.054 [‡]
Primary and secondary outcomes			
Cecal intubation rate, n (%)	255 (96.9)	249 (94.7)	.191 [‡]
The splenic flexure intubation time (s), median ± IQR	94.0 ± 58.0	83.0 ± 50.5	.011 ^{§*}
The hepatic flexure intubation time (s), median ± IQR	175.0 ± 112.0	160.0 ± 94.5	.017 ^{§*}
The cecal intubation time (s), median ± IQR	223.0 ± 165.0	206.0 ± 158.5	.049 ^{§*}
Adenoma detection rate, n (%)	67 (25.5)	60 (22.8)	.476 [‡]
Insertion pain score (0 = none; 10 = max)	4 (0-10)	5 (0-10)	<.001 ^{§*}
Changes in patient position, n (%)	194 (73.8)	216 (82.1)	.021 ^{‡*}
Manual pressure used, n (%)	206 (78.3)	218 (82.9)	.186 [‡]

[†]Student t test; [‡]Chi-square test; [§]Wilcoxon rank-sum test; *P value <.05, statistically significant.

WI group, water immersion group; AI, air insufflation group; mean ± SD, mean ± standard deviation; median ± IQR, median ± interquartile ranges; BMI, body mass index.

hepatic flexure intubation times were 177.0 ± 83.0 s and 166.0 ± 73.5 s ($P = .015$), and the CIT were 223.0 ± 118.0 s and 206.0 ± 130.5 s ($P = .045$) for the WI group and the AI group under good bowel preparation conditions. The median of the pain score was 4 (WI group) and 6

(AI group) under good bowel preparation conditions ($P < .001$). The frequency of position changes and manual pressure showed no statistically significant differences between the WI group and the AI group ($P > .05$) (Table 3).

Table 2. Comparison of WI Group Versus AI Group Under Excellent Bowel Preparation

	WI (n = 28)	AI (n = 38)	P
Baseline characteristics			
Age (years), mean ± SD	50.4 ± 10.6	49.7 ± 12.7	.804 [†]
Female, n (%)	7 (25.0)	17 (44.7)	.099 [‡]
BMI (kg/m ²), median ± IQR	23.1 ± 2.2	23.0 ± 1.8	.425 [§]
Previous major abdominal or pelvic surgery, n (%)	7 (25.0)	14 (36.8)	.307 [‡]
Primary and secondary outcomes			
Cecal intubation rate, n (%)	28 (100.0)	37 (97.4)	.387 [¶]
The splenic flexure intubation time (s), median ± IQR	69.5 ± 27.3	74.0 ± 26.5	.884 [§]
The hepatic flexure intubation time (s), median ± IQR	103.5 ± 33.8	107.0 ± 28.5	.928 [§]
The cecal intubation time (s), median ± IQR	128.0 ± 29.5	127.0 ± 30.0	.509 [§]
Insertion pain score (0 = none; 10 = max)	2 (0-5)	5 (1-9)	<.001 ^{§*}
Changes in patient position, n (%)	10 (35.7)	22 (57.9)	.075 [‡]
Manual pressure used, n (%)	18 (64.3)	27 (71.1)	.560 [‡]

[†]Student t test; [‡]Chi-square test; [§]Wilcoxon rank-sum test; [¶]Fisher exact test; *P value <.05, statistically significant.

WI group, water immersion group; AI, air insufflation group; mean ± SD, mean ± standard deviation; median ± IQR, median ± interquartile ranges; BMI, body mass index.

Table 3. Comparison of WI Group Versus AI Group Under Good Bowel Preparation

	WI (n = 186)	AI (n = 171)	P
Baseline characteristics			
Age (years), mean ± SD	52.1 ± 10.9	51.4 ± 11.9	.544 [†]
Female, n (%)	96 (51.6)	96 (56.1)	.391 [‡]
BMI (kg/m ²), median ± IQR	22.3 ± 2.4	22.6 ± 2.4	.105 [§]
Previous major abdominal or pelvic surgery, n (%)	51 (27.4)	63 (36.8)	.052 [‡]
Primary and secondary outcomes			
Cecal intubation rate, n (%)	183 (98.4)	166 (97.1)	.487 [‡]
The splenic flexure intubation time (s), median ± IQR	96.0 ± 52.0	80.5 ± 45.0	.001 ^{§*}
The hepatic flexure intubation time (s), median ± IQR	177.0 ± 83.0	166.0 ± 73.5	.015 ^{§*}
The cecal intubation time (s), median ± IQR	223.0 ± 118.0	206.0 ± 130.5	.045 ^{§*}
Insertion pain score (0 = none; 10 = max)	4 (0-10)	6 (0-10)	<.001 ^{§*}
Changes in patient position, n (%)	139(74.7)	143 (83.6)	.051 [‡]
Manual pressure used, n (%)	151 (81.2)	149 (87.1)	.125 [‡]

[†]Student t test; [‡]Chi-square test; [§]Wilcoxon rank-sum test; *P value <.05, statistically significant.

WI group, water immersion group; AI, air insufflation group; mean ± SD, mean ± standard deviation; median ± IQR, median ± interquartile ranges; BMI, body mass index.

Under Fair Bowel Preparation Conditions

CIRs were comparable (35 patients (87.5%) vs. 35 patients (81.4%) in the WI group and AI group, respectively) ($P = .445$). Under fair bowel preparation conditions, the splenic flexure intubation time (134.0 ± 123.0 s vs. 105.0 ± 48.0 s; $P < .001$), the hepatic flexure intubation

time (390.0 ± 335.0 s vs. 208.0 ± 143.0 s; $P < .001$), and the CIT (601.0 ± 369.0 s vs. 304.0 ± 220.0 s; $P < .001$) showed significant differences between the AI group and the WI group. The median of the pain score was 3 in the WI group and 4 in the AI group ($P = .012$). The frequency of position changes and manual pressure showed no statistically

Table 4. Comparison of WI Group Versus AI Group Under Fair Bowel Preparation

	WI (n = 40)	AI (n = 43)	P
Baseline characteristics			
Age (years), mean ± SD	51.6 ± 13.4	54.3 ± 13.3	.365 [†]
Female, n (%)	21 (52.5)	22 (51.2)	.903 [‡]
BMI (kg/m ²), median ± IQR	23.8 ± 4.9	22.6 ± 3.0	.106 [§]
Previous major abdominal or pelvic surgery, n (%)	16 (40.0)	19 (44.2)	.824 [‡]
Primary and secondary outcomes			
Cecal intubation rate, n (%)	35 (87.5)	35 (81.4)	.445 [‡]
The splenic flexure intubation time (s), median ± IQR	134.0 ± 123.0	105.0 ± 48.0	<.001 ^{§*}
The hepatic flexure intubation time (s), median ± IQR	390.0 ± 335.0	208.0 ± 143.0	<.001 ^{§*}
The cecal intubation time (s), median ± IQR	601.0 ± 369.0	304.0 ± 220.0	<.001 ^{§*}
Insertion pain score (0 = none; 10 = max)	3 (0-9)	4 (0-10)	.012 ^{§*}
Changes in patient position, n (%)	38 (95.0)	40 (93.0)	.705 [¶]
Manual pressure used, n (%)	33 (82.5)	31 (72.1)	.259 [‡]

[†]Student t test; [‡]Chi-square test; [§]Wilcoxon rank-sum test; *P value <.05, statistically significant.

WI group, water immersion group; AI, air insufflation group; mean ± SD, mean ± standard deviation; median ± IQR, median ± interquartile ranges; BMI, body mass index.

significant differences between the WI group and the AI group under various bowel preparation conditions ($P > .05$) (Table 4).

DISCUSSION

This study showed that the WI group was superior to the AI group in terms of abdominal pain score under various bowel preparation conditions. The CIR in the two groups were similar under various bowel preparation conditions. There was no significant difference between the two groups on ADR in all patients. No significant difference was observed between the WI group and the AI group regarding the intubation time (including the splenic flexure intubation time, the hepatic flexure intubation time, and the CIT) under excellent bowel preparation conditions, while the use of WI was characterized by a significantly longer intubation time under good bowel preparation conditions and fair bowel preparation conditions.

AI colonoscopy might lengthen and distend the colon, which leads to colonoscopy-related pain.¹⁹ To overcome this limitation, water was used during the insertion of the colonoscope. WI colonoscopy can facilitate the colonoscope to open and pass the lumen. The infused water in the colon flows to the lower colon because of gravity, thereby opening and passing through the lumen.^{20,21} During the withdrawal of the procedure, air was used. Our study showed that the WI method can increase patient comfort in comparison with the AI group under various bowel preparation conditions.

Under any bowel preparation conditions, there was no significant difference in CIR between the two groups. However, it was found in our study that low-quality bowel preparation was associated with increasing colonoscopy difficulty and incomplete colonoscopy examinations whether by the WI method or the AI method. A multi-center trial found that compared with fair bowel preparation conditions, excellent and good bowel preparation conditions could increase the CIR and decrease the rate of procedure difficulty.²² Considering these factors, colonoscopy performed with a high-quality bowel preparation was important.

Previous research has shown that the detection rate of neoplastic lesions in patients was significantly decreased under poor bowel preparation conditions.²³ These studies considered that inadequate bowel preparation impeded the diagnostic ability of standard colonoscopy significantly. While some studies²⁴ reported that low-quality bowel preparation decreased the detection rate of small

polyps in which the diameter was ≤ 9 mm, others²² showed a similar trend regardless of the size of colonic lesions. We investigated the difference between WI colonoscopy and AI colonoscopy on ADR in all patients. Results of the analysis demonstrated that ADR was similar ($P > .05$). The number of patients was too little under different bowel preparation conditions in our research, and so we did not assess the differences in ADR stratifying by colon cleanliness between the two groups. In future, we will increase the sample size to further explore the differences between WI colonoscopy and AI colonoscopy in relation to ADR under various bowel preparation conditions.

Based on excellent bowel preparation conditions, the use of WI did not prolong the time to reach the cecum. However, as bowel preparation conditions became worse, the time of reaching the cecum in the WI group was significantly longer than that in the AI group. A possible reason for this was that having a lot of feces remaining in the bowel lumen, which were mixed with the water, could result in a decrease in the visibility in the intestinal lumen. In severe cases, it was impossible to continue the examination, and so the endoscopists needed a large amount of water to rinse the lumen repeatedly until it was cleaned, which would waste a lot of time. Our results differed from those of Leung et al.,⁷ who found a trend toward a shortened CIT in the WI group. However, others indicated that the CIT among the two groups showed no significant difference.²⁵

Other intubation times (the splenic flexure intubation time and the hepatic flexure intubation time) were also recorded as important outcomes because the purpose of our research was to evaluate whether the intubation times of WI colonoscopy were longer than that of AI colonoscopy under various bowel preparation conditions. Our outcomes demonstrated that the time to splenic flexure and hepatic flexure in the two groups were similar under excellent bowel preparation conditions. The splenic flexure intubation time and the hepatic flexure intubation time were significantly prolonged in the WI group under good and fair bowel preparation conditions. We considered that this phenomenon was likely related to the unclear vision through turbid water in the WI group.

Our research has some advantages in its study of WI colonoscopy in comparison with previous reports. First, our trial compared WI colonoscopy with AI colonoscopy in terms of bowel preparation conditions. Second, with its increased sample size, our study had adequate power to evaluate some outcomes (including abdominal pain score, CIR, the intubation times, etc.).

CONCLUSIONS

Compared with AI colonoscopy, WI colonoscopy can decrease colonoscopy-related pain in patients for unsedated colonoscopy under various bowel preparation conditions, but there is no significant difference in CIR. WI colonoscopy requires longer CIT in patients with good and fair bowel preparation conditions. In addition, WI colonoscopy does not significantly increase ADR.

LIMITATIONS

This study had several limitations. First, it was a single-center study. Second, the study population was only Chinese subjects. In the future, we intend to carry out multicenter research. Third, there is no unified standard for assessing the quality of bowel preparation by WI colonoscopy at present. Fourth, a validated bowel grading scale (such as those developed by Ottawa²⁶ and Boston²⁷) was not used in this study. However, we adopted a simplified scale (the Aronchik bowel preparation scale).¹⁷

Ethics Committee Approval: This study was approved by the Human Ethics Committee of the First Affiliated Hospital of Harbin Medical University and the ethics committee approval number was 201316.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.S.J., Y.Y.L.; Design - N.S.J., Y.Y.L.; Supervision - N.S.J., Y.Y.L.; Resource - C.Y.Y., M.Z.B.; Materials - Y.Y.L., C.Y.Y., M.Z.B.; Data Collection and/or Processing - N.S.J., S.G.Y., W.F.; Analysis and/or Interpretation - N.S.J., S.G.Y.; Literature Search - N.S.J., W.F., Z.H.C.; Writing - N.S.J., Y.Y.L.; Critical Reviews - N.S.J., Y.Y.L.

Conflict of Interest: The authors have no conflict of interest to declare.

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