

## Retrospective Study

**Evidence to suggest adoption of water exchange deserves broader consideration: Its pain alleviating impact occurs in 90% of investigators**

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**Abstract**

**AIM:** To determine variations in colonoscopy real-time insertion pain among investigators using three different insertion techniques.

**METHODS:** From March 2013 through June 2014, 18-85-year-old diagnostic and 50-70-year-old screening patients were enrolled at each center to on-demand sedation colonoscopy with water exchange (WE), water immersion

(WI) and insufflation with air or CO<sub>2</sub> for insertion and withdrawal [air or carbon dioxide (AICD)]. Data were aggregated for analysis. Primary outcome: Variations in real-time maximum insertion pain (0 = none, 1-2 = discomfort, 10 = worst).

**RESULTS:** One thousand and ninety-one cases analyzed: WE ( $n = 371$ ); WI ( $n = 338$ ); AICD ( $n = 382$ ). Demographics and indications were comparable. The WE group had the lowest real-time maximum insertion pain score, mean (95%CI): WE 2.8 (2.6-3.0), WI 3.8 (3.5-4.1) and AICD 4.4 (4.1-4.7),  $P < 0.0005$ . Ninety percent of the colonoscopists were able to use water exchange to significantly decrease maximum insertion pain scores. One investigator had high insertion pain in all groups, nonetheless WE achieved the lowest real-time maximum insertion pain score. WE had the highest proportions of patients with painless unsedated colonoscopy (*vs* WI,  $P = 0.013$ ; *vs* AICD,  $P < 0.0005$ ); unsedated colonoscopy with only minor discomfort (*vs* AICD,  $P < 0.0005$ ), and completion without sedation (*vs* AICD,  $P < 0.0005$ ).

**CONCLUSION:** Aggregate data confirm superiority of WE in lowering colonoscopy real-time maximum insertion pain and need for sedation. Ninety percent of investigators were able to use water exchange to significantly decrease maximum insertion pain scores. Our results suggest that the technique deserves consideration in a broader scale.

**Key words:** Colonoscopy; Painless colonoscopy; Water immersion; Water exchange; Colonoscopy pain

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**Core tip:** Randomized controlled trials (RCTs) have shown water exchange (WE) to have considerable advantage in decreasing colonoscopy insertion pain. Assessment of individual investigators' performance using WE in RCTs is usually not reported. We assessed the performance of individual investigators in 3 RCTs comparing WE, water immersion and gas insufflation (with air or carbon dioxide) during insertion, to determine whether observations are reproducible across investigators and what factors might contribute to variations. Aggregate data show that individual investigators had significant variations in insertion pain scores and use of adjunct maneuvers together with short insertion time, but the pain alleviating impact of WE occurs in 90% of them. WE has the highest proportions of patients with painless unsedated colonoscopy; complete unsedated colonoscopy with only minor discomfort and completion without sedation.

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## INTRODUCTION

Water exchange (WE) and water immersion (WI) are two colonoscopy techniques that entail infusion of water to distend the lumen during the insertion phase. Randomized controlled trials (RCTs) have shown WE (airless insertion, infused water aspirated predominantly during insertion to clear the view and minimize distension) to have considerable advantage in decreasing colonoscopy real-time maximum insertion pain when compared with WI (water infused as adjunct to insufflation, and aspirated predominantly during withdrawal without attempting to maximize colon cleanliness during insertion) and air<sup>[1-3]</sup> or carbon dioxide insufflation<sup>[3,4]</sup>. WE is a relatively new technique, and requires new maneuvers not entirely intuitive to colonoscopists<sup>[5]</sup>. In spite of this, in a previous report focused on individual investigators' performance<sup>[6]</sup>, WE has shown reproducibility and repeatability in decreasing maximum insertion pain, usually not reported in RCTs. Some of the factors associated with difficult colonoscopy (*e.g.*, prior abdominal surgery, low body mass index) and insertion pain are favorably influenced by WE<sup>[2,3,7,8]</sup>.

We assessed the performance of individual investigators in three recently completed RCTs in a multinational setting, to determine whether the effect of WE in reducing real-time maximum insertion pain is reproducible across investigators and what factors (*e.g.*, use of adjunct maneuvers of loop reduction and abdominal compression, insertion time, *etc.*) might contribute to variations among them.

## MATERIALS AND METHODS

Patient-related and procedure-related factors were collected prospectively at our centers (NCT01781650, 01780818, 01954862): St. Barbara Hospital, Iglesias (Italy); N. S. di Bonaria Hospital, San Gavino Monreale (Italy) and the Vitkovice Hospital, Ostrava (Czech Republic).

From March 2013 through June 2014, 18-85-year-old diagnostic and 50-70-year-old screening patients were enrolled and randomized to WE, WI or insufflation with air or carbon dioxide (AICD) at each site. Sedation was available on-demand at patients' request<sup>[2,3]</sup>. Local Ethics Committees approved the protocols. Written informed consent was obtained from all patients at enrollment. All authors had access to the study data, reviewed and approved the final manuscript. Statistical review of the study was performed by a biomedical statistician.

### Study procedures

Colonoscopies were performed by 10 board-certified endoscopists, five with experience in about 10000 AICD, 260 WE and 120 WI. One investigator had experience in about 7200 AICD, 260 WE, 800 WI. The last four investigators had experience in about 3000-7000 AICD and 150 WE. One had experience in 800 WI, the

remaining three in 90 WI.

A split-dose bowel preparation was used to clean the colon<sup>[2,3]</sup>. Enrolled patients were assigned to the different insertion techniques by computer-generated lists, with block allocation and stratification based on participating endoscopists. Group assignment was kept in sealed envelopes that were opened just before the start of the procedure. The patients, but not endoscopists and assisting nurses, were blinded to the insertion method used: The monitors were concealed from patients' view. Endoscopists were blinded to insufflation gas used: Light source and insufflators were concealed from the view. At discharge patients were asked to guess which insertion method had been used (infusion of water or insufflation), and investigators which gas had been insufflated. If no more than half of the responses were correct, their blinding was considered adequate<sup>[2,3]</sup>.

Colonoscopy began with the patients in the left lateral position without premedication. High-resolution wide-angle variable-stiffness adult video colonoscopes (Olympus HD 180) were used. Variable stiffness was used at the discretion of the investigators, but its record was not kept<sup>[2,3]</sup>. Cardiopulmonary function was monitored throughout.

In patients randomized to WE and WI, insufflation was turned off before starting the procedure. After the rectosigmoid junction was reached, the colon was irrigated with water at 37 °C using flushing pumps<sup>[2,3]</sup>.

Water exchange involved infusion of water during insertion to distend the lumen to the minimum required to reach the cecum. When opaque water was encountered, infusion and near-simultaneous suction were applied until clear water was in front of the instrument. Residual air pockets, feces and infused water were removed predominantly during insertion<sup>[2,3]</sup>.

Water immersion involved the infusion of water during the insertion phase to aid passage to the cecum without attempting to clear the colon contents, with limited use of insufflation when necessary<sup>[2,3]</sup>. Infused water was removed predominantly during withdrawal.

In the AICD group colonoscopy was performed in the usual fashion with the minimal insufflation required to reach the cecum<sup>[2,3]</sup>. In all arms insufflation was used during withdrawal to obtain adequate distension of the lumen for exploration<sup>[2,3]</sup>.

In all groups loop reduction, position change and abdominal compression were applied in that sequence as needed when the instrument failed to advance, and not per protocol at determined anatomic locations. Cecal intubation was defined as reaching beyond the ileocecal valve with adequate visualization of the appendix orifice.

### **Pain assessment and sedation**

Pain was assessed using a numeric rating scale (NRS) with faces outlines and verbal descriptors, with a score 0 = absence of pain, 1-2 = simply "discomfort", 10 = the worst possible pain. Before the procedure, a

nurse explained the NRS to the patients. They were informed that the request for pain information was meant to assess the need and dosage of sedation<sup>[2,3]</sup>, and to let the colonoscopist be alerted to the need to use maneuvers to minimize discomfort (*e.g.*, removal of colonic content, loop reduction, change in patient position and/or abdominal compression). At the discretion of the assisting nurse, at irregular intervals, patients were asked about discomfort or pain several times during the procedure and encouraged to report it spontaneously. Responses were recorded and the real-time maximum insertion pain score noted. On-demand sedation was offered at a NRS score  $\geq 2$  (discomfort). If patients accepted, sedation was started with an intravenous dose of 2 mg of midazolam, with step-ups of 1 mg (up to 5 mg) if the patients continued to report pain<sup>[2,3]</sup>. To avoid bias by the colonoscopist, medication was administered based on the patients' confirmation that the pain was no longer tolerable, and not at the discretion of the endoscopist. No other analgesic or sedative medications were administered. At discharge, a blinded nurse recorded patients' recalled maximum insertion pain using the same NRS in the absence the personnel who performed the procedure.

### **Study endpoints**

The primary outcome was real-time maximum insertion pain score recorded during the insertion phase of colonoscopy. Secondary outcomes included recalled pain at discharge, individual performance of investigators in terms of several procedural outcomes; analysis of painless unsedated colonoscopy, unsedated colonoscopy completed with only discomfort (NRS = 1-2), and complete unsedated colonoscopy with any pain score.

### **Statistical analysis**

Standard descriptive statistics were used to assess the distribution of the study variables and to compare them. Pain values were computed using mean at 95%CI and analyzed by using the *t*-test and analysis of variance (ANOVA) where appropriate. *P* values < 0.05 were considered significant.

## **RESULTS**

The database stored data relative to 1091 patients randomly allocated to WE (*n* = 371), WI (*n* = 338) or AICD (*n* = 382). Overall, demographics, body mass index (BMI), previous abdominal surgery and indications were comparable (Table 1).

In greater detail, Table 1 shows that age was comparable among the study groups and individual investigators. Indications for colonoscopy are reported in Table 2. Abdominal pain had comparable proportions among methods and individual investigators, except for Investigator number 1 and Investigator number 8 that had significantly higher proportions in the WE group. The other indications were comparable among

**Table 1 Water-aided colonoscopy and insufflation colonoscopy: Baseline characteristics and indications of 1091 patients**

	WE (n = 371)	WI (n = 338)	AICD (n = 382)	P value <sup>1</sup>
Age, yr, mean (± SD)	59 (12.2)	59 (11.6)	59 (12.0)	0.627
Females, n (%)	149 (40.2)	140 (41.4)	151 (39.5)	0.873
Males, n (%)	222 (59.8)	198 (58.6)	231 (60.5)	
BMI, mean (± SD)	26.7 (4.8)	26.5 (4.7)	26.4 (4.7)	0.607
Previous abdominal surgery, n (%)	141 (38.0)	116 (34.3)	116 (30.4)	0.087
Indications for colonoscopy, n (%)				
Abdominal pain	68 (18.3)	52 (15.4)	59 (15.4)	0.127
Bleeding	90 (24.3)	89 (26.3)	108 (28.3)	0.076
Change in bowel habits	73 (19.7)	64 (18.9)	60 (15.7)	0.977
Anemia	8 (2.2)	12 (3.6)	7 (1.8)	0.048
Diverticulosis	4 (1.1)	5 (1.5)	7 (1.8)	0.787
Other	46 (12.4)	37 (10.9)	46 (12.0)	0.403
Screening	82 (22.1)	79 (23.4)	95 (24.9)	0.361

<sup>1</sup>ANOVA. n: Number of patients; WE: Water exchange for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; WI: Water immersion for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; AICD: Insufflation with air or CO<sub>2</sub> for insertion and withdrawal; SD: Standard deviation.

**Table 2 Variations among investigators**

	Real-time maximum insertion pain, mean (95%CI)			P value						
	WE (n = 371)	WI (n = 338)	AICD (n = 382)		Females (%)	BMI (± SD)	Previous abdominal surgery (%)	Abdominal compression (%)	Loop reduction (%)	Insertion time, min (± SD)
<b>All investigators</b>	<b>2.8</b> (2.6-3.0)	<b>3.8</b> (3.5-4.1)	<b>4.4</b> (4.1-4.7)	<b>&lt; 0.0005<sup>1</sup></b> <b>WE vs WI &lt; 0.0005<sup>2</sup></b> <b>WE vs AICD &lt; 0.0005<sup>2</sup></b> <b>WI vs AICD 0.002<sup>2</sup></b>						
<b>Investigator</b>	<b>WE</b>	<b>WI</b>	<b>AICD</b>	<b>Females (%)</b>	<b>BMI (± SD)</b>	<b>Previous abdominal surgery (%)</b>	<b>Abdominal compression (%)</b>	<b>Loop reduction (%)</b>	<b>Insertion time, min (± SD)</b>	
1	2.1 (1.7-2.5)	4.0 (3.4-4.7)	4.7 (4.1-5.3)	46.3	26.1 (4.9)	51.3	57.5	61.3	13 (6.5)	
2	2.9 (2.4-3.3)	3.3 (2.8-3.9)	4.1 (3.5-4.7)	32.9	27.0 (4.8)	46.8	67.1	63.3	11 (5.5)	
3	2.3 (1.0-3.6)	2.3 (1.0-3.6)	4 (2.9-5.2)	28.6	27.5 (4.4)	7.1	57.1	7.1	11 (4.4)	
4	2.4 (1.7-3.2)	1.9 (0.6-3.3)	2.8 (2.0-3.5)	28.6	25.6 (4.2)	10.7	71.4	21.4	15 (6.7)	
5	2.9 (1.8-4.0)	3.7 (2.3-5.1)	3.5 (2.2-4.8)	46.2	24.6 (3.3)	7.7	92.3	84.6	9 (2.8)	
6	2.4 (1.6-3.3)	2.6 (1.5-3.7)	3.5 (2.5-4.5)	60.9	28.4 (6.8)	13.0	73.9	52.2	10 (4.0)	
7	2.4 (1.6-3.2)	3.7 (2.3-5.1)	4.3 (3.0-5.6)	17.6	26.4 (2.5)	41.2	64.7	82.4	12 (7.2)	
8	2.8 (2.0-3.6)	2.4 (1.7-3.0)	2.4 (1.4-3.3)	50.0	25.6 (4.0)	35.7	92.9	92.9	15 (5.2)	
9	2.9 (2.3-3.5)	4.1 (3.4-4.9)	6.0 (5.3-6.7)	37.7	28.4 (5.2)	45.9	36.1	34.4	9 (3.1)	
10	5.3 (4.4-6.2)	7.1 (6.3-8.0)	7.0 (6.2-7.9)	50	27.2 (5.6)	35.7	21.4	10.7	8 (3.0)	
P values	< 0.0005 <sup>1</sup>	< 0.0005 <sup>1</sup>	< 0.0005 <sup>1</sup>	0.074 <sup>1</sup>	0.025 <sup>1</sup>	< 0.0005 <sup>1</sup>	< 0.0005 <sup>1</sup>	< 0.0005 <sup>1</sup>	< 0.0005 <sup>1</sup>	

<sup>1</sup>ANOVA; <sup>2</sup>χ<sup>2</sup>. n: Number of patients; WE: Water exchange for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; WI: Water immersion for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; AICD: Insufflation with air or CO<sub>2</sub> for insertion and withdrawal; SD: Standard deviation; BMI: Body mass index.

methods, except for Anemia (0.048).

Table 3 shows that female patients were equally distributed among study groups and individual investigators. There were significant differences in terms of BMI within the WE and WI groups ( $P = 0.025$  and  $P < 0.0005$ ,

respectively). The AICD group had the lowest proportion of patients with previous abdominal surgery, comparable among individual investigators ( $P = 0.405$ ). Among the 10 individual investigators there were significant differences in terms of use of abdominal compression,

**Table 3** Water exchange for insertion group, significant factors associated with increased pain score of Investigator number 8 vs all the other investigators, *n* (%)

	Investigator number 8 ( <i>n</i> = 28)	All other investigators ( <i>n</i> = 343)	<i>P</i> value
Abdominal pain as indication, females and males	11 (39.3)	57 (16.6)	0.003 <sup>1</sup>
Females with abdominal pain as indication	9 (32.1)	21 (6.1)	< 0.0005 <sup>1</sup>
Females with previous abdominal surgery, any indication for colonoscopy	6 (21.4)	24 (7.0)	0.018 <sup>1</sup>

<sup>1</sup>χ<sup>2</sup>.**Table 4** Investigator number 8, significant differences associated with increase in real-time maximum insertion pain score among methods, *n* (%)

	WE ( <i>n</i> = 28)	WI ( <i>n</i> = 28)	AICD ( <i>n</i> = 24)	<i>P</i> value
Females and males, abdominal pain as indication	11 (39.3)	2 (7.1)	7 (29.2)	0.017 <sup>1</sup> WE vs WI 0.004 <sup>2</sup> WE vs AICD 0.446 <sup>2</sup> WI vs AICD 0.064 <sup>2</sup>
Females with abdominal pain as indication	9 (32.1)	1 (3.6)	3 (12.5)	0.008 <sup>1</sup> WE vs WI 0.005 <sup>2</sup> WE vs AICD 0.059 <sup>2</sup> WI vs AICD 0.352 <sup>2</sup>
Females with abdominal pain as indication and previous abdominal surgery	6 (21.4)	1 (3.6)	1 (4.2)	0.031 <sup>1</sup> WE vs WI 0.043 <sup>2</sup> WE vs AICD 0.069 <sup>2</sup> WI vs AICD 0.911 <sup>2</sup>

<sup>1</sup>ANOVA; <sup>2</sup>χ<sup>2</sup>; *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; WI: Water immersion for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; AICD: Insufflation with air or CO<sub>2</sub> for insertion and withdrawal; SD: Standard deviation; BMI: Body mass index.

loop reduction and cecal intubation time.

### Primary outcome analysis

The number of patients examined by each colonoscopist ranged from 12 to 80 per group.

Table 2 shows the analysis of the performance of the individual investigators. There were significant differences of mean real-time maximum insertion pain score among WE, WI and AICD, mean (95%CI): WE 2.8 (2.6-3.0), WI 3.8 (3.5-4.1) and AICD 4.4 (4.1-4.7), *P* < 0.0005; differences were significant also within each study group. WE consistently showed the lowest real-time maximum insertion pain scores, and with the exception of Investigator number 8, who showed WE to have higher pain scores than all the other insertion techniques, the trend that WE was the least painful was observed in all the rest of investigators, regardless of their prior experience with the insertion technique used (Table 2). The WE group showed significant variations in terms of BMI, previous abdominal surgery, abdominal compression, loop reduction and insertion time among individual investigators.

Table 3 shows that, compared with all the other investigators, the WE group of Investigator number 8 had a significantly higher proportion of patients with abdominal pain as indication (39.3% vs 16.6%, *P* = 0.003), cohort that included mostly irritable bowel syndrome (IBS) patients; and a significantly higher

proportion of female patients (32.1% vs 7.0%, *P* < 0.0005) with a significantly higher incidence of previous abdominal surgery: 21.4% vs 7.0%, *P* = 0.018 (Table 3).

The same analysis across Investigator's number 8 study groups (Table 4) showed that his WE group had a higher proportion of cases with abdominal pain as indication (ANOVA among groups *P* = 0.017; WE 39.3% vs WI 7.1%, *P* = 0.004); in particular women (ANOVA among groups *P* = 0.008; WE 32.1% vs WI 3.6%, *P* = 0.005; vs AICD 12.5%, *P* = 0.059). This WE group of female patients with abdominal pain as indication showed also a higher incidence of previous abdominal surgery (ANOVA among groups *P* = 0.031): WE 21.4% vs WI 3.6%, *P* = 0.043; vs AICD 4.2%, *P* = 0.069. The comparisons of WE vs AICD lacked enough power (type II error) to show significance.

Investigator number 10, with infrequent use of loop reduction or abdominal compression and short mean insertion time (Table 2), had high real-time maximum insertion pain scores in all groups, but the use of WE brought insertion pain down in this investigator: ANOVA among groups *P* = 0.004.

### Secondary outcomes analysis

Compared with AICD and WI, WE had the highest proportion of patients with painless unsedated colonoscopy (Table 5): 13.5%, vs WI 7.7% (*P* = 0.013); vs

**Table 5** Pain during insertion, patients' tolerance and sedation, *n* (%)

	WE ( <i>n</i> = 371)	WI ( <i>n</i> = 338)	AICD ( <i>n</i> = 382)	<i>P</i> value
Painless unsedated colonoscopy <sup>2</sup>	50 (13.5)	26 (7.7)	23 (6.0)	WE vs WI 0.013 <sup>1</sup> WE vs AICD < 0.0005 <sup>1</sup> WI vs AICD 0.374 <sup>1</sup>
Unsedated, completed with only discomfort <sup>2</sup>	134 (36.1)	106 (31.4)	87 (22.8)	WE vs WI 0.180 <sup>1</sup> WE vs AICD < 0.0005 <sup>1</sup> WI vs AICD 0.009 <sup>1</sup>
Completed without sedation	321 (86.5)	287 (84.9)	292 (76.4)	WE vs WI 0.537 <sup>1</sup> WE vs AICD < 0.0005 <sup>1</sup> WI vs AICD 0.004 <sup>1</sup>
On-demand sedation	50 (13.5)	51 (15.1)	90 (23.6)	WE vs WI 0.537 <sup>1</sup> WE vs AICD < 0.0005 <sup>1</sup> WI vs AICD 0.004 <sup>1</sup>

<sup>1</sup> $\chi^2$ ; <sup>2</sup>Pain score based on numeric rating scale (NRS): 0 = absence of pain, 1-2 = discomfort, 10 = maximum pain. *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; WI: Water immersion for insertion, insufflation with air or CO<sub>2</sub> for withdrawal; AICD: Insufflation with air or CO<sub>2</sub> for insertion and withdrawal; SD: Standard deviation.

AICD 6.0% ( $P < 0.0005$ ). Compared with AICD, WE and WI showed a significantly higher proportion of unsedated colonoscopies with only discomfort, corresponding to NRS values of 1-2: WE 36.1%, vs WI 31.4% ( $P = 0.180$ ); vs AICD 22.8% ( $P < 0.0005$ ); WI vs AICD  $P = 0.009$  (Table 5). WE and WI achieved also a significantly higher proportion of procedures completed without sedation: WE 86.5%, vs WI 84.9% ( $P = 0.537$ ); vs AICD 76.4% ( $P < 0.0005$ ); WI vs AICD  $P = 0.004$  (Table 5). Accordingly, WE and WI showed low proportions of patients requesting on-demand sedation: WE 13.5%, vs WI 15.1% ( $P = 0.537$ ); vs AICD 23.6% ( $P < 0.0005$ ); WI vs AICD  $P = 0.004$  (Table 5).

### Procedural outcomes

Cecal intubation rates (WE 98.7%, WI 97.9% and AICD 97.9%;  $P = 0.692$ ) and total procedure times [minutes ( $\pm$  standard deviation, SD): WE 23 (9.7), WI 22 (11.7) and AICD 22 (11.0),  $P = 0.177$ ] were comparable. A complete report has already been presented elsewhere<sup>[2,3]</sup>. Comparisons of amount of water infused and aspirated during insertion and during withdrawal attested to the correct application of WE and WI methods<sup>[2,3]</sup>.

## DISCUSSION

In this study aggregate data confirm superiority of WE in lowering insertion pain compared with WI and AICD. The pain alleviating impact of water exchange shows the lowest mean real-time maximum insertion pain scores in 90% of the investigators, despite their pain scores were significantly different within the WE, WI and AICD groups, and regardless their significantly different individual performances in terms of use of adjunct maneuvers and insertion time (Tables 2 and 3). A plausible explanation of the effect of WE in decreasing real-time maximum insertion pain is the avoidance of the variable elongation of the colon induced by different amounts of insufflated gas, with the associated loop formation<sup>[9]</sup> that leads to insertion pain<sup>[10]</sup>. Full understanding, however, will require

additional investigation.

Previous abdominal surgery is associated with higher colonoscopy pain score<sup>[11-14]</sup> or with difficult procedures<sup>[15]</sup>. The AICD group showed the lowest proportion of patients with previous abdominal surgery and had comparable BMI values among individual investigators (Table 3); nevertheless, AICD pain scores were almost invariably higher than the other two groups (Table 2). Compared with WE, WI had a lower proportion of patients with previous abdominal surgery; and yet also WI showed a trend toward higher pain scores than WE (Table 2).

With the exception of Investigator number 8, the consistent pattern of pain scores being lowest in the WE group qualifies WE as the best method for achieving low pain scores during the insertion phase of colonoscopy, with a reproducible effect among different colonoscopists. Several factors contributed to the aberrant finding of Investigator's number 8 higher real-time maximum insertion pain score in the WE group compared with the WI and AICD groups: His WE group had a significantly higher proportion of female patients with abdominal pain as indication (this cohort comprised IBS cases) and with previous abdominal surgery. All these are risk factors for difficult<sup>[15]</sup> or painful colonoscopy<sup>[1,11-14,16-22]</sup>, with expected laborious intubation and increased need for sedation<sup>[11,22,23]</sup>.

Moreover, Investigator number 8 had experience in only 150 WE and 90 WI procedures. WE is a relatively new technique, and requires new maneuvers not entirely intuitive to colonoscopists. Collectively, all these factors contributed to the higher real-time maximum insertion pain score achieved in his WE group of patients.

Our data show that WE is effective in achieving significantly higher proportions of painless unsedated procedures, completion with only minor discomfort or without sedation. These two last outcomes are also achieved by WI.

Unsedated colonoscopy represents an important option for many patients<sup>[24,25]</sup> and has important implications in terms of patient satisfaction, medical related

complications<sup>[26,27]</sup> and cost savings in health care systems, particularly in settings where the use of sedation is discretionary and targeted also to low-risk patients<sup>[28,29]</sup>. The scheduled unsedated option may also have an impact on no-show due to lack of an escort, improving patients' adherence to colonoscopy, particularly important in screening settings<sup>[30]</sup>.

Promotion of on-demand sedation colonoscopy and successful completion of the unsedated option minimizes institutional resources and lessens patients' burdens<sup>[6,31]</sup>.

Multiple published reports have indicated colonoscopists around the world were able to harness the pain reduction impact of WE<sup>[2,3,7,8,32-40]</sup>.

The limitations of our study require comment. The endoscopists and the nurse assistants were not blinded to the WE and WI insertion techniques. However, interactions with patients were standardized, colonoscopists' bias was minimized and pain recording was very accurate<sup>[2,3]</sup>. The unblinded real-time maximum insertion pain scores obtained during colonoscopy were internally validated by correlating them with the blinded recalled maximum insertion pain scores recorded at discharge: the Pearson correlation range was 0.6-0.9 ( $P < 0.0005$ )<sup>[2,3]</sup>. The blinded pain recording after the procedure validated the unblinded one collected during the examination<sup>[2,3]</sup>. Mean correct patients' guesses about insertion method used (36%) and investigators' about insufflated gas (41%) confirmed their adequate blinding<sup>[2,3]</sup>.

Our study has certain notable features. To the best of our knowledge, it has the largest sample of multiple individual investigators' real-time maximum insertion pain scores obtained in a head-to-head randomized controlled comparison of WE, WI and AICD. Patients were recruited from a routine clinical setting in different community hospitals at multinational sites. The important finding is the reproducibility and repeatability of WE in attenuation of maximum insertion pain when compared with WI and AICD.

In summary, in this head-to-head randomized controlled comparison of WE, WI and AICD with reliable real-time maximum insertion pain scores, minimization of investigators' bias and adequate patient blinding, despite variations in pain scores by individual investigators, WE is superior to WI and AICD in attenuating real-time maximum insertion pain.

We conclude that the high proportion of colonoscopists able to use WE to decrease insertion pain in the current study, as well as in previous published reports, suggest that the technique deserves consideration in a broader scale.

## COMMENTS

### Background

Water exchange (WE) and water immersion (WI) are two colonoscopy techniques that entail infusion of water to distend the lumen during the insertion phase. WE is characterized by airless introduction to the cecum, infused water is aspirated predominantly during this phase to clear the view and minimize distension. In WI water is infused as an adjunct to insufflation and aspirated predominantly during withdrawal, without attempting to maximize

colon cleanliness during insertion. Randomized controlled trials (RCTs) have shown WE to have considerable advantage in decreasing colonoscopy real-time maximum insertion pain when compared with WI or with air or carbon dioxide insufflation. WE shows its beneficial effect in decreasing colonoscopy pain also in patients presenting with factors associated with difficult and painful colonoscopy (e.g., prior abdominal surgery, low body mass index).

### Research frontiers

The authors assessed the performance of individual investigators in three recently completed RCTs in a multinational setting, to determine whether the effect of WE in reducing real-time maximum insertion pain is reproducible across investigators, and what procedural factors (e.g., use of adjunct maneuvers of loop reduction and abdominal compression, insertion time, etc.) might contribute to variations among them.

### Innovations and breakthroughs

The study has the largest sample of multiple individual investigators' real-time maximum insertion pain scores obtained in a head-to-head randomized controlled comparison of WE, WI and air or carbon dioxide (AICD). Patients were recruited from a routine clinical setting in different community hospitals at multinational sites. The data confirm superiority of WE in lowering insertion pain compared with WI and AICD. Its pain alleviating impact shows the lowest mean real-time maximum insertion pain scores in 90% of the investigators, despite their significantly different insertion pain scores within the WE, WI and AICD groups, along with significantly different individual performances in terms of use of adjunct maneuvers and insertion time.

### Applications

WE achieves higher proportions of painless unsedated procedures, or completed with only minor discomfort, decreasing the need for sedation. Promotion of on-demand sedation colonoscopy and successful completion of the unsedated procedures lessens patient's burdens.

### Terminology

WE: A colonoscopy insertion technique that entails airless insertion; water is infused to facilitate progression of the instrument to the cecum and is aspirated predominantly during this phase to clear the view and minimize distension. WI: A colonoscopy insertion technique that entails infusion of water as an adjunct to insufflation to help reaching the cecum; water is aspirated predominantly during withdrawal, without attempting to maximize colon cleanliness during insertion.

### Peer-review

The article described the difference in colonoscopy real-time maximum insertion pain among WE, WI and AICD and among individual investigators in routine clinical settings. It is useful to analyze colonoscopy pain produced by different techniques in order to reduce the suffering of patients. It is a meaningful research in clinical practice. The study had a logical design in methods, the analysis of the difference of pain among WE, WI and AICD was detailed and produced credible results.

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