Comparison of Right Colon Adenoma Miss Rates Between Water Exchange and Carbon Dioxide Insufflation

A Prospective Randomized Controlled Trial

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Goals: To test the hypothesis that water exchange (WE), when compared with carbon dioxide (CO_2) insufflation, significantly reduces the right colon adenoma miss rate (rAMR) in a blinded randomized controlled trial with cap-assisted colonoscopy.

Background: The unblinded consecutive group observational data showed that WE significantly decreased rAMR. The unblinded data are limited by potential bias.

Study: Consecutive patients aged 45 years or more were randomized to undergo insertion with WE or CO_2. Withdrawal and polypectomy were performed with CO_2 in both groups to the hepatic flexure. The colonoscope was reinserted to the cecum. A second colonoscopist re-examined the right colon. The second colonoscopist was unaware, but made a guess, of the initial insertion method. The number of additional adenomas divided by the total number detected in both examinations equaled rAMR.

Results: Among 262 patients (131/group), demographic variables were similar. The body mass index was significantly higher in the WE group. Compared with CO_2, WE significantly decreased rAMR [18.0% (33/183) vs. 34.6% (62/179), $P = 0.0025$] and right colon serrated polyp miss rate [17.4% (27/155) vs. 39.3% (33/84), $P = 0.002$]. Multivariate logistic regression analysis showed that WE was an independent predictor of rAMR (odds ratio, 0.42; 95% confidence interval, 0.21-0.86), and so was ≥ 2 adenomas in the right colon (odds ratio, 2.35; 95% confidence interval, 1.17-4.76). Whether the second colonoscopist guessed the insertion method correctly or not, and demographic and procedure variables were not associated with rAMR.

Conclusions: The randomized controlled trial validated unblinded observational data showing that WE significantly decreased rAMR and right colon serrated polyp miss rate (clinical trial registration number: NCT03845933).

Key Words: colonoscopy, water exchange, adenoma miss rate, serrated polyp miss rate, adenoma detection rate

(*J Clin Gastroenterol* 2021;55:869–875)

The American College of Gastroenterology colorectal cancer (CRC) screening guidelines identified colonoscopy as the gold standard for screening and surveillance.[1] Colonoscopy has been estimated to prevent CRC but postcolonoscopy CRCs (PCCRCs) still occur. Of all PCCRCs, ~60% have been attributed to missed lesions.[2] A meta-analysis of tandem colonoscopy studies reported a pooled miss rate for all adenomas of 26%.[3] Case-control studies have consistently demonstrated that protection against cancers in the right colon attributed to colonoscopy ranges from 40% to 60%, which is lower than the 80% attained in the left colon.[4,5] Other reports have shown a right colon adenoma miss rate (rAMR) of up to 34% to 39%.[6–8] Right colon neoplasms are prone to be missed because they are smaller and have a nonpolypoid appearance, despite more advanced histology.[9] Observational data have shown that water exchange (WE) colonoscopy significantly decreased rAMR.[7] The unblinded data are limited by potential bias.

The cardinal feature of WE is gasless insertion into the cecum in clear water and near-complete removal of infused water, confirmed by almost equal volumes of infused and suctioned water upon arrival to the cecum. WE maximizes cleanliness during insertion. The cecum is reached with a shorter colonoscope length and less looping with WE.[10] It can be assumed that the combination of a meticulously clean colon and a short colonoscope with superb tip control contributes to the positive attributes of WE. These include improvement in overall and right colon adenoma detection rates (ADRs) and nonpolypoid ADR[10–12] and significant increases in the right colon advanced ADRs.[12] Compared with conventional colonoscopy, cap-assisted colonoscopy has been reported to increase ADR and reduce AMR.[13,14] To optimize yield, cap-assisted colonoscopy was adopted in both study arms in the current randomized controlled trial (RCT).

Received for publication July 15, 2020; accepted September 14, 2020.
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In this particular project, F.W.L. was involved in the design of the study, critical evaluation and discussion of the data, and revision of the manuscript.

F.W.L. is supported in part by Veterans Affairs (VA) and American Society of Gastrointestinal Endoscopy (ASGE) research funds.

The authors declare that they have nothing to disclose.
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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jcge.com.

DOI: 10.1097/MCG.0000000000001454

Approximately 35% of CRCs are derived from the serrated pathway.[15] Serrated polyps (SPs) include hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSAs/Ps), and traditional serrated adenomas (TSAs). The presence of SPs, even small and diminutive proximal HPs, was associated with higher rates of synchronous and metachronous advanced neoplasia.[16,17] SPs pose a challenge for detection because they are pale and flat. Increased detection of SPs in the proximal colon by WE has been reported.[18]

In the current RCT with cap-assisted colonoscopy, we compared rAMR between WE and carbon dioxide (CO_2) insufflation. The primary outcome was rAMR determined by tandem inspection of the right colon by blinded observers. We hypothesized that WE could reduce rAMR compared with the effect of CO_2. The secondary outcomes included the right colon SP miss rate (rSPMR), right colon SP detection rates (SPDRs), and ADR for the 2 colonoscopy methods.

MATERIALS AND METHODS

Study Design and Registration

The current protocol was approved by the Joint Institutional Review Board of Taiwan (19-002-T-1) and registered at *ClinicalTrials.gov* (NCT03845933). Patients at the Evergreen General Hospital in Taoyuan, Taiwan, were randomized. We screened consecutive outpatients referred for colonoscopy between April and October 2019 and recruited those meeting the inclusion criteria. Written informed consent was obtained from all participants. All authors had access to the study data and reviewed and approved the final manuscript.

Participants and Randomization

Consecutive patients aged 45 years or more, who underwent colonoscopy for screening and surveillance, and who had positive fecal immunochemical tests were eligible. Exclusion criteria included familial polyposis syndromes, personal history of CRC or inflammatory bowel disease, previous colonic resection, known obstructive lesions of the colon, gastrointestinal bleeding, American Society of Anesthesiology classification of physical status grade 3 or higher, and refusal to provide written informed consent.

Patients were randomized in a 1:1 ratio to undergo cap-assisted colonoscopy with WE or CO_2 insufflation during insertion. Randomization was conducted using a computer-generated random sequence. Stratification based on colonoscopists and colonoscopy indications was performed. The code was placed in an opaque envelope kept by an independent research assistant; the envelope was opened immediately before the procedure.

Colonoscopy Procedures

All patients received a split dose of 3-L polyethylene glycol for bowel preparation. All procedures were performed with moderate sedation (intravenous fentanyl plus midazolam) unless the patient requested no sedation. Colonoscopies were performed by 2 experienced colonoscopists (C.L.C. and Y.L.K.) using standard colonoscopes (CF-Q260AL/I; Olympus Medical Systems Corp., Tokyo, Japan). A reusable cap (MAJ-1991; Olympus) was fitted to the tip of the colonoscope. The edge of the cap protruded ~2 mm beyond the scope tip. The antispasmodic medication was not administered.

Colonoscopy was initiated with the patient in the left lateral position. In the WE group, warm water (32 to 35°C) was infused using a flushing pump (AFU-100; Olympus) to guide insertion. Details of WE techniques have been described earlier.[10–12] The infused water was removed mainly during insertion. When the cecum was reached, most of the water was suctioned. We aimed to remove 90% of the water infused during insertion. In the CO_2 group, colonoscopy was performed with minimal insufflation to aid insertion, and cleaning was performed during withdrawal.

Upon arriving at the cecum, CO_2 insufflation was used in both groups; the scope was withdrawn from the cecum to the hepatic flexure with the patient kept in the left lateral position. All polyps identified were removed. The hepatic flexure was marked by forceps, and the scope was reinserted into the cecum by the first colonoscopist with CO_2 insufflation. A tandem inspection of the right colon was performed by a second colonoscopist who stayed outside the endoscopic room and was blinded to the initial insertion method. Cleaning of the right colon was allowed during the second examination. All polyps found and removed herein were placed in different jars and counted as lesions missed by the first colonoscopist. No retroflexion was performed in either the first or second right colon examination. After the second withdrawal to the mark of the hepatic flexure, the remainder of the colon was examined by the first colonoscopist. The second colonoscopist also guessed which insertion method had been used. Adequate blinding was considered achieved if $\leq 67\%$ of the guesses were correct.[19]

The right colon included the cecum, ascending colon, and hepatic flexure. The proximal colon included the right and transverse colon. Polyp search and removal were performed during withdrawal in both groups. All proximal colon polyps were removed irrespective of their size and appearance. All diminutive polyps with hyperplastic appearance (based on narrow-band imaging) in the rectosigmoid colon were documented by photography and left alone. All polyps removed during the procedures were submitted for histologic examination by pathologists blinded to the research protocol. Adenomas included tubular/villous adenomas, SSAs, and TSAs. The SPs included HPs, SSAs/Ps, and TSAs. Advanced adenomas were defined as lesions meeting one of the following criteria: (1) lesions ≥ 10 mm in size; (2) lesions with a villous component; and (3) lesions with high-grade dysplasia.

The proportion of infused water removal during insertion was defined as the amount of aspirated water divided by the amount of infused water upon arrival at the cecum. Bowel preparation quality was evaluated according to the Boston Bowel Preparation Scale (BBPS) score by the first colonoscopist after cleaning during withdrawal. Insertion time was defined as the time between scope insertion and cecal intubation. Withdrawal time was defined as the time from cecal intubation to the time when the colonoscope was withdrawn from the anus, including the time used for cleaning, inspection, and polyp removal. The total procedure time was the sum of the insertion and withdrawal times. The time taken for cleaning, inspection, and polyp removal, respectively, was separately recorded during the tandem right colon examination.

Detection rates were based on the findings of the first colonoscopist, defined as the proportion of colonoscopies with at least 1 adenoma or SP. Lesions detected during the tandem right colon examination were used for the calculation of miss rates of the first colonoscopist. The number of

additional adenomas or SPs detected during the tandem examination divided by the total number of each detected in both examinations was defined as the rAMR and rSPMR, respectively.

Adenomas per positive colonoscopy (APPC) was defined as the total number of adenomas detected divided by the number of colonoscopies with at least one adenoma and has been found to be a complimentary indicator of colonoscopy quality.[3]

Statistical Analysis

In our reported observational study, compared with CO_2 insufflation, WE showed a significantly lower rAMR (17.5% vs. 33.8%, $P=0.034$).[7] Sample size estimation based on our published data indicated the need for 109 patients in each arm, providing 80% statistical power at a 5% level of significance. We overenrolled patients in case the blinded tandem examinations in the RCT revealed results different from those in the observational study with unblinded colonoscopists.

Summary statistics are presented as frequencies and percentages in the case of categorical variables and as the means with SDs in the case of continuous variables. The analysis was performed using an intention-to-treat approach. The Student *t* test for continuous factors, Wilcoxon rank-sum test for ordinal variables, and the χ^2 test for categorical variables were used to assess differences in the demographic and clinical characteristics of the patients. Reported risk factors of AMR included increased age, male sex, higher body mass index (BMI), poor bowel preparation, shorter insertion time, shorter withdrawal time, increased number of adenomas, and small adenoma size.[20–25] Other factors linked to increased finding of adenomas or incomplete examination that might, in turn, lead to increased miss rate of adenomas included active smoking, family history of CRC, colonoscopy indication, colonoscopist characteristics, and prior abdominal or pelvic surgery.[26–28] Excessive correct guesses would also invalidate blinding. Univariate and multivariate logistic regression analyses were used to assess which of the demographic and procedural data, including the correctness of guessing, were independent predictors of rAMR in the current study. Factors with a $P<0.1$ on univariate analysis were further entered in the multivariate logistic regression analysis. The odds ratio (OR) with 95% confidence interval (CI) is used to describe the influence of various factors on miss rates. All statistical analyses were performed using SAS version 9.3 or later (SAS Institute Inc., Cary, NC). The criterion for statistical significance was $P<0.05$.

RESULTS

A total of 448 patients were assessed for their eligibility to participate in the study. A total of 262 patients (mean age, 57.0 ± 8.5 y; 49% male individuals) were randomized, with 131 patients in each group (Fig. 1). The patients' baseline demographic and clinical characteristics are summarized in Table 1. There were no significant differences between the 2 groups with respect to age, sex, active smoking, history of abdominal surgery, family history of CRC, or colonoscopy indication. Patients in the WE group had a significantly higher BMI (25.4 vs. 24.3 kg/m^2, $P=0.01$).

Compared with CO_2, WE significantly decreased rAMR [18.0% (33/183) vs. 34.6% (62/179), $P=0.0025$] (Table 2). WE also significantly decreased the rSPMR [17.4% (27/155) vs. 39.3% (33/84), $P=0.002$] (Table 2). Multivariate logistic regression showed that the colonoscopy method (WE) was an independent predictor of rAMR (OR, 0.42; 95% CI, 0.21-0.86; $P=0.017$),

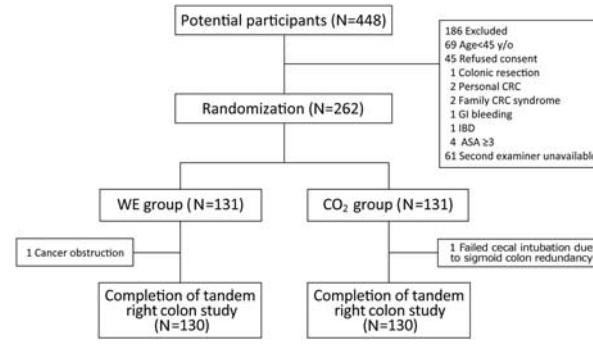

FIGURE 1. Study flowchart. ASA indicates American Society of Anesthesiology; CO_2, carbon dioxide; CRC, colorectal cancer; GI, gastrointestinal; IBD, inflammatory bowel disease; WE, water exchange.

and so was ≥2 adenomas in the right colon (OR, 2.35; 95% CI, 1.17-4.76; $P=0.017$) (Table 3). Demographic variables including BMI and procedural variables including correctness of guessing were not independent predictors of rAMR.

Procedural details are shown in Table 4. The cecum was intubated with the assigned method in 130 patients in the WE group and in 129 patients in the CO_2 group. One additional patient in each group had successful cecal intubation after the insertion method was switched. Finally, 130 patients in each group completed 2 examinations of the right colon. WE directed at near-complete removal netted 98% of infused water upon arrival to the cecum. The insertion time for WE was significantly longer than that for CO_2 ($P<0.0001$). The overall withdrawal times were comparable. The total procedure time in the WE group was significantly longer than that in the CO_2 group by ~5 minutes (38.5 ± 10.8 vs. 33.7 ± 8.6 min, $P<0.0001$). The inspection times between the groups during overall withdrawal and during the first and tandem right colon examinations were similar. A significantly lower proportion of patients in the WE group required abdominal compression or position change to achieve cecal intubation. A significantly higher proportion of patients in the WE group had excellent bowel preparation, defined as a BBPS score ≥8. Conscious sedation was provided for >95% of patients in

TABLE 1. Demographics Details and Indications for Colonoscopy

Baseline Characteristics	WE Group (N = 131)	CO_2 Group (N = 131)	*P*
Age, mean (SD) (y)	56.7 (8.8)	57.3 (8.3)	0.53
Gender, male, n (%)	61 (46.6)	67 (51.1)	0.54
Body weight, mean (SD) (kg)	66.8 (11.7)	65.0 (13.0)	0.23
Body mass index, mean (SD) (kg/m^2)	25.4 (3.4)	24.3 (3.5)	0.01
Active smoker, n (%)	23 (17.6)	20 (15.3)	0.74
Previous abdominal surgery, n (%)	48 (36.6)	41 (31.3)	0.43
Family history of CRC in first degree relative <60 y, n (%)	4 (3.1)	7 (5.3)	0.54
Indications for colonoscopy, n (%)			0.97
Screening	53 (40.5)	54 (41.2)	
Surveillance	62 (47.3)	63 (48.1)	
Positive fecal immunochemical test	16 (12.2)	14 (10.7)	

CRC indicates colorectal cancer; WE, water exchange.

TABLE 2. Right Colon Per-polyp Miss Rates (Number of Adenomas/SPs Missed by First Examiner as Indicated by Column Head)

Miss Rate	n/N (%) [95% CI] WE Group	n/N (%) [95% CI] CO_2 Group	*P*
rAMR	33/183 (18.0) [12.8-25.4]	62/179 (34.6) [27.0-44.4]	0.0025
Size category (mm)			
≤5	31/160 (19.4) [13.6-27.6]	58/164 (35.4) [27.3-45.7]	0.007
6-9	1/16 (6.3) [0.9-44.4]	2/9 (22.2) [5.6-88.9]	0.30
≥10	1/7 (14.3) [2.0-100.0]	2/6 (33.3) [8.3-100.0]	0.49
rSPMR	27/155 (17.4) [11.9-25.4]	33/84 (39.3) [27.9-55.3]	0.002
Size category (mm)			
≤5	26/141 (18.4) [12.6-27.1]	30/66 (45.5) [31.8-65.0]	0.001
6-9	0/11 (0.0)	2/16 (12.5)	N/A
≥10	1/3 (33.3) [4.7-100.0]	1/2 (50.0) [7.0-100.0]	0.77

CI indicates confidence interval; N/A, not applicable; rAMR, right colon adenoma miss rate; rSPMR, right colon serrated polyp miss rate; SP, serrated polyp; WE, water exchange.

both groups, and WE significantly reduced the doses of fentanyl and midazolam. The blinded colonoscopists' guesses about the insertion method were 66% and 55% in the WE and CO_2 groups, respectively. One patient in each group developed delayed postpolypectomy bleeding. No other complications were reported.

TABLE 3. Multivariate Logistic Regression Analysis of the Miss of at Least One Adenoma in the Right Colon

Variable	OR	95% CI	*P*
WE group vs. CO_2 group	0.420	0.206-0.858	0.017
Age (for a 5-y increase)	1.057	0.871-1.282	0.576
Female vs. male	1.296	0.646-2.701	0.465
Body mass index (for a 1-kg/m^2 increase)	1.059	0.967-1.159	0.214
Active smoker	0.709	0.292-1.725	0.449
Family history of CRC in first degree relative <60 y	1.130	0.266-4.790	0.869
Colonoscopy indication (screening vs. positive FIT)	0.463	0.174-1.234	0.124
Colonoscopy indication (surveillance vs. positive FIT)	0.768	0.305-1.934	0.575
Colonoscopist	1.271	0.622-2.599	0.511
BBPS score (for a 1-point increment)	0.975	0.571-1.664	0.925
Colonoscopy insertion time (for a 1-min increment)	1.014	0.962-1.068	0.610
Withdrawal inspection time during first right colon examination (for a 1-min increment)	1.099	0.957-1.261	0.181
≥2 adenomas vs. ≤1 adenoma in right colon during index examination	2.354	1.165-4.757	0.017
Maximal adenoma size ≤5 vs. ≥6 mm	0.930	0.491-1.764	0.825
Guess of insertion method by blinded colonoscopist (correct vs. incorrect)	0.934	0.512-1.705	0.825

BBPS indicates Boston Bowel Preparation Scale; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; OR, odds ratio; WE, water exchange.

TABLE 4. Colonoscopy Procedural Data

Variable	mean (SD) WE Group (N = 131)	mean (SD) CO_2 Group (N = 131)	*P*
Cecal intubation by assigned method, n (%)	130 (99.2)	129 (98.5)	1.00
Completion of tandem right colon examination, n (%)	130 (99.2)*	130 (99.2)*	1.00
Insertion time (min)	14.0 (6.5)	7.7 (5.6)	<0.0001
Cleaning time during withdrawal (min)	3.2 (2.2)	4.8 (2.4)	<0.0001
Inspection time during withdrawal (min)	17.3 (5.2)	17.4 (4.7)	0.80
Treatment time during withdrawal (min)	4.1 (3.9)	3.8 (4.0)	0.58
Total withdrawal time (min)	24.6 (8.0)	26.0 (6.9)	0.12
Total procedure time (min)	38.5 (10.8)	33.7 (8.6)	<0.0001
Inspection time of first right colon examination (min)	6.6 (2.0)	6.1 (2.4)†	0.08
Inspection time of second right colon examination (min)	5.2 (1.8)†	5.4 (1.8)†	0.30
Water infused during insertion (mL)	1499.6 (665.4)	39.1 (236.7)	<0.0001
Water aspirated during insertion (mL)	1460.9 (657.1)	136.8 (189.7)	<0.0001
Water infused during withdrawal (mL)	260.8 (195.9)	482.3 (249.3)	<0.0001
Water aspirated during withdrawal (mL)	331.1 (210.8)	463.4 (227.3)	<0.0001
Length of colonoscope in colon upon reaching cecum (cm)	75.5 (12.7)	76.8 (11.1)†	0.38
Need for abdominal compression to facilitate cecal intubation, n (%)	63 (48.1)	108 (82.4)	<0.0001
Need for position change to facilitate cecal intubation, n (%)	23 (17.6)	44 (33.6)	0.004
BBPS score ≥8, n (%)	29 (22.1)	16 (12.2)†	0.0485
Right colon BBPS score	2.0 (0.2)	2.0 (0.2)†	0.21
Correct guess of insertion method by blinded examiners, n (%)	87 (66.4)†	72 (55.0)†	0.08
Colonoscopy with moderate conscious sedation, n (%)	130 (99.2)	128 (97.7)	0.62
Fentanyl dose (μg/kg)	1.043 (0.282)	1.124 (0.305)	0.03
Midazolam dose (mg/kg)	0.062 (0.021)	0.068 (0.023)	0.02

*One patient in the WE group had an ascending colon cancer with luminal obstruction and tandem examination was not performed. One patient in the CO_2 group had failed cecal intubation.

†Data for the 130 patients with complete tandem examination.

BBPS indicates Boston Bowel Preparation Scale; WE, water exchange.

Detection of adenomas and SPs by the first colonoscopist is reported in Table 5. Compared with CO_2, WE had higher but statistically nonsignificant overall and right colon ADRs. This is possibly a type 2 error because of the small sample size for these 2 measures. WE achieved a significantly higher proximal colon ADR (61.8% vs. 48.9%, $P=0.047$). WE also showed higher right colon SPDR (45.8% vs. 23.7%, $P=0.0003$) and proximal colon SPDR (56.5% vs. 40.5%, $P=0.01$). The screening and surveillance intervals were shortened in 6.9% (9/131) and 16.0% (21/131) of patients in the WE and CO_2 groups, respectively, ($P=0.0119$) after incorporating the findings of the tandem

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TABLE 5. Detection of Adenomas and SPs by the First Examiner

Variable	n (%) [95% CI] WE Group (N = 131)	CO_2 Group (N = 131)	*P*
Overall ADR	95 (72.5) [64.0-80.0]	81 (61.8) [52.9-70.2]	0.09
ADR for screening indication	38 (71.7) [57.7-83.2]	29 (53.7) [39.6-67.4]	0.07
ADR for surveillance indication	41 (66.1) [53.0-77.7]	40 (63.5) [50.4-75.3]	0.85
Combined overall ADR by first and blinded second examiners	98 (74.8) [66.5-82.0]	92 (70.2) [61.6-77.9]	0.49
Right colon ADR	70 (53.4) [44.5-62.2]	56 (42.7) [34.1-51.7]	0.11
Combined right colon ADR by first and blinded second examiners	75 (57.3) [48.3-65.9]	77 (58.8) [49.8-67.3]	0.90
Proximal colon ADR	81 (61.8) [52.9-70.2]	64 (48.9) [40.0-57.7]	0.047
Overall advanced ADR	21 (16.0) [10.2-23.5]	20 (15.3) [9.6-22.6]	1.00
Right colon advanced ADR	12 (9.2) [4.8-15.5]	7 (5.3) [2.2-10.7]	0.34
Overall APPC, mean (SD)	2.9 (2.61)	2.9 (2.41)	0.83
Right colon APPC, mean (SD)	2.1 (1.42)	2.1 (1.75)	0.85
Right colon SPDR	60 (45.8) [37.1-54.7]	31 (23.7) [16.7-31.9]	0.0003
Proximal colon SPDR	74 (56.5) [47.6-65.1]	53 (40.5) [32.0-49.4]	0.01

ADR indicates adenoma detection rate; APPC, adenoma per positive colonoscopy; CI, confidence interval; SP, serrated polyp; SPDR, serrated polyp detection rate; WE, water exchange.

examination of the right colon (Supplemental Table, Supplemental Digital Content 1, http://links.lww.com/JCG/A618).[29]

DISCUSSION

To improve on the study design over our earlier unblinded observational study,[7] we attempted a blinded evaluation of the missed lesions by the second observer who was unaware of the initial insertion method. Despite the efforts, we were unable to unequivocally confirm adequate blinding because the correct guesses of the insertion method by the supposedly blinded observer were high. This was not surprising, however, because of the cleanliness of the colon and the presence of some residual water used in the initial WE insertion. Failure of blinding was disappointing and could have introduced bias in the detection of the missed lesions. The failure would also invalidate the finding that WE insertion decreased miss rates. We then analyzed the results by comparing the miss rates between the groups with correct and incorrect guesses. The results showed that there was no significant difference in the miss rates between those with correct and incorrect guesses of the insertion method (Table 6). In addition, in the multivariate analyses, the correctness of the guesses was not an independent predictor of the miss rate (Table 3). These negative findings provide the reassurance that WE as the initial insertion method did indeed significantly decrease miss rates regardless of any appearance of bias.

WE merited attention because of the reproducible significant increase in the overall ADR in RCTs with near-complete (91% to 100%) removal of infused water.[10–12] In contrast to these findings, a recent study of total underwater colonoscopy versus CO_2 insufflation suggested that insertion WE significantly increased AMR (36% vs. 23%, $P = 0.025$).[30] In that RCT, noncorrect application of insertion WE with incomplete (only 66%) removal of infused water when performing total underwater colonoscopy was related to the higher AMR. Inaccurate application of WE negatively impacted patient outcomes and could have discouraged colonoscopists who might consider its adoption. Subsequent observational data showed that with near-complete (89%) removal of infused water during insertion, WE significantly reduced rAMR.[7] We focused on the right colon because of the clinical significance of the rAMR. In this study, we emphasized the proper use of WE by striving to achieve near-complete removal of infused water during insertion. Our results showed a significant benefit of WE when 98% of the infused water was removed during insertion.

Multivariate logistic regression analysis showed that WE (new finding) and the presence of ≥ 2 adenomas (confirmation of similar reported findings in the entire colon)[24] were independent predictors of rAMR. BMI was significantly higher in the WE group but was not an independent predictor of rAMR. The inspection time during the first right colon examination was numerically longer in the WE group (6.6 vs. 6.1 min, $P = 0.08$; Table 4) but it was unassociated with rAMR based on logistic regression analysis (Table 3).

PCCRCs can arise from missed or incompletely removed lesions.[2] Both are remediable by colonoscopists with improved techniques. In a recent analysis, Anderson et al[31] reported the possible missed lesion as the most important cause for PCCRC, occurring in up to 85% of patients. Colonoscopy methods that help to decrease rAMR might reduce the occurrence of PCCRC in the right colon. The current results show that WE fits well in this framework.

The reduction in rAMR by WE has implications in surveillance intervals. After incorporating the findings of the

TABLE 6. Right Colon Miss Rates of Adenoma According to Correct and Incorrect Guesses by the Blinded Examiners

Right Colon Miss Rates	n/N (%) [95% CI] Colonoscopy with Correct Guesses	Colonoscopy with Incorrect Guesses	*P*
Per-polyp AMR	55/209 (26.3) [20.2-34.3]	40/153 (26.1) [19.2-35.6]	0.975
Per-participant AMR	41/159 (25.8) [19.2-33.3]	30/103 (29.1) [20.6-38.9]	0.572

AMR indicates adenoma miss rate; CI, confidence interval.

tandem examination of the right colon, the right colon ADR increased by 4% and 16% and the screening/surveillance intervals were shortened by 7% and 16% of patients in the WE and CO_2 groups, respectively (Table 6).[29] These findings demonstrated that WE provided a more appropriate categorization of the follow-up interval than CO_2 insufflation.

The overall ADR in the current study was well above the suggested benchmark ($\geq$25%)[32]; some adenomas were missed. In studies with ADR ranging from 67% to 72%, AMRs ranging from 28% to 16% were reported.[6,14] Despite reduced rAMR, the miss rate was 18%, suggesting there is room for improvement, even with WE. Future studies, such as those combining WE with computer-aided detection, might be helpful. Indeed, computer-aided detection-assisted colonoscopy has been reported to significantly reduce AMR.[33]

The "serrated neoplastic pathway" describes the progression of SPs to CRC.[15] Patients who were found to have proximal colon SPs at their baseline colonoscopies had an increased risk for the development of any neoplasia at the surveillance examination.[16] Proximal colon SPDR was widely variable,[34] suggesting a high miss rate of proximal colon SPs for some colonoscopists. However, data regarding SPMR in the proximal and right colon are sparse. Clark et al[6] reported an rSPMR of 23.3% with a simple repeat forward-view examination. Germane to the discussion of WE significantly decreasing rSPMR compared with the effect of CO_2, Leung et al[18] reported a significant increase in proximal colon SPDR using WE compared with air insufflation. Further research with WE may help to determine the association between colonoscopist detection and miss rates of SPs in the proximal/right colon and the risk of PCCRC.

One limitation of the current report is that the majority [94% (89/95)] of the missed adenomas were diminutive ($\leq$5 mm), consistent with the result of a recent meta-analysis.[25] Nevertheless, patients with multiple diminutive adenomas are at higher risk of developing metachronous advanced adenomas and consequently benefit from closer surveillance, as suggested by the guidelines on surveillance after screening and polypectomy.[29] In addition, patients with small and diminutive proximal colon HPs carry a higher risk of synchronous advanced neoplasia than patients without any serrated lesions.[17] In this study, WE significantly increased proximal colon ADR and proximal/right colon SPDR compared with the effect of CO_2. The adoption of WE in a CRC screening program may have the potential to reduce the incidence of metachronous advanced neoplasia and thus decrease the PCCRC risk. Indeed, WE has been reported to significantly increase advanced ADR.[35] Another limitation was that right colon BBPS scores were not significantly different between the WE and CO_2 groups, most likely because of the small sample size. Other reports have shown that WE resulted in higher BBPS scores than air insufflation in the right colon.[10–12] Third, the significant difference in BMI between the 2 groups could have introduced confounding issues as higher BMI was reported to increase AMR.[21] Interestingly, contrary to the expectation, the WE group with a significantly higher BMI had a significantly lower rAMR. The multivariate logistic regression analysis did not confirm BMI as an independent predictor for rAMR. Lastly, this was a single-center study; generalizability to other settings is unknown.

There are several unique strengths of this study. The withdrawal inspection times in the 2 arms during the first right colon examination were comparable. The APPC was not significantly different between the 2 study arms. Taken together, these data suggest that equivalent quality techniques were used during WE and CO_2 withdrawal inspections. The appropriate sample size for rAMR, and an attempt at blinding the examiners performing the tandem examination ensured optimal results. The high ADR in both groups (more than double the recommended standard) also attested to the high quality of the examinations. The WE group achieved 98% removal of infused water during insertion, confirming the appropriate application of WE.

In conclusion, the significant reductions in rAMR and rSPMR add noteworthy attributes to WE. The use of WE for CRC prevention is justified to accumulate data on reduced missed lesions and PCCRC. Combining WE with computer-aided detection might be helpful to further increase the detection rate and decrease the miss rate. Future studies should address the hypothesis that a significant reduction in rAMR and rSPMR by WE prevents PCCRC.

ACKNOWLEDGMENTS

Part of data had been reported in DDW 2020.

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