Comparing adenoma and polyp miss rates for total underwater colonoscopy versus standard CO_2: a randomized controlled trial using a tandem colonoscopy approach

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Abstract

Background and Aims:

Although water exchange may improve adenoma detection when compared to CO_2, it is unclear whether water is a better medium to fill the lumen during withdrawal and visualize the mucosa. Total underwater (TUC) involves the use of water exchange with the air valve off during insertion followed by the inspection of the mucosa under water. Our goal was to use a tandem colonoscopy design to compare miss rates for TUC to standard CO_2 for polyps and adenomas.

Methods

We randomized participants (NCT03231917; clinicaltrials.gov) to undergo tandem colonoscopies using TUC or CO_2 first. In TUC, water exchange was performed during insertion and withdrawal was performed under water. For the CO_2 colonoscopy both insertion and withdrawal were performed with CO_2. The main outcomes were miss rates for polyps and adenomas for the first examination calculated as the number of additional polyps/adenomas detected during the second examination divided by the total number of polyps/adenomas detected for both examinations. Inspection times were calculated by subtracting time for polypectomy and care was given to keep the times equal for both examinations.

Results

A total of 121 participants were randomized with 61 having CO_2 first. The overall miss rate for polyps was higher for the TUC first group (81/237; 34%) as compared to the CO_2 first cohort (57/264; 22%)(p=0.002). In addition, the overall miss rate for all adenomas was higher for the TUC first group (52/146; 36%) as compared with the CO_2 group (37/159; 23%) (p=0.025). However, 1 of the 3 endoscopists had higher polyp/adenoma miss rates for CO_2 but these were not statistically significant differences. The insertion time was longer for TUC than CO_2. After adjusting for times, participant characteristics and bowel preparation, the miss rate for polyps was higher for TUC than CO_2.

Conclusions

We found that TUC had an overall higher polyp and adenoma miss rate than colonoscopy performed with CO_2, and TUC took longer to perform. However, TUC may benefit some endoscopists, an issue that requires further study.

Introduction

Although water can be used to facilitate colonoscope insertion[1-13], the use of 2 techniques using water have been evaluated for their effects on adenoma detection as compared to standard insertion methods that use air or CO_2[14, 15]. These techniques are called water exchange (WE) and water immersion (WI). In WI, water is used to distend the colon during insertion and is removed largely during withdrawal. WI uses enough water during insertion to identify the luminal direction, but dirty water is removed primarily during withdrawal. WE is a slower insertion technique in which the air valve is turned off and clean water is infused and dirty water is suctioned during insertion and the instrument is not advanced until the lumen is clean. WE also involves aspiration of retained gas pockets during insertion. Both WE and WI use air or CO_2 rather than water to distend the lumen during withdrawal, and therefore it is not known whether visualization of the mucosa using water as a medium, as opposed to air or CO_2, increases adenoma detection[16]. In contrast to the other methods, TUC involves water exchange (WE) during insertion followed by continuous water infusion (rather than gas) on withdrawal in order to distend the lumen for total underwater mucosal visualization.

The use of water during colonoscopy may improve adenoma detection through several possible mechanisms[17]. It may help to further clear the bowel of any residual stool. In addition, because water may allow for mucosal inspection without fully distending the lumen like air does, water techniques might increase the yield for flat lesions. Very flat lesions may be less visible with full distention of the lumen. Finally, water has a magnifying effect, which may also increase detection. Thus, TUC, in which the entire procedure including withdrawal is performed underwater, could potentially improve polyp detection compared to gas insufflation.

The goal of our study was to use TUC in tandem with standard CO_2 insufflation to determine if water is a better medium than CO_2 for visualizing and detecting polyps and adenomas. Our goal was to randomize patients to tandem colonoscopy performed first with either TUC or CO_2 followed by the other medium in order to compare miss rates for polyps and adenomas. Our hypothesis was that TUC was associated with a lower adenoma and polyp miss rate for tandem performance of colonoscopy than CO_2.

Methods

We conducted a randomized trial of tandem colonoscopies comparing TUC to CO_2 insufflation. Our study was approved by the Institutional Review Boards at the White River Junction Veterans Affairs Medical Center and Indiana University. All patients were consented with written consent before the colonoscopies. In one group, TUC was used as the first method for mucosal inspection whereas in a second group, CO_2 insufflation was used first.

Study Population

Eligible subjects were adults 50-80 years who presented for colonoscopy at White River Junction VAMC, Indianapolis VAMC, and Indiana University. Exclusion criteria included a co-morbid status of American Society of Anesthesiologists physical status classification system ASA of III (severe systemic disease) or higher, inflammatory bowel disease (IBD), surgical resection of the large bowel, as well as the use of non-aspirin anticoagulants. Finally, potential subjects who did not report a clear effluent in the most recent bowel movement at time of colonoscopy were excluded from the study.

Randomization

The participants were randomized using a random number generator, stratified by endoscopist/site. The results of the randomization were opened before the initial insertion of the colonoscope, informing the endoscopist which method was first, CO_2 or TUC.

Colonoscopy

Consenting adults were randomized to undergo colonoscopy with either TUC or CO2 insufflation for the first colonoscopy followed by an examination using the other technique. All examinations were performed by 1 of 3 experienced endoscopists (J.C.A., C.J.K., D.K.R.). Participants were sedated using propofol or moderate sedation with midazolam/fentanyl and diphenhydramine. All colonoscopies were performed with high definition colonoscopes (Olympus CF-HQ190L; Olympus, Tokyo, Japan).

The randomization envelope was opened before the initial insertion. An assistant measured the inspection time with a stopwatch from insertion of scope into the rectum until the cecum was reached, stopping the watch during insertion for polyp resection in

both techniques or for time spent washing or suctioning (in CO_2 arm only). For the arm where CO_2 insufflation was used first, the lumen was distended with the gas during insertion. When the TUC technique was used first, the air valve was shut off and water was infused and any residual stool or air was suctioned out during insertion. After the cecum was intubated, the endoscopist attempted to intubate the terminal ileum. The mucosal inspection was then initiated during withdrawal when the distention with water or CO2 was adequate for visualization. Measurement of withdrawal and inspection times was initiated at this point. Inspection time was the withdrawal time minus the time for biopsy or polypectomy or for time spent washing or suctioning (in CO_2 arm only). The assistant with a stopwatch announced the withdrawal time periodically with the goal to equalize inspection times.

When the withdrawal of the colonoscope reached the rectum and after the retro-flexion was performed, the endoscopist re-inserted the colonoscope using the other technique. For the examinations with TUC as the first method, water was suctioned out of the lumen as CO_2 was introduced into the lumen during the second insertion. Upon withdrawal, the remaining water was aspirated and CO_2 was used to distend the lumen to allow for adequate inspection of the mucosa. In the group in which CO_2 is used first, CO_2 was suctioned out during the second colonoscopy as the endoscope was inserted with water infusion. As the endoscope was withdrawn, water was infused with the air valve turned off. Inspection was not started until after cecal intubation and the lumen was filled with water allowing for adequate visualization of the mucosa through the infused water. Inspection time was measured as outlined above.

Outcomes

The primary outcome measure and study endpoint was the miss rate for polyps and adenomas in the 2 study groups [18]. Miss rates were also calculated for participant level for each technique. Adenoma-level miss rates were calculated as the number of additional adenomas detected during the second examination (for both insertion and withdrawal) divided by the total number of adenomas detected during insertion and withdrawal for both examinations. These miss rates were reported for the technique used for the first examination. Participant-level miss rates were calculated as the number of participants with one or more adenomas detected during the second

examination, divided by the total number of participants with at least one adenoma in either examination. We also examined proximal (cecum, ascending colon, transverse colon and splenic flexure) adenoma miss rates as a secondary outcome, which were calculated as above. Finally, we also calculated serrated polyp (hyperplastic, sessile serrated polyp and traditional serrated adenoma)

For each polyp, we estimated size by open forceps, and noted location, method of removal, whether polyps were detected by insertion or withdrawal and whether CO_2 or TUC was used for mucosal inspection.

We used the Boston Bowel preparation score to assess the quality of the preparation. We also used a scale of good (3), fair (2) and poor (1) to assess the clarity or turbidity of the water during TUC for 3 segments, right, transverse and left colons.

Co-variates

Data collected included participant age and sex, examination indication, personal history of colorectal neoplasia, family history of CRC, time (total procedure, insertion and inspection), volume of water infused during insertion and withdrawal, quality of bowel preparation as measured by the Boston Bowel Preparation Score and medications provided during the procedure.

Statistical considerations

In calculating a sample size required to detect a clinically important difference in miss rates between TUC and CO_2 we used the following assumptions: a 30% adenoma miss rate for regular colonoscopy[19, 20]; a 10% adenoma miss rate with TUC; 50% of participants would have at least one adenoma, and participants with adenomas would have an average of 2 adenomas. We based this in part on a tandem study using cap because the cap had similar reported increase in adenoma detection to water exchange[18]. For the study to have 80% power to detect a 3-fold reduction in adenoma miss rates, by using a chi-square test with a 5% significance level, the study needed 60 adenomas per group. We assumed that each participant would have on average 2 polyps and planned to enroll at least 120 participants (60 at each site).

Participants who underwent initial colonoscopy with TUC were compared with participants who underwent colonoscopy with CO_2 first for differences in age and propofol dose by using 2-sample t-tests, for differences in sex and indication by using

chi square tests, and for a difference in quality of bowel preparation by using a Mantel-Haenszel test for ordered categories. Logistic regression was used to compare the miss rates between participants who underwent TUC first and participants who underwent CO_2 first. The model was adjusted for participant age, sex, family history of CRC, examination indication, time for inspection, insertion time and volume of water infused/aspirated. A generalized estimating equation was used to control for the effect of the endoscopist.

Results

From May 2017 to May /2018, a total of 121 participants (93 male) were randomized with 61 having CO_2 1st and 60 TUC 1st (WRJ/VAMC endoscopist: 25 TUC 1st/26 CO_2 1st; Indiana University endoscopist: 24 TUC 1st/ 26 CO_2 1st; Indianapolis VAMC endoscopist: 11 TUC 1st /9 CO_2 1st). We had 160 individuals at both sites that did not meet criteria, 23% due to age (37/160), 43% due to ASA III or higher (69/160), 3% (4/160) due to colonic resection, 3% were on non-aspirin anti coagulation medications (6/160), 11% due to poor preparation quality (17/160), 4% who had IBD (6/160) and 13% due to endoscopic concerns such as enrollment in another trial (21/160).

It should be noted that some of the colonoscopies performed by the Indianapolis VAMC endoscopist were performed at Indiana University. The average age was 63.4 years. 18 (14.9%) participants had a family history of CRC. The indications for colonoscopy were diagnostic (n=8), screening (n=38) and surveillance (n=75). The bowel preparation regimens used included Colyte (n=63; 52%), Miralax (n-27; 22.3%), MoviPrep (n=1; 0.8%), Nulytely (n=15; 12.4%) and Suprep (n=15; 12.4%). With regard to sedation, 70 (57.8%) received propofol and the rest received moderate sedation. The mean (+ S.D.) Boston Bowel Preparation Score was similar for examinations with TUC first (8.4$\pm$1.0) and CO_2 first (8.5$\pm$0.9). The results for all examinations and participants as well as across all of the sites are in Tables 1, 2, 3, and 4.

With regard to times, the average insertion time for TUC was statistically greater than that for CO2 (6.5 $\pm$ SD (3.7) versus 4.2 $\pm$ 2.7 minutes respectively; $p < 0.001$). The average withdrawal time was slightly shorter for TUC than for CO_2 but this difference was not statistically significant (11.0 $\pm$ SD (4.5) versus 11.7 $\pm$ 4.9 minutes respectively; $p = 0.27$). Finally, the average inspect time for TUC was slightly longer for TUC than for CO_2

but this difference was not statistically significant (8.1 ± SD (1.7) versus 7.7 ± 1.4 minutes respectively; p = 0.09). There were no adverse events to report at any of the sites.

There were no differences in miss rates for CO_2 and TUC for polyps, any adenoma, adenoma < 6 mm and serrated polyps when examined on a per participant basis. These data are shown in Table 5.

The scale for clarity and turbidity was used in 103 of the 121 examinations performed with TUC. Only 33 (32%) had a score of 9 or good for all segments whereas 65 (63%) had a score of 5 to 9 and only 5 (5%) had a score of 3 or less or poor visibility in all segments. With regard to specific segments, 49 out of 103 (48%) reported good clarity for all right colon segments, 54 (52%) reported good for the transverse colon segments and 46 (45%) had a score of good for the left colon segments. The score was acceptable for all segments for a similar proportion for all endoscopists 94% (44/47) for WRJ VAMC endoscopist, 85% (17/20) for Indiana VAMC endoscopist and 86% (31/36) for Indiana University endoscopist. 11 patients had poor visualization in 1 segment. There were no significant differences in terms detection or miss rates.

The overall miss rate for all polyps was 27.5% (138/501) and higher for the TUC first group (81/237; 34%) as compared with the CO_2 first cohort (57/264; 22%) (p=0.002). In addition, the overall miss rate for all adenomas was 29.2% (89/305) and higher for the TUC first group (52/146; 36%) as compared with the CO_2 group (37/159; 23%) (p=0.025). There were some differences among the endoscopists. Whereas the WRJ VAMC endoscopist had a higher miss rate when using CO_2, the 2 Indiana University (IU) endoscopists had a lower miss rate when using CO_2 for polyps and any adenoma. None of these differences between CO_2 and H2O miss rates were significant (p <0.05) for the WRJ VAMC endoscopist. However, some of the differences for the IU endoscopists were statistically significant. These data are shown in Table 6.

With regard to polyps detected on insertion, there were a similar number of polyps for the TUC groups (n=29) as compared with the CO_2 (n=37).

After adjusting for covariates, we observed that CO_2 was less likely than TUC to miss any polyp and proximal adenomas. Because univariate testing showed that “type of sedation” was not significantly different between TUC and CO_2 groups after taking endoscopists into consideration, it was not selected into the multivariate model. There

was a trend for a lower miss rate for any adenomas or adenomas <6 mm when using CO_2 as compared to TUC. The results of 4 separate GEE models are shown in Tables 6 and 7.

Discussion

This is the first randomized trial comparing TUC with standard CO_2 insufflation during colonoscopy. Using a tandem design, we observed that total underwater colonoscopy (TUC) had higher miss rates and thus was inferior to CO_2 for detecting polyps and adenomas.

Water colonoscopy can be time consuming and consume valuable resources such as procedural time for endoscopists and staff when applied to standard colonoscopy practice. Thus, our data demonstrating that TUC is not superior and in fact may be inferior to CO_2 do not support the use of this technique for the purpose of adenoma detection.

Some previous studies have demonstrated that using water during colonoscopies may increase adenomas detection[14, 15, 21]. All of these studies have used 2 different techniques, water exchange (WE) and water immersion (WI). WE, in particular has been shown to increase adenoma detection but it is not clear whether the reason is better mucosal visualization with the water or other attendant features associated with WE[17]. In particular, WE may dramatically change the quality of the bowel preparation, allowing for more adenomas to be detected. In addition, WE is associated with a longer insertion time, potentially increasing adenoma detection. Most importantly, the withdrawal in WE is performed using air or CO_2 for luminal distention. Thus, the previous studies have not been designed to examine whether a water filled colon is superior to a gas-filled colon for detecting adenomas.

In contrast, our trial compared visualization of mucosa using CO_2 versus water to distend the lumen. All of the participants used split dose bowel preparation resulting in good bowel preparation scores for examinations using both TUC and CO_2. Another strength of our study was the tandem design using each participant as their own control. We also used high-definition colonoscopies for all examinations. Furthermore, our analysis accounted for insertion time, withdrawal time, inspection time, quality of bowel preparation, as well as volume of water used. As observed in other studies, we observed a longer insertion time for WE compared with insertion with CO_2. In addition, we also observed that the quality of bowel preparation was also similar for both arms. Not surprisingly, we

observed that more water was used in the TUC groups than the air groups. Despite a longer insertion time for the water group, the overall absolute adenoma and polyp miss rates were lower for the CO_2 group, an outcome that held after adjustment for all other co-variates.

One interesting finding is that although there was a statistically significant higher overall miss rate for TUC, there were differences among the endoscopists. Although 2 endoscopists had a statistically significant higher miss rate for TUC, one had a numerically lower miss rate for TUC. Thus, like many aspects of colonoscopy performance, it is possible that the effects of water filling during withdrawal on detection may be operator dependent.

In terms of reasons why the water was not superior to CO_2, our anecdotal impression is that a central issue may be the lack of clarity of the water in the lumen during withdrawal Of 103 examinations in which the clarity was rated as good, fair, or poor, only 33 had good quality (as opposed to fair or poor) for all segments. Our anecdotal observation was that although the WE process consistently removed the green mucus usually present in even a well cleaned colon, the water seemed to induce production of white mucus. Small white mucus particles were often suspended in the water during withdrawal, requiring ongoing and often time-consuming water exchange during withdrawal. It is possible that technical changes could reduce this production of mucus. For example, we infused room temperature sterile water during TUC. Perhaps body temperature water or saline solution would be associated with less stimulation of new mucus production during TUC. Alternatively, inclusion of mucolytic agent in the water infusion might prevent this problem. We recommend that investigations to address how to prevent stimulation of new mucus production by water infusion be specifically undertaken.

Although the endoscopists were experienced with colonoscopy and use of water techniques such as exchange, there may have been a learning curve with TUC but the numbers were too small to draw any conclusions. There was a trend for a faster time of insertion for TUC but not CO_2 as the trial progressed but this was not statistically significant (data not shown).

One interesting observation is that the ease and speed of terminal intubation was faster underwater than when using CO_2, although the difference was not statistically

different. This observation is likely due to the decrease distention of the cecum and better visualization of the terminal ileum. Thus, TUC may be helpful in examinations where TI intubation is important, but more studies are needed to substantiate this finding.

One limitation was that like all detection trials, our study was not blinded to the investigators. This might have led to a bias, and all detection trials depend on the efforts of the investigators to remain unbiased. We made efforts to keep our withdrawal inspection times equal for both groups. It should be noted, although the insertion time was longer in the water group, there was a lower overall miss rate for the CO_2 group. Another limitation is that our results are applicable to those relatively healthy patients with ASA of I or II, with no history of bowel resection or IBD and not on any non-aspirin anti coagulants. Finally, another limitation was that nearly all of the adenomas in this trial were less than 1 cm and were tubular adenomas.

In summary, we observed that TUC was inferior to CO_2 with respect to adenoma miss rates, perhaps due to decreased clarity from mucous. In fact, for some outcomes we observed a decrease in adenoma detection when using water. We also observed that the insertion time was significantly longer in the TUC than in the CO_2 arms. Thus, we observed a longer procedure time with no benefit in adenoma miss rate. Our data suggest that water filling of the lumen during withdrawal, after water exchange during insertion, does not consistently increase adenoma detection and is not associated with a lower miss rate. Given the variation between endoscopists in this study with regard to detection with TUC, we recommend that others perform controlled trials of water exchange followed by water filling during withdrawal for its effect on detection.

Table 1 Participant and examination characteristics by site

		White River Junction VAMC endoscopist		Indiana University endoscopist		Indiana VAMC endoscopist	
		TUC first N (%)	CO_2 first N (%)	TUC first N (%)	CO_2 first N (%)	TUC first N (%)	CO_2 first N (%)
Average age (years ± S.D.)		64.1(7.5)	63.7(6.5)	63.4(7.6)	64.8(9.3)	61.6(7.6)	58.2(9.6)
Sex (% male)		23 (92)	25 (96)	12 (50)	17 (65)	9 (82)	7 (78)
Family history of CRC		2 (8)	4 (15)	3 (13)	4 (15)	2 (18)	3 (33)
Indication	Diagnostic	2 (8)	5 (19)	1 (4)	0 (0)	0 (0)	0 (0)
	Screening	10 (40)	12 (46)	3 (13)	5 (19)	4 (36)	4 (44)
	Surveillance	13 (52)	9 (35)	20 (83)	21 (81)	7 (64)	5 (56)
Personal history of adenomas		11 (44)	9 (35)	19 (79)	21 (81)	5 (45)	3 (33)
4 l PEG preparation used		25 (100)	26 (100)	9 (38)	6 (23)	6 (55)	6 (67)
Sedation used	CS	19 (76)	21 (81)	0 (0)	0 (0)	6 (55)	5 (56)
	MAC	6 (24)	5 (19)	24 (100)	26 (100)	5 (45)	4 (44)

TUC: Total underwater colonoscopy
CRC: Colorectal cancer
PEG: Polyethylene glycol
CS: Conscious sedation
MAC: Monitored anesthesia care

Table 2 Participant and examination characteristics across all sites

		TUC first N (%) Total=60	CO_2 first N (%) Total=61	*P* value
Average Age (years ± SD)		63.4 (7.5)	63.4 (8.4)	1.00
Sex (% male)		44 (73%)	49 (80%)	0.40
Family history of CRC		7 (11)	11 (18)	0.68
Indication	Diagnostic	3 (5%)	5 (8%)	0.54
	Screening	17 (28%)	21 (34%)	
	Surveillance	40 (67%)	35 (57%)	
Personal history of adenomas		35 (58%)	33 (54%)	0.72
Split dose preparation		60 (100)	61 (100)	1.0
4 l PEG preparation used		40 (67%)	38 (62%)	0.76
Sedation used	CS	25 (42%)	26 (43%)	1.0
	MAC	35 (58%)	35 (57%)	

TUC: Total underwater colonoscopy
CRC: Colorectal cancer
PEG: Polyethylene glycol
CS: Conscious sedation
MAC: Monitored anesthesia care

Table 3. Results of examinations by site

	White River Junction VAMC endoscopist		Indiana University endoscopist		Indianapolis VAMC endoscopist	
	TUC arms	CO_2 arms	TUC arms	CO_2 arms	TUC arms	CO_2 arms
Average total insertion time (minutes + SD)	6.6 (4.3)	5.1 (3.0)	7.2 (3.2)	3.3 (2.3)	4.2 (2.3)	3.8 (1.9)
Average total withdrawal time (minutes + SD)	10.2 (4.2)	9.4 (1.3)	11.1 (4.7)	13.4 (6.1)	12.8 (4.5)	9.4 (1.3)
Average inspection time during withdrawal (minutes + SD)	8.2 (0.6)	8.1 (0.4)	8.1 (2.4)	7.1 (1.8)	7.6 (1.5)	8.0 (1.7)
Average water infused during insertion (mL + SD)	705.5 (399.1)	203.5 (241.6)	905.5 (534.2)	96.9 (105.9)	745.0 (380.4)	124.1 (93.1)
Average water aspirated during insertion (mL + SD)	397.0 (366.6)	262.0 (302.9)	682.9 (450.7)	220.4 (198.5)	461.3 (411.8)	166.3 (136.5)
Average water infused during withdrawal (mL + SD)	891.5 (365.9)	184.6 (162.1)	1105.9 (436.0)	185.9 (217.8)	962.5 (367.6)	234.3 (157.2)
Average water aspirated during withdrawal (mL + SD)	1023.0 (334.1)	359.5 (313.9)	983.7 (564.6)	290.8 (228.4)	756.3 (286.8)	267.5 (157.7)
Average bowel preparation score Mean (SD)	8.5 (0.7)	8.5 (0.9)	8.3 (1.2)	8.3 (1.1)	8.3 (1.1)	8.8 (0.7)
Average time for successful terminal intubation (secs)	20.0 (31.0)	31.6 (38.5)	11.7 (20.8)	7.4 (7.0)	N/A	N/A

TUC: Total underwater colonoscopy

Table 4. Results of all examinations by technique

	TUC arms	CO_2 arms	*P* value
Average total insertion time (minutes + SD)	6.5 (3.7)	4.2 (2.7)	0.0001
Average total withdrawal time (minutes + SD)	11.0 (4.5)	11.7 (4.9)	0.27
Average inspection time during withdrawal (minutes + SD)	8.1 (1.7)	7.7 (1.4)	0.09
Average water infused during insertion (mL + SD)	795.4 (463.8)	145.8 (180.3)	0.0001
Average water aspirated during insertion (mL + SD)	525.5 (428.6)	228.8 (241.4)	0.0001
Average water infused during withdrawal (mL + SD)	991.7 (405.6)	193.5 (185.8)	0.0001
Average water aspirated during withdrawal (mL + SD)	962.0 (445.2)	315.8 (260.0)	0.0001
Average Boston Bowel Preparation Score (Mean [SD])	8.4 (1.0)	8.5 (0.9)	0.17
Average time for successful terminal intubation (secs)	18.5(29.5)	26.2 (35.5)	0.14

TUC: Total underwater colonoscopy

Table 5. Miss rates per participants (number of participants with polyp/adenoma missed in first examination as indicated by column head)

Finding	TUC first (N=60)	CO_2 first (N=61)	*P* value
Polyp	39/60 (65%)	32/61 (52%)	0.20
Adenoma	27/60 (45%)	23/61 (38%)	0.48
Adenoma < 6 mm	25/60 (42%)	29/61 (48%)	0.52
Any serrated polyp	14/60 (23%)	14/61 (23%)	1.0

TUC: Total underwater colonoscopy

Table 6. Polyp miss rates for all examinations as well as for each site

Polyp	Endoscopist	TUC first	CO_2 first	*P* value
Any polyp	All	81/237 (34%)	57/264 (22%)	0.002
	WRJ VAMC endoscopist	19/62 (31%)	17/39 (44%)	0.2
	Indiana Univ endoscopist	46/136 (34%)	34/185 (18%)	0.002
	Indianapolis VAMC endoscopist	16/39 (41%)	6/40 (15%)	0.01
Any adenoma	All	52/146 (36%)	37/159 (23%)	0.025
	WRJ VAMC endoscopist	14/51 (27%)	10/21 (48%)	0.11
	Indiana Univ endoscopist	29/73 (40%)	24/115 (21%)	0.0075
	Indianapolis VAMC endoscopist	9/22 (41%)	3/23 (13%)	0.047
Any proximal adenoma	All	35/103 (34%)	21/100 (21%)	0.06
	WRJ VAMC endoscopist	7/38 (18%)	5/12 (42%)	0.13
	Indiana Univ endoscopist	21/47 (45%)	16/78 (21%)	0.005
	Indianapolis VAMC endoscopist	7/18 (39%)	0/10 (0%)	0.03
Adenoma 6-9 mm	All	5/28 (18%)	0/15 (0%)	0.14
	WRJ VAMC endoscopist	2/14 (14%)	0/2 (0%)	1.00
	Indiana Univ endoscopist	3/11 (27%)	0/13 (0%)	0.08
	Indianapolis VAMC endoscopist	0 (0%)	0 (0%)	1.00
Adenoma < 6 mm	All	45/109 (41%)	36/128 (28%)	0.04
	WRJ VAMC endoscopist	12/33 (36%)	10/18 (56%)	0.24
	Indiana Univ endoscopist	24/57(42%)	23/89(26%)	0.047
	Indianapolis VAMC endoscopist	9/19 (47%)	3/21 (14%)	0.038
Serrated Polyp	All	22/69 (32%)	18/82 (22%)	0.20
	WRJ VAMC endoscopist	3/7 (43%)	6/11 (55%)	1.00
	Indiana Univ endoscopist	10/45 (22%)	10/60 (17%)	0.62
	Indianapolis VAMC endoscopist	9/17 (53%)	2/11 (18%)	0.11

TUC: Total underwater colonoscopy

Table 7. Logistic regression models predicting adenoma and polyp miss rates comparing CO_2 with TUC (reference)

Factor	Adjusted Odds Ratio	95% CI	*P* value
Polyp miss rate	0.28	0.11-0.71	0.007
Adenoma miss rate	0.32	0.09-1.19	0.09
Proximal adenoma miss rate	0.16	0.03-0.89	0.036
Adenoma < 6 mm miss rate	0.22	0.05-1.05	0.06

Adjusted Odd Ratios shown represent the results of separate Generalized Estimating Equations, adjusted for participant age, sex, family history of CRC, examination indication, time for inspection, insertion time, volume of water infused/aspirated

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Acronyms

Total underwater colonoscopy: TUC

Water exchange: WE

Water immersion: WI

Adenoma detection rate: ADR

American Society of Anesthesiologists: ASA

US Multi-Society Task Force on Colorectal Cancer: USMSTF

Serrated polyp detection rate: SDR

Sessile serrated adenomas/polyps: SSA/P

Traditional serrated adenomas: TSA

Hyperplastic polyps: HP

Boston Bowel Preparation Scale: BBPS

American Society for Gastrointestinal Endoscopy: ASGE

Colorectal Cancer: CRC

Body Mass Index: BMI

Inflammatory bowel disease: IBD

PEG: Polyethylene glycol

CS: Conscious sedation

MAC: Monitored anesthesia care