

# Carbon Dioxide Insufflation or Warm-water Infusion for Unsedated Colonoscopy: A Randomized Controlled Trial in Patients with Chronic Constipation in China

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## ABSTRACT

**Aims:** The effect of carbon dioxide (CO<sub>2</sub>) insufflation and warm-water infusion during colonoscopy on patients with chronic constipation remains unknown. We evaluated CO<sub>2</sub> insufflation and warm-water irrigation versus air insufflation in unsedated patients with chronic constipation in China. **Patients and Methods:** This randomized, single-center, controlled trial enrolled 287 consecutive patients, from January 2014 to January 2015, who underwent colonoscopy for chronic constipation. Patients were randomized to CO<sub>2</sub> insufflation, warm-water irrigation and air insufflation colonoscopy insertion phase groups. Pain scores were assessed by the visual analog scale (VAS). The primary outcome was real-time maximum insertion pain, recorded by an unblinded nurse assistant. At discharge, the recalled maximum insertion pain was recorded. Meanwhile, patients were requested to select the VAS at 0, 10, 30, and 60 min after the procedure. In addition, cecal intubation and withdrawal time, total procedure time, and adjunct measures were recorded. **Results:** A total of 287 patients were randomized. The correlation between real-time and recalled maximum insertion pain ((Pearson coefficient  $r = 0.929$ ;  $P < 0.0001$ ) confirmed internal validation of the primary outcome. The mean real-time maximum pain scores during insertion  $2.9 \pm 2.1$  for CO<sub>2</sub>,  $2.7 \pm 1.9$  for water achieved a significantly lower pain score compared with air ( $5.7 \pm 2.5$ ) group (air vs CO<sub>2</sub>  $P < 0.001$ ; air vs water  $P < 0.001$ ). However, no significant pain score differences were found between the patients in the CO<sub>2</sub> and water groups (CO<sub>2</sub> vs water,  $P = 0.0535$ ).  $P$  values in painless colonoscopy and only discomfort colonoscopy (pain 1–2) were, respectively, 6 (6.4%) and 8 (8.5%) for air; 17 (17.7%) and 29 (30.2%) for CO<sub>2</sub>; 16 (16.5%) and 31 (31.9%) for water. At 0, 10, 30, and 60 min postprocedure, pain scores showed in the CO<sub>2</sub> and water groups had significantly reduced than in air group. Insertion time was significantly different between air ( $10.6 \pm 2.5$ ) and CO<sub>2</sub> ( $7.2 \pm 1.4$ ) (air vs CO<sub>2</sub>  $P < 0.001$ ), air and water ( $6.9 \pm 1.3$ ) (air vs water  $P < 0.001$ ). However, CO<sub>2</sub> and was not significantly different in cecum-intubated time (CO<sub>2</sub> vs water,  $P = 0.404$ ). CO<sub>2</sub> and water group in extubation time were significantly different, respectively, CO<sub>2</sub> ( $7.9 \pm 1.1$ ) and water ( $8.0 \pm 1.1$ ) (CO<sub>2</sub> vs water,  $P = 0.707$ ). CO<sub>2</sub> or water group required less implementation of adjunct measures and more willingness to repeat the procedure. **Conclusions:** Compared with air, the CO<sub>2</sub> or water-aided method reduced real-time maximum pain and cecum-intubated time for chronic constipated patients in unsedated colonoscopy. The CO<sub>2</sub> insufflation or warm-water irrigation may be a simple and inexpensive way to reduce discomfort in unsedated patients with constipation. This study demonstrated an advantage of using CO<sub>2</sub> insufflation and warm-water irrigation during colonoscopy in unsedated constipated patients in China.

**Key Words:** Air insufflation, carbon dioxide insufflation, constipation, unsedated colonoscopy, warm-water infusion

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## INTRODUCTION

Chronic constipation is a common health problem that is highly prevalent in the general population worldwide.<sup>[1]</sup> The global prevalence of chronic idiopathic constipation is estimated to be approximately 14%.<sup>[2]</sup> Despite being considered a functional disorder, it has a substantial negative impact on the patient's health-related quality of life. An epidemiological study of China's community groups showed that the prevalence of chronic constipation is 4%-6%, and it increased with age. The prevalence of chronic constipation can be as high as 22% for people older than 60 years in the general population. Colonoscopy is the gold standard for the evaluation of colon disease.<sup>[3]</sup> Thus, performing a colonoscopy because of constipation is common. Endoscopists generally think that performing a colonoscopy for patients with constipation is more difficult than for patients without constipation. Constipation as an indication for colonoscopy was an independent factor that was associated with a prolonged insertion time.<sup>[3]</sup> Colonoscopy can lead to abdominal distension and pain. In addition, if individuals experience bloating and abdominal pain after colonoscopy, this may reduce the individual's willingness to undergo the next screening or surveillance procedure. Thus, the discomfort after colonoscopy plays a pivotal role in determining adherence to the screening program. Sedation colonoscopy has been associated with a variety of adverse hemodynamic effects,<sup>[4,5]</sup> and scheduled unsedated colonoscopy has patient-centered advantages.<sup>[6]</sup>

In China, patients are required to pay the medical bills themselves, and hence most people tend to opt for cheaper unsedated colonoscopy. The increasing demand for colonoscopy has renewed interest in unsedated procedures and alternative techniques, such as carbon dioxide insufflation and warm-water infusion, which have been suggested to improve patient tolerance for colonoscopy compared with air insufflation.

Several studies have shown that CO<sub>2</sub> insufflation is safe and effective<sup>[7-13]</sup> in reducing the pain and discomfort experienced after colonoscopy. Current European guidelines, therefore, strongly recommend the use of CO<sub>2</sub> insufflation for colonic endoscopic procedures.<sup>[14]</sup>

In 1999, Baumann reported a new method that used water infusion instead of air infusion during colonoscopy.<sup>[15]</sup> In colonoscopy, this water method is an easier and more efficient method compared with the traditional air method. It decreases the sedation rate and the patient's pain, and also increases the cecal intubation rate without reducing the disease detection rate and without increasing the detection time.<sup>[16-18]</sup> However, despite the clinical evidence, the impact of CO<sub>2</sub> insufflation and warm-water infusion

for unsedated colonoscopy in patients with constipation remains unknown. To our knowledge, this is the first report focusing on such patients. The aim of the current randomized controlled trial (RCT) is to assess the impact of CO<sub>2</sub> insufflation and warm-water infusion on patients with chronic constipation.

## PATIENTS AND METHODS

### Ethics statement

The study protocol was approved by the Ethics Committee for Human Research of Subei People's Hospital and adhered to the tenets of the Declaration of Helsinki. The study is in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulation. Written informed consent was obtained from all study subjects. We explained risk and benefits on the consent form. Participants were voluntary, and individuals could withdraw from the trial at any time.

### Equipment

Colonoscope was with water jet channels (CF-H180DI/L; Olympus Medical Systems, Tokyo, Japan) in all study procedures.

The Olympus UCR CO<sub>2</sub> intraluminal insufflation unit was used for CO<sub>2</sub> examinations.

### Water intervention

In this group, the air pump of the endoscopy machine was turned off before the colonoscope tip was inserted through the anus. Warm-water infusion comprises of simultaneous infusion of warm-water (approximately 37°C, using flushing pumps (Olympus OFP2)) and suction of residual feces. Water is infused to identify the lumen. To clear the view, water exchange is used. The residual feces are removed simultaneously by suction to keep the lumen from being excessively distended. Most of the water infused was aspirated predominantly during withdrawal. Mucosal examination was carried out during withdrawal.

### Patients

Between January 2014 and January 2015, 300 consecutive patients who underwent colonoscopy for chronic constipation as the sole indication at Gastroenterology Department of Subei People's Hospital, JiangSu, China, were enrolled into this study. Participants were diagnosed with functional constipation, according to the Roman III standard.<sup>[19]</sup> All individuals provided written informed consent before entering the trial. Exclusion criteria were as follows: Suspected hemodynamic instability, severe cardiovascular and pulmonary problems and inability to communicate well, which might interfere with the patient completing the visual analog scale (VAS). An unblinded assistant

recorded real-time maximum insertion pain scores during colonoscopy, another blinded assistant recorded the recalled pain scores at discharge and the third assistant administered the postprocedure questionnaire to document postprocedure pain scores. Randomization was done by means of a computer-generated random number sequence (mixed block size), taking into account three different endoscopists. Allocation was concealed and kept in a sealed envelope, opened after the informed consent signature. The patient, but not the endoscopist, was blinded to the randomization group. All colonoscopies were performed with the patient in an unsedated state. Patients who were unable to complete the entire colonoscopy were excluded from the analysis.

### Study end points

Real-time insertion pain was chosen as the primary outcome. We used a VAS to assess their pain. The score was graded from 0 (no pain at all), 1–2 (only discomfort) to 10 (the most severe), and the assessment was completely delegated to nurses based on their ability to accurately assess the pain of colonoscopy. Real-time pain scores were obtained every 1–2 min with the precise timing at the discretion of the nurse assistant to avoid leading the colonoscopist to engage in maneuvers at predictable intervals to bias the observations. The maximum pain score recorded was noted as the real-time maximum insertion pain score. After the procedure, at discharge, another nurse blinded to the examination asked patients to quantify the pain experienced by placing a mark over the pain scale when the personnel who performed the colonoscopy were not present. The maximum pain score was noted.<sup>[20,21]</sup>

Secondary outcomes included postprocedure pain, cecal intubation, withdrawal time, and total procedure time. In addition, endoscopic findings, position changes, abdominal compression, and patient satisfaction and willingness to repeat the examination were recorded.

All three endoscopists participating in the study were experienced in diagnostic and therapeutic colonoscopies (each having performed more than 4000 colonoscopies) including carbon dioxide insufflation and water infusion.

### Statistical analysis

The data were analyzed using SPSS statistical analysis software (IBM SPSS Statistics, version 20, USA). Descriptive statistics were computed for all variables. Continuous variables are presented as the mean  $\pm$  standard deviation (SD). Analysis of variance, Chi-square, and *t* tests were used to compare proportions and means for normally distributed data, as appropriate. A *P* value of  $<0.05$  was considered statistically significant.

## RESULTS

A total of 300 patients were enrolled into the study. Of these, 287 patients completed the questionnaire. The other 13 patients were excluded as follows: Eight decided not to undergo colonoscopy and three requested sedation. The patients who requested sedation were one patient in the CO<sub>2</sub> insufflation group and two in air insufflation group, and two patients had poor bowel preparation (one patient in the CO<sub>2</sub> insufflation group and one in the air insufflation group). There were 96 patients randomized to receive CO<sub>2</sub> insufflation, 97 who underwent colonoscopy with water infusion and 94 who underwent the standard treatment with air. All patient colonoscopies were completed to the cecum [Figure 1].

The mean age of the participants was  $54.5 \pm 11.6$  years, and 140 were male (48.8%) and 147 female (51.2%). The mean body mass index (BMI) of the participants was  $23.7 \pm 2.4$ . No differences were identified among the three groups in the distribution of baseline characteristics, including age, gender, and BMI [Table 1].

*P* values of real-time maximum insertion mean pain were  $5.7 \pm 2.5$  for air,  $2.9 \pm 2.1$  for CO<sub>2</sub>,  $2.7 \pm 1.9$  for water (air vs CO<sub>2</sub> *P*  $< 0.001$ ; air vs warm-water *P*  $< 0.001$ ; CO<sub>2</sub> vs water, *P* = 0.0535) [Table 2].

The mean recalled maximum pain scores reported to the blinded observer at discharge were as follows: Compared with air groups ( $5.9 \pm 2.7$ ), CO<sub>2</sub> ( $3.2 \pm 2.4$ ) and water groups ( $2.7 \pm 2.1$ ) were significantly less painful (air vs CO<sub>2</sub> *P*  $< 0.001$ ; air vs water *P*  $< 0.001$ ), and both were not found to be significantly different (CO<sub>2</sub> vs water, *P* = 0.0167) [Table 2].

To summarize [Table 2], pain score trends were similar for the primary outcome and for recalled pain at discharge: CO<sub>2</sub> and water achieved significantly lower pain scores, and both were significantly less painful than air. CO<sub>2</sub> and air were comparable, as well, water and air were comparable. There was a correlation between the unblinded real-time maximum pain scores obtained during colonoscopy and the recalled pain scores reported by patients to the blinded observer at the time of discharge. Pearson's correlation was 0.929 and a *P* value  $<0.001$ , demonstrating that blinded recording provided internal validation of unblinded recording.

Air group had the lowest proportion of painless (pain score 0) (6.4%; vs CO<sub>2</sub> 17.7%, vs water (16.5%)). The proportion of patients reporting only discomfort (pain score 1–2) insertion (air 8.5%, CO<sub>2</sub> 30.2%, water 31.9%) was significantly different, air being significantly lower than CO<sub>2</sub> (*P*  $< 0.001$ )

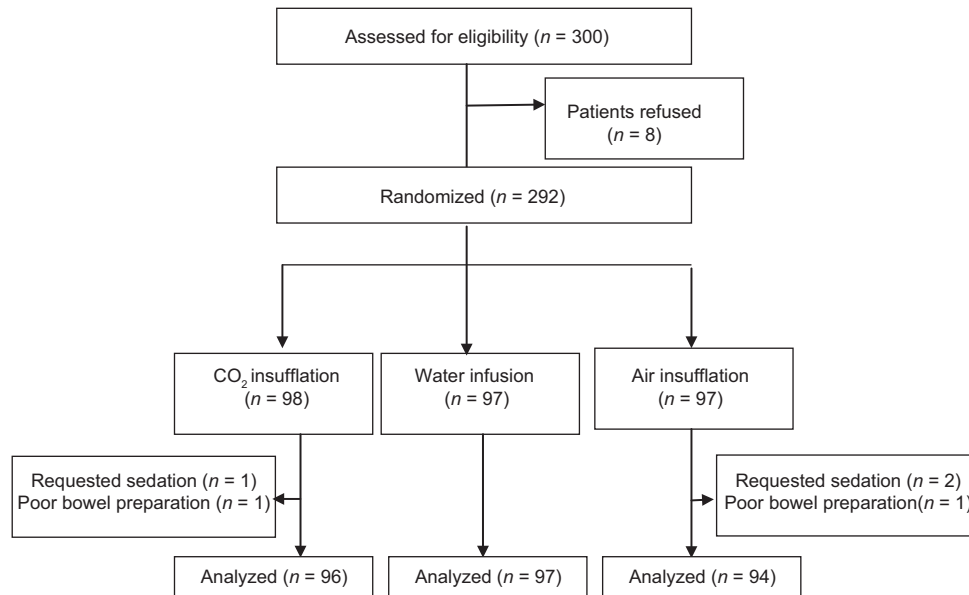


Figure 1: Flow of participants through the trial

**Table 1: Baseline patient characteristics and distribution of endoscopic findings**

Parameters	Air (n=94)	CO <sub>2</sub> (n=96)	Water (n=97)	P value
Age, mean±SD, years	55±10.7	54.3±11.7	54.3±12.4	0.891 <sup>a</sup>
Gender, n (%)				
Female	49 (52.1)	47 (48.9)	51 (52.6)	0.861 <sup>b</sup>
BMI, mean±SD, kg/m <sup>2</sup>	24.6±2.3	23.6±2.4	23.1±2.4	0.411 <sup>a</sup>
Distribution of findings, n (%)				
No pathological findings	31 (32.9)	32 (33.3)	31 (31.9)	0.938 <sup>b</sup>
Hyperplastic polyp	25 (26.6)	27 (28.1)	30 (30.9)	0.797 <sup>b</sup>
Adenoma	12 (12.8)	14 (14.6)	13 (13.4)	0.933 <sup>b</sup>
Carcinoma	0	0	0	
Melanosis coli	8 (8.5)	8 (8.3)	9 (9.3)	0.970 <sup>b</sup>
Diverticulum	8 (8.5)	7 (7.3)	7 (7.2)	0.932 <sup>b</sup>
Inflammatory bowel disease	3 (3.2)	2 (2.1)	2 (2.1)	0.847 <sup>b</sup>
Angiodysplasia	7 (7.4)	6 (6.3)	5 (5.2)	0.808 <sup>b</sup>

<sup>a</sup>One-way ANOVA. <sup>b</sup> $\chi^2$ -test, number (%) of patients. SD: Standard deviation, BMI: Body mass index

and water ( $P < 0.001$ ). The number of patients who requested sedation was 2 (2.1%; air), 1 (1.1%; CO<sub>2</sub>), and 0 (0%; water). There were no significant differences on-demand sedation among the three insufflation groups ( $P = 0.0352$ ) [Table 2].

The distribution of endoscopic findings is shown in Table 1. Overall, no significant differences were found among the three groups. There were no pathological findings in 32.8% of patients in this study as the primary diagnosis, and the proportion of patients who had no pathological findings was 32.9% (air), 33.3% (CO<sub>2</sub>), and 31.9% (water). The presence of hyperplastic polyps was the secondary outcome. Overall, 28.6% of patients had hyperplastic polyps and the

proportion of patients with hyperplastic polyps among the three insufflation groups was 26.6% (air), 28.1% (CO<sub>2</sub>), and 30.9% (water). Adenoma had the third highest overall proportion (13.6%), and the proportion of adenoma among the three insufflation groups was 12.8% (air), 14.6% (CO<sub>2</sub>), and 13.4% (water). No carcinoma was found in any patient in the three groups.

Table 3 shows the comparison of outcomes among the three insufflation groups. In the time to reach the cecum, there were significant differences between air and CO<sub>2</sub> ( $10.6 \pm 2.5$  vs  $7.2 \pm 1.4$ , respectively;  $P < 0.001$ ), as well as between air and water groups ( $10.6 \pm 2.5$  vs  $6.9 \pm 1.3$ , respectively;  $P < 0.001$ ). However, the cecum-intubation did not significantly differ between the CO<sub>2</sub> and water groups ( $7.2 \pm 1.4$  vs  $6.9 \pm 1.3$ , respectively;  $P = 0.404$ ). For extubation time, water insufflation group was longer than CO<sub>2</sub> (CO<sub>2</sub> vs water,  $P = 0.707$ ).

The frequency of position changes among the three insufflation groups was 45 (47.9%; air), 23 (23.9%; CO<sub>2</sub>), and 20 (20.6%; water), and frequency of manual pressure was 53 (56.4%; air), 19 (19.8%; CO<sub>2</sub>), and 21 (21.6%; water) [Table 2]. Compared with air group, CO<sub>2</sub> and water groups showed significantly less adjunct measures ( $P < 0.001$ ).

The proportion of patients who reported that they would be willing to have the procedure repeated in the future under the same circumstances was much more (90) 93.8% in the CO<sub>2</sub> group and (91) 93.8% in the water group than (58) 61.7% in the air group.

No significant adverse events (hemodynamic and cardiopulmonary events) occurred during the period.

## DISCUSSION

In contrast to some earlier studies, this study evaluated the effect of CO<sub>2</sub> insufflation or warm-water irrigation for chronic constipated patients in unsedated colonoscopy and real-time maximum insertion pain as the primary outcome,<sup>[21,22]</sup> as well, combined with postprocedure pain score.

Constipation as an indication for colonoscopy was an independent factor that was associated with a prolonged insertion time.<sup>[3]</sup> Constipated patients suffered much more uncomfortable procedure because of abdominal pain and distension in colonoscopy. Sedation colonoscopy may increase the risks of adverse events especially in the elderly or those with cardiorespiratory problems, what is more, in China, considering the own high medical costs, most of the patients tend to go unsedated for their examinations. We need to find a good method to solve this problem. Previous studies showed CO<sub>2</sub> insufflation or water-aided procedure improved the levels of procedure-related tolerance and pain, in comparison with air. However, despite the clinical evidence, the impact of CO<sub>2</sub> insufflation and warm-water infusion for unsedated colonoscopy in patients with constipation remains unknown. We therefore designed a randomized study to

assess the efficacy of CO<sub>2</sub> insufflation and warm-water infusion for constipated patients in unsedated colonoscopy.

The current findings show that CO<sub>2</sub> insufflation or warm-water infusion in patients improves not only the levels of procedure-related pain, but also postprocedure-related pain, in comparison with air, without affecting the cecal intubation and adenoma detection rates. Collectively, our data show that compared with air, CO<sub>2</sub> or water was effective in reducing real-time maximum insertion pain score or recalled pain scores for constipated patients, but there was no difference between CO<sub>2</sub> and water [Table 2].

We use real-time maximum insertion pain recorded by an unblinded nurse assistant as the primary outcome, to compensate for potential bias introduced by the unblinded nurse, blinded recalled pain at discharge was used to validate the unblinded real-time insertion pain scores.<sup>[21,22]</sup> Real-time insertion pain scores distinguished CO<sub>2</sub> from air groups and water from air. On the other hand, recalled pain scores at discharge confirmed both CO<sub>2</sub> and water to be less painful than air. Combining real-time insertion pain scores with recalled pain scores at discharge, we can confirm that CO<sub>2</sub> insufflation or warm-water infusion can relieve pain during procedure in colonoscopy for constipated patients.

In addition, abdominal pain was measured at 0, 10, 30, and 60 min after the procedure [Figure 2]. The present study shows that CO<sub>2</sub> insufflation or warm-water infusion in patients with constipation who are undergoing unsedated colonoscopy improves the level of postprocedure-related tolerance and pain, compared with air insufflation.

However, contrasting results have also been shown. Chen reported that CO<sub>2</sub> insufflation does not reduce pain scores during colonoscope insertion in unsedated patients.<sup>[23]</sup> Regarding water infusion, Park *et al.*<sup>[24]</sup> reported opposite results in Korean patients who had low discomfort scores and who were examined using the air method, and there was no attenuation of discomfort by water-aided method. In the current study, however, the water infusion method significantly reduced discomfort in unsedated patients. Garborg<sup>[25]</sup> reported that water exchange was a good

**Table 2: Pain score**

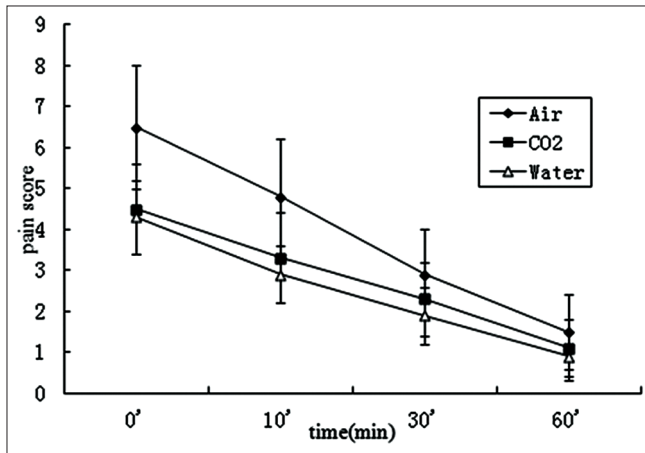
Parameters	Air (n=94)	CO <sub>2</sub> (n=96)	Water (n=97)	P value
Primary outcome: Real-time maximum	5.7±2.5	2.9±2.1	2.7±1.9 (0.000) <sup>a</sup>	A vs C 0.000 A vs W 0.000 C vs W 0.535
Insertion pain score mean±SD				
Pain score at discharge mean±SD	5.9±2.7	3.2±2.4	2.7±2.1 (0.000) <sup>a</sup>	A vs C 0.000 A vs W 0.000 C vs W 0.167
Painless colonoscopy (pain 0), n (%)	6 (6.4)	17 (17.7)	16 (16.5)	0.044 <sup>b</sup>
Only discomfort colonoscopy (pain 1-2), n (%)	8 (8.5)	29 (30.2)	31 (31.9)	0.000 <sup>b</sup>
Requested sedation, n (%)	2 (2.1)	1 (1.1)	0	0.352 <sup>b</sup>

<sup>a</sup>One-way ANOVA. <sup>b</sup>χ<sup>2</sup>-test. SD: Standard deviation, A: Air, C: CO<sub>2</sub>, W: Water

**Table 3: Outcome measures**

Parameters	Air (n=94)	CO <sub>2</sub> (n=96)	Water (n=97)	P value		
				A vs C	A vs W	C vs W
Time to cecal intubation, mean±SD, min	10.6±2.5	7.2±1.4	6.9±1.3	(0.000) <sup>a</sup> 0.000	0.000	0.404
Extubation time, mean±SD, min	7.5±1.3	7.9±1.1	8.0±1.1	(0.011) <sup>a</sup> 0.016	0.005	0.707
*Total procedure time, mean±SD, min	18.2±3.1	15.1±1.8	14.9±1.7	(0.000) <sup>a</sup> 0.000	0.000	0.638
Position change, n (%)	45 (47.9)	23 (23.9)	20 (20.6)		0.000 <sup>b</sup>	
Abdominal compression, n (%)	53 (56.4)	19 (19.8)	21 (21.6)		0.000 <sup>b</sup>	
Willingness to repeat, n (%)	58 (61.7)	90 (93.8)	91 (93.8)		0.000 <sup>b</sup>	

<sup>a</sup>One-way ANOVA. <sup>b</sup>χ<sup>2</sup>-test. SD: Standard deviation, A: Air, C: CO<sub>2</sub>, W: Water. \*Total procedure time was the sum of the cecal intubation time and the withdrawal time



**Figure 2:** Mean pain score groupwise at 0, 10, 30, and 60 min postprocedure

alternative to CO<sub>2</sub> insufflation for colonoscope insertion. However, our current results indicate that there was no significant difference between the water group and CO<sub>2</sub> group for the primary outcomes of abdominal pain during intubation, after the procedure.

The current study showed that CO<sub>2</sub> insufflation and warm-water infusion shorten cecal intubation time, total procedure time, and that a significantly higher proportion of patients examined using the CO<sub>2</sub> insufflation or water-aided method expressed willingness to repeat the scheduled unsedated colonoscopy compared with air group. In extubation time, warm-water infusion required much more time than CO<sub>2</sub> insufflation [Table 3]. The plausible reason was that water exchange is used to lavage and clean the bowel, and dirty water is suctioned from the colon during insertion and subsequent suction during withdrawal. However, we found that the time taken to infuse and suction water was well balanced by the reduced time to insert the colonoscope into the cecum, and the total procedure time was almost same as CO<sub>2</sub> insufflation, but, less than that of using the standard air insufflation technique.

However, Chen *et al.*<sup>[23]</sup> suggested that CO<sub>2</sub> insufflation is necessary in only the extubation phase of the colonoscopy and not during intubation. Szura *et al.*<sup>[26]</sup> reported that CO<sub>2</sub> insufflation during screening unsedated colonoscopy does not decrease the duration of the procedure or that of cecal intubation. In this study, CO<sub>2</sub> insufflation is effective during intubation and decrease duration of the procedure or that of cecal intubation, which is not consistent with some literature.

Position changes and abdominal compression, needed less frequently when using CO<sub>2</sub> and water, had almost similar proportions between the two groups [Table 3]; this may

suggest an easier insertion phase. Air group required many more position changes, this reaching significance versus CO<sub>2</sub> or water, reflecting a more difficult insertion and more frequent need for adjunct maneuvers.

Some authors<sup>[2,27,28]</sup> performed a systematic review of studies and showed that constipation was not associated with the development of colorectal cancer and constipation alone should not be an indication for colonoscopy. However, we found a certain proportion of hyperplastic polyps, adenomas, and colon melanosis [Table 1]. Our sample size is small, we had no long-term followup, and the relationship between colorectal cancer and constipation is not confirmed. In the present study, hyperplastic polyps and adenomas were the main endoscopic findings [Table 1]. Previous studies<sup>[29-31]</sup> reported that a higher adenoma detection rate might be observed in patients who underwent water infusion, but we did not find any significant difference in either the prevalence of hyperplastic polyps or adenomas across the three groups.

## CONCLUSION

For constipated patients, insufflation with CO<sub>2</sub> or water reduced real-time maximum insertion pain and improved insertion time, total procedure time, procedure-related tolerance and pain, and patients required fewer assistance measures, compared with air insufflation. The cecal intubation and neoplasia detection rates were not affected. There were no significant differences between the water group and CO<sub>2</sub> group for the primary outcomes of real-time abdominal pain during intubation. The CO<sub>2</sub> and water-aided method may be a simple and inexpensive way to reduce discomfort in unsedated patients; these methods are controlled by the colonoscopist easily. This suggests that CO<sub>2</sub> and water insufflation are necessary. Warm-water or CO<sub>2</sub> in the insertion phase seems to be an important item to investigate further, and it could improve the acceptance and tolerability of unsedated colonoscopy in patients with constipation.

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## Conflicts of interest

There are no conflicts of interest.

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