

Water exchange versus carbon dioxide insufflation in unsedated colonoscopy: a multicenter randomized controlled trial

Authors

Kjetil Garborg^{1,2}, Michał F. Kaminski³, Wolfgang Lindenburger⁴, Håvard Wiig^{1,4}, Audun Hasund¹, Ewa Wronski³, Rolf Bruun Bie⁵, Britta Kleist⁵, Leif Løvdal⁵, Øyvind Holme^{1,2}, Mette Kalager^{2,6,7}, Geir Hoff^{2,7,8}, Michael Brethauer^{2,9}

Institutions

Institutions are listed at the end of the article.

submitted 4. April 2014
accepted after revision 15. September 2014

Bibliography

DOI <http://dx.doi.org/10.1055/s-0034-1390795>
Published online: 20.11.2014
Endoscopy 2015; 47: 192–199
© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 0013-726X

Corresponding author

Kjetil Garborg, MD
Department of Medicine
NordICC Study Centre
Sorlandet Hospital
P.B. 416
4604 Kristiansand
Norway
Fax: +4738073597
Kjetil.Garborg@sshf.no



Scan this QR-Code to watch the video comment.

Background and study aims: Compared with air insufflation, water exchange and carbon dioxide (CO_2) insufflation have been shown to reduce colonoscopy discomfort; however, head-to-head studies of the two methods are lacking. We aimed to compare water exchange and CO_2 insufflation directly with regard to pain during primary unsedated colonoscopy.

Methods: Patients willing to undergo unsedated colonoscopy at three centers in Norway and Poland were randomized 1:1 to water exchange or CO_2 insufflation during colonoscope insertion. Patients were blinded to group allocation. The primary end point was the proportion of patients reporting moderate or severe procedural pain on a 4-point verbal rating scale (VRS-4) at discharge. Secondary outcomes included the proportion of patients reporting no pain on the VRS-4.

Introduction



Sedation during colonoscopy is associated with a risk for complications, high costs, and post-procedural activity restrictions and need for escort. Unsedated colonoscopy should be an option at the patient's discretion [1], but refinement of colonoscopy technique and equipment is necessary for the procedure to be completed at a tolerable level of discomfort.

Several trials have shown that carbon dioxide (CO_2) insufflation during colonoscopy is associated with less discomfort than is air insufflation, primarily because of a reduction in post-procedural pain [2]. Water exchange, a water-aided colonoscopy technique that employs the constant infusion and removal of water during insertion to the cecum without the use of air or CO_2 , has also been shown to reduce discomfort during colonoscopy compared with standard air insufflation [3–5]. Few studies have compared water-aided colonoscopy with CO_2 insufflation [6, 7]. Moreover, most previous trials of water-aided co-

Results: A total of 473 patients were randomized. A discharge pain questionnaire was completed by 226 of 234 patients (97%) in the water exchange group versus 226 of 239 patients (95%) in the CO_2 group ($P=0.37$). Moderate or severe pain was reported by 47 of 226 patients (21%) in the water exchange group versus 60 of 226 patients (27%) in the CO_2 group ($P=0.15$). No pain was reported by 100 of 226 patients (44%) and 69 of 226 patients (31%) in the water exchange and CO_2 groups, respectively ($P=0.003$). On-demand sedation was used in 15 patients (6%) in each group ($P=0.95$).

Conclusions: There was no significant reduction in moderate or severe pain in a comparison of water exchange with CO_2 insufflation. The secondary outcome of no pain was significantly more frequent in the water exchange group.

Clinical trials registry number: NCT01633333.

lonoscopy included predominantly male patients, were single-center trials, or were carried out by few endoscopists [8]. Our aim was to compare water exchange colonoscopy with CO_2 insufflation in a multicenter randomized controlled trial comprising a gender-balanced study population to improve the generalizability of the results.

Patients and methods



Study design and end points

This was a prospective, multicenter, single-blinded randomized controlled trial. Patients were randomized 1:1 to colonoscopy with water exchange or CO_2 insufflation during colonoscope insertion (► Fig. 1). Randomization lists were generated by a computer in blocks of six (three patients allocated to water exchange and three to CO_2), stratified by gender. Study collaborators not involved in the colonoscopy procedures randomized the patients and prepared a sealed envelope for each patient containing information on group

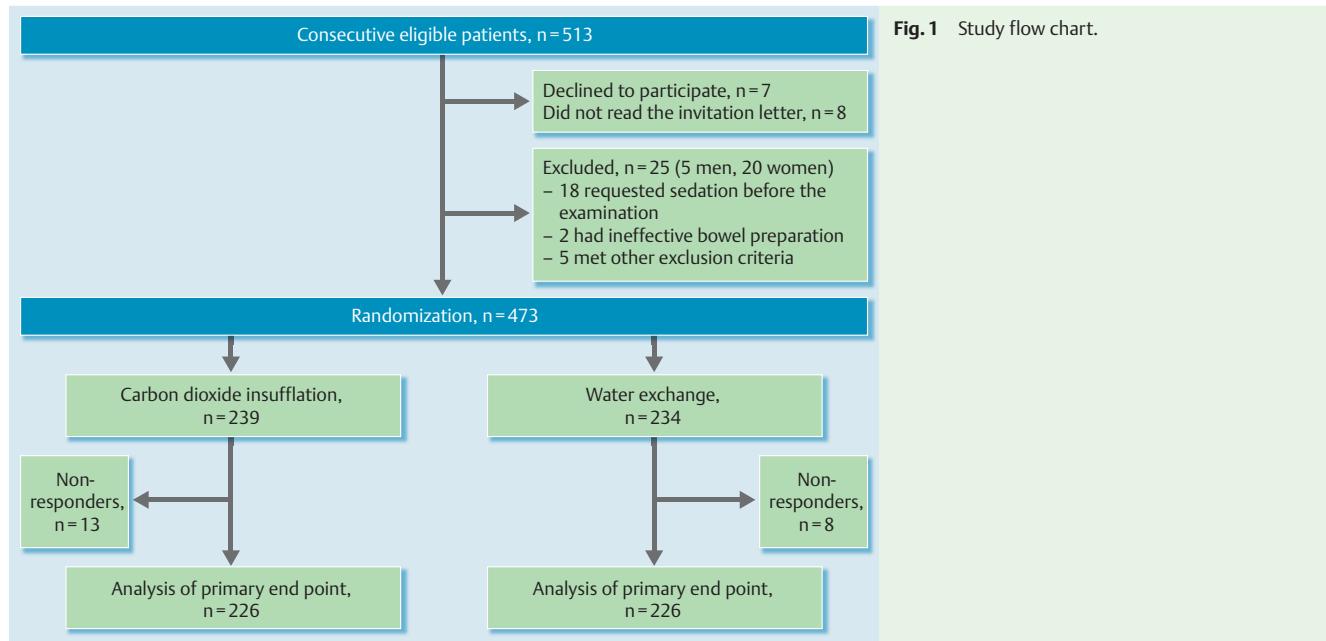


Fig. 1 Study flow chart.

allocation. To obtain a study population balanced at baseline for each endoscopist in regard to colonoscopy method and patient gender, separate sets of envelopes were provided for each endoscopist, with consecutively numbered envelopes in blocks of six for men and women. The study procedures were performed by six endoscopists experienced in unsedated colonoscopy. After informed consent had been obtained, the endoscopy assistant opened an envelope to determine group allocation. Patients were blinded to their group allocation until all data were collected. They were not informed about which method was being used, and they were prevented from watching the procedure on the monitor during colonoscope insertion. To assess the effect of blinding, patients were asked at discharge to guess which method had been used. Also at discharge, a secretary blinded to group allocation asked each patient to report procedural pain on a 4-point verbal rating scale (VRS-4) with self-explanatory categories (no, slight, moderate, or severe pain).

The primary study end point was the proportion of patients reporting moderate or severe pain versus no or slight pain at discharge, as measured on the VRS-4. Sedation was available on demand. If cecal intubation failed because of severe pain and the patient declined sedation, there was an option for the endoscopist to attempt to complete the unsedated procedure with an ultrathin colonoscope to ensure the best possible patient care [9]. These cases were considered intubation failures according to the intention-to-treat principle and were defined for statistical analysis of the primary end point as patients having severe pain because pain scores at discharge could reflect the examination with the ultrathin instrument. Procedural data from the rescue examinations with ultrathin colonoscopes were excluded from the analyses.

The proportions of patients reporting no pain on the VRS-4 were compared in a post hoc analysis. Secondary end points included pain scores recorded in real time during colonoscopy on an 11-point numeric rating scale (NRS-11) ranging from 0 (no pain) to 10 (very severe pain). The principle of the NRS-11 was explained to the patients before the procedure. During colonoscope insertion, the assisting nurse asked the patient to indicate the highest NRS-11 score after each of the five colonic segments (sigmoid,

splenic flexure, transverse colon, hepatic flexure, and ascending colon/cecum) had been negotiated. The colonoscope configuration displayed on a magnetic endoscope imager (ScopeGuide; Olympus Europa, Hamburg, Germany) and visible anatomical landmarks were used to ascertain progress through each colonic segment. The highest NRS-11 score during insertion was defined as maximum pain, and the mean of all segmental NRS-11 scores was defined as overall pain. Other secondary end points were the proportion of patients requesting sedation or analgesia during colonoscope insertion, cecal intubation rate, cecal intubation time, total procedure time, post-procedural involuntary anal leakage (yes/no), and proximal and overall detection of polyps and adenomas. The need for external abdominal pressure during colonoscope insertion was recorded (yes/no). Bowel preparation was assessed with the Boston Bowel Preparation Scale [10]. Post-procedural involuntary anal leakage within 24 hours after colonoscopy was recorded on a take-home questionnaire returned in a prepaid envelope, but only at the Norwegian centers [11]. Polyps were routinely removed during withdrawal. The trial was approved by the regional ethics committees in Norway and Poland and registered at www.clinicaltrials.gov (NCT01633333).

Patients

Patients were enrolled at two centers in Norway (Kristiansand and Arendal) and one center in Poland (Warsaw). Inclusion criteria were colorectal cancer screening or polyp surveillance as an indication for colonoscopy, age 50 to 80 years, and willingness to undergo primary unsedated colonoscopy. At the Norwegian centers, consecutive participants in a population-based screening colonoscopy trial were eligible [12]. Consecutive patients scheduled for unsedated screening or polyp surveillance colonoscopy were eligible at the Polish center.

Exclusion criteria were demand for sedation or analgesia before the start of the procedure, previous partial or total colonic resection, pregnancy, and unwillingness or inability to provide informed consent. Additional exclusion criteria were relevant for the subset of patients recruited in the screening trial at the Norwegian centers (need of long-term nursing for somatic or psychosocial reasons or mental retardation, ongoing cytotoxic treat-

ment or radiotherapy for malignant disease, severe chronic cardiac or pulmonary disease [New York Heart Association class III or IV], lifelong anticoagulant treatment, coronary or cerebrovascular incident requiring hospitalization during the past 3 months, residence abroad or unknown). A split-dose bowel preparation regimen was recommended to all patients, and the vast majority used 3 to 4L of polyethylene glycol solution.

Colonoscopy techniques and equipment

The water exchange method used in the current trial has been described in detail by Leung et al. [13]. We used the same type of adult colonoscope with water jet channels (CF-H180DI/L; Olympus Medical Systems, Tokyo, Japan) in all study procedures. A magnetic endoscope imager (ScopeGuide) was used in all procedures. A water pump with a foot pedal (OFP-2; Olympus) was used in the water exchange group but not in the CO₂ group. This equipment allows the simultaneous infusion and suction of water. In the water exchange group, the CO₂ pump was switched off during colonoscope insertion. Water at body temperature was infused as needed to identify the lumen and simultaneously suctioned out during colonoscope insertion. Opaque liquid was suctioned and replaced by clean water while it was continuously attempted to keep the residual water volume at a minimum. Residual gas pockets were suctioned out. The CO₂ pump was switched on when the cecum was intubated. If the gas pump had to be switched on to reach the cecum, the colonic segment and reason for the switch to CO₂ were recorded. The intention-to-treat cecal intubation rate in the water exchange group was defined as the proportion of cases in which there was no need to use CO₂ during intubation. The overall cecal intubation rate also included cases in which the CO₂ pump had to be switched on to reach the cecum. CO₂ insufflation was used during insertion in the CO₂ group and during withdrawal in both groups. Syringes with water were used as needed in the CO₂ group for cleansing purposes, and the volume was recorded.

Cecal intubation was defined as reaching beyond the ileocecal valve to allow optimal inspection of the cecal pole. High definition monitors and Olympus EVIS EXERA II 180 series video processors and light sources were used in all procedures.

Colonoscopist training

All participating colonoscopists attended a 2-day practice course arranged for the purpose of this trial in which hands-on training was supervised by a colleague experienced in the water exchange method. Each training case was performed as a video-transmitted "live endoscopy" to allow interactive participation among all endoscopists. After the meeting, all endoscopists practiced the water exchange method to reach an intention-to-treat cecal intubation rate of 90% or higher in the last 30 cases before entering the trial. All endoscopists also completed an e-learning course on the Boston Bowel Preparation Scale (<https://www.cori.org/bbps/>), and several training videos were discussed to facilitate inter-rater agreement on the bowel preparation scores.

Power estimates and statistical methods

Earlier reports in the literature indicated that procedural pain could be expected to be approximately 50% lower with water exchange than with air insufflation [3–5]. Two earlier Norwegian trials comparing CO₂ insufflation and air insufflation showed no significant reduction in pain during colonoscopy when CO₂ was used [14, 15]. Based on these data, we assumed that a comparison between water exchange and CO₂ insufflation would result in a

difference in pain scores similar to that reported for water exchange versus air insufflation. Observational data from 2011 from one of the centers in the current study indicated that 23% of patients reported moderate or severe procedural pain (<10% received sedation or analgesia) after colonoscopy with CO₂ insufflation. In order to show a 50% reduction in the proportion of patients with moderate or severe pain in the water exchange group compared with the CO₂ group, with 80% power and a significance level of 5%, 229 patients had to be included in each group, assuming that 80% completed the pain score questionnaire. Proportions, including the primary end point, were compared with the chi-squared test or Fisher's exact test, as appropriate. The Cochran–Armitage test for trend was performed to compare VRS-4 pain scores overall across study groups and to justify a post hoc comparison of the proportions of patients reporting no procedural pain. Univariable logistic regression analyses were used to assess the effect of individual baseline variables and endoscopist on the primary end point. Variables significant at $P \leq 0.25$ in univariable analyses as well as potential interaction terms were analyzed in a multivariable logistic regression model to assess the adjusted effect of colonoscopy technique on the primary end point. To account for a possible center effect, using the same covariates as in the unconditional model, we also constructed a conditional logistic regression model with endoscopy center as a fixed effect. To assess variability in VRS-4 pain scores and account for clustering on individual endoscopists, a mixed effects logistic regression analysis with random endoscopist intercept was done and compared with the standard logistic regression model by the likelihood ratio test. Continuous variables were checked for normality and compared by using appropriate parametric or non-parametric tests. The NRS-11 pain scale was treated as a continuous variable for the presentation of mean scores with 95% confidence intervals, and as an ordered multinomial variable for group comparison with the Mann–Whitney test. All tests were two-sided, and P values of less than 0.05 were considered statistically significant. Statistical analyses were performed with Stata 13.1 software (StataCorp, College Station, Texas, USA).

Results

▼

Baseline variables

Between June 2012 and December 2013 (with different starting dates at the trial centers), 513 consecutive patients were considered for inclusion in the trial, and 473 were randomized (► Fig. 1). The groups were well balanced with regard to demographic and baseline characteristics (► Table 1). At discharge, 41% in the CO₂ group and 53% in the water exchange group guessed correctly as to which group they had been allocated to ($P=0.35$). Procedural data are summarized in ► Table 2.

Patient pain

At discharge, 226 of 239 patients (95%) in the CO₂ group versus 226 of 234 patients (97%) in the water exchange group completed the questionnaire on procedural pain ($P=0.37$). The remaining patients left the endoscopy center without completing the questionnaire (reasons not recorded). Moderate or severe pain as measured by the VRS-4 (primary end point) was reported by 60 of 226 patients (27%) in the CO₂ group versus 47 of 226 patients (21%) in the water exchange group ($P=0.15$) (► Fig. 2). Of these, 9 procedures in the CO₂ group and 1 in the water exchange group failed to reach the cecum as a result of pain; they were

| | CO ₂ (n=239) | Water exchange (n=234) | P value |
|--|----------------------------|---------------------------|-------------------|
| Women, n (%) | 118 (49) | 114 (49) | 0.89 ¹ |
| Age, mean (SD), y | 61 (3.7) | 60 (4.5) | 0.72 ² |
| Body mass index, mean (SD) | 26.7 (4.1) | 26.9 (3.8) | 0.61 ² |
| Previous abdominal surgery, n (%) | 71 (30) | 59 (25) | 0.27 ¹ |
| Diverticulosis, n (%) | 59 (25) | 47 (20) | 0.45 ¹ |
| Screening as indication for colonoscopy, n (%) | 219 (92) | 208 (89) | 0.31 ¹ |

SD, standard deviation.

¹ Chi-squared test.

² Student's t test.

completed with an ultrathin colonoscope and defined as having severe procedural pain with the allocated method, as explained in the methods section. All of these 10 procedures were aborted in the sigmoid colon with the allocated method, and the mean (standard deviation [SD]) sigmoid colon NRS-11 score was 8.9 (1.2).

Overall, VRS-4 pain scores were significantly higher in the CO₂ group than in the water exchange group ($P=0.007$, Cochran–Armitage test for trend). No procedural pain on the VRS-4 was reported by 69 of 226 patients (31%) in the CO₂ group versus 100 of 226 patients (44%) in the water exchange group ($P=0.003$) (Fig. 2).

Sedation or analgesia during the procedure was required by 15 patients (6%) in each group ($P=0.95$). Midazolam was used in 13 patients in the CO₂ group and 14 patients in the water exchange group, with mean (SD) doses of 2.4 mg (0.3) and 2.7 mg (0.7), respectively ($P=0.19$). Fentanyl was used in 11 patients in the

CO₂ group and 15 patients in the water exchange group, with mean (SD) doses of 48 µg (13) and 47 µg (16), respectively ($P=0.86$). One patient in the CO₂ group received 50 mg of pethidine. Female sex was the only independent predictor of moderate or severe pain in multivariable logistic regression analyses (Table 3). Accounting for center effects with conditional logistic regression had only a marginal, insignificant effect on the results (Table 3). There was no significant interaction between patient sex and colonoscopy technique or patient sex and previous abdominal surgery (data not shown). Heterogeneity in VRS-4 pain scores among individual endoscopists is shown in Fig. 3. However, there was no significant association between individual endoscopist and the primary outcome in univariable logistic regression, multivariable logistic regression, or mixed effects logistic regression with random endoscopist intercept (data not shown).

Table 2 Procedural outcomes in the carbon dioxide and water exchange groups.

| | CO ₂ (n=239) | Water exchange (n=234) | P value |
|---|----------------------------|---------------------------|---------------------|
| Sedation/analgesia used on demand, n (%) | 15 (6) | 15 (6) | 0.95 ¹ |
| Intention-to-treat cecal intubation rate, ² n (%) | 219 (92) | 197 (84) | 0.01 ¹ |
| Overall cecal intubation rate, n (%) | 219 (92) | 227 (97) | 0.02 ³ |
| Cecal intubation time, median (IQR), min | 11 (7–16) | 15 (11–21) | <0.001 ⁴ |
| Total procedure time, median (IQR), min | 24 (19–31) | 30 (24–38) | <0.001 ⁴ |
| External abdominal pressure, n (%) | 121 (51) | 90 (38) | 0.003 ¹ |
| Boston Bowel Preparation Scale score, median (IQR) | 7 (6–9) | 7 (6–9) | 0.76 ⁴ |
| Any water used during insertion, n (%) | 113 (47) | 234 (100) | <0.001 ³ |
| Volume of water used to reach cecum, mean (SD), mL | 39 (64) | 537 (365) | <0.001 ⁵ |
| Volume of water in suction bottle when cecum was reached, mean (SD), mL | 172 (120) | 527 (377) | <0.001 ⁵ |
| Procedures per endoscopist, median (IQR) | 25 (18–51) | 25 (17–49) | 0.94 ⁴ |
| Maximum pain during colonoscope insertion (NRS-11), ⁶ median (IQR) | 5.0 (3–8) | 5.0 (3–7) | 0.006 ⁴ |
| Overall pain during colonoscope insertion (NRS-11), ⁷ median (IQR) | 2.4 (1.4–3.8) | 2.0 (1.0–3.2) | 0.02 ⁴ |
| Post-procedural involuntary anal leakage, ⁸ n (%) | 0 (0) | 2 (1) | 0.24 ³ |
| Polyp detection rate, n (%) | 113 (47) | 148 (63) | <0.001 ¹ |
| Adenoma detection rate, n (%) | 74 (31) | 81 (35) | 0.40 ¹ |
| Advanced adenoma detection rate, ⁹ n (%) | 20 (8) | 17 (7) | 0.66 ¹ |
| Proximal adenoma detection rate, ¹⁰ n (%) | 42 (18) | 49 (21) | 0.35 ¹ |
| Adenomas per procedure | 0.60 | 0.66 | 0.48 ⁴ |
| Sessile serrated adenoma detection rate, n (%) | 20 (8) | 30 (13) | 0.12 ¹ |

IQR, interquartile range; SD, standard deviation; NRS-11, 11-point numeric rating scale.

¹ Chi-squared test.

² Cecal intubation rate when 30 procedures in the water exchange group are defined as intubation failures because the CO₂ pump was switched on during intubation.

³ Fisher's exact test.

⁴ Mann–Whitney test.

⁵ Student's t test.

⁶ Includes all procedures.

⁷ Includes only procedures completed to the cecum.

⁸ Based on 356 feedback questionnaires (variable registered only at the Norwegian centers).

⁹ Advanced adenomas: adenomas ≥ 10 mm in diameter, or with villous components, or with high grade dysplasia.

¹⁰ Proximal to the splenic flexure.

Table 1 Baseline characteristics in the carbon dioxide and water exchange groups.

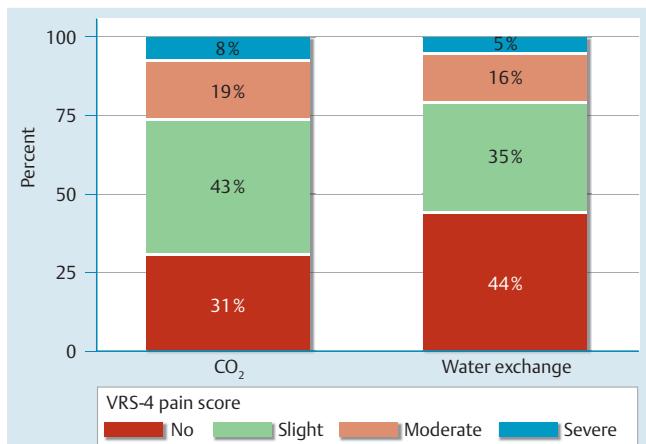


Fig. 2 Pain scores reported on a 4-point verbal rating scale after CO₂ or water exchange colonoscopy. Moderate or severe pain versus no or slight pain: $P=0.15$; no pain versus slight, moderate, or severe pain: $P=0.003$ (chi-squared test). Total percentage in the CO₂ column exceeds 100% because of rounding.

Maximum and overall procedural pain scores on the NRS-11 scale (secondary end point) are shown in **Table 2**. NRS-11 scores by patient sex are shown in **Fig. 4**, and segmental scores are shown in **Fig. 5**.

Data regarding involuntary anal leakage after the procedure were available from 181 of 239 patients in the CO₂ group and 175 of 234 patients in the water exchange group; the results are presented in **Table 2**.

Cecal intubation

In 30 patients in the water exchange group, the CO₂ pump had to be switched on to reach the cecum for various reasons (12 because of insufficient bowel preparation and the remainder because of difficulties in finding the colonic lumen). All 30 procedures were completed to the cecum. Consequently, the intention-to-treat cecal intubation rate was 92% (219 of 239) in the CO₂ group versus 84% (197 of 234) in the water exchange group ($P=0.01$), and the overall cecal intubation rate in the water exchange group was 97% (227 of 234) versus 92% in the CO₂ group ($P=0.02$). Pain was the reason for cecal intubation failure in 10 of 20 patients (50%) in the CO₂ group and 2 of 7 patients (29%) in the water exchange group ($P=0.04$).

Polyp detection

The proportion of patients in whom at least one polyp was detected (including all histologic subtypes) was 47% (113 of 239) in the CO₂ group versus 63% (148 of 234) in the water exchange group ($P<0.001$); however, the difference between the adenoma and sessile serrated adenoma detection rates did not reach statistical significance (**Table 2**). There were no serious procedural complications in either group.

Discussion

The principal intention with water-aided colonoscopy is to ease insertion of the instrument and thereby cause less discomfort for the patient than occurs with air or CO₂ insufflation. Several small trials in specialized patient groups or health care settings have indicated such an effect, but the evaluation of pain during colonoscopy has not been standardized. We used several methods to evaluate procedural pain, with results that warrant discussion.

We chose a simple VRS-4 pain scale as the primary end point variable because it has long been used in the Norwegian national endoscopy quality assurance program [11]. Although the VRS-4 has not, to our knowledge, been directly validated for the evaluation of pain during colonoscopy, it has been validated and shown to be comparable with other pain-rating scales in distinguishing levels of pain intensity in an experimental setting [16]. The dichotomy of the VRS-4 into no or slight versus moderate or severe pain was chosen to highlight the pain categories that we considered to be the most important clinically. It may, however, be argued that no pain is an equally or even more relevant end point. The difference between the proportions of patients reporting moderate or severe pain in the water exchange and CO₂ groups observed in the current trial was not statistically significant. However, this does not preclude the existence of a clinically relevant difference. First, our sample size was calculated with the hypothesis of a 50% reduction in moderate or severe pain based on observations in trials in which water exchange was compared with air insufflation [3–5], and an assumption that procedural pain scores for CO₂ and air insufflation are not significantly different [14, 15]. Since the planning of our trial, a meta-analysis of seven randomized controlled trials concluded that CO₂ is associated with significantly lower procedural pain scores than is air insufflation, despite the fact that five of these trials did not show a significant difference [2]. Another recent study also showed that CO₂ is associated with less procedural pain than is air insufflation [7]. Consequently, our hypothesis may have been overly optimistic and resulted in an underpowered trial to detect a

Table 3 Univariable and multivariable logistic regression analyses for moderate or severe pain during colonoscopy.

| Predictors of moderate or severe pain on the VRS-4 | Univariable analysis | | | Multivariable analysis ¹ | | | Multivariable analysis (fixed center effect) ¹ | | |
|---|----------------------|-----------|---------|-------------------------------------|-----------|---------|---|-----------|---------|
| | OR | 95 % CI | P value | OR | 95 % CI | P value | OR | 95 % CI | P value |
| Water exchange technique (ref. CO ₂ insufflation) | 0.73 | 0.47–1.12 | 0.15 | 0.73 | 0.46–1.14 | 0.16 | 0.73 | 0.47–1.14 | 0.17 |
| Female sex (ref. male sex) | 3.23 | 2.03–5.15 | <0.001 | 3.10 | 1.93–4.98 | <0.001 | 3.01 | 1.87–4.85 | <0.001 |
| Previous abdominal surgery (ref. no previous abdominal surgery) | 1.63 | 1.03–2.60 | 0.04 | 1.31 | 0.81–2.12 | 0.28 | 1.39 | 0.85–2.29 | 0.19 |

VRS-4, 4-point verbal rating scale; OR, odds ratio; CI, confidence interval; ref., reference.

¹ Values are adjusted for all other variables in the model.

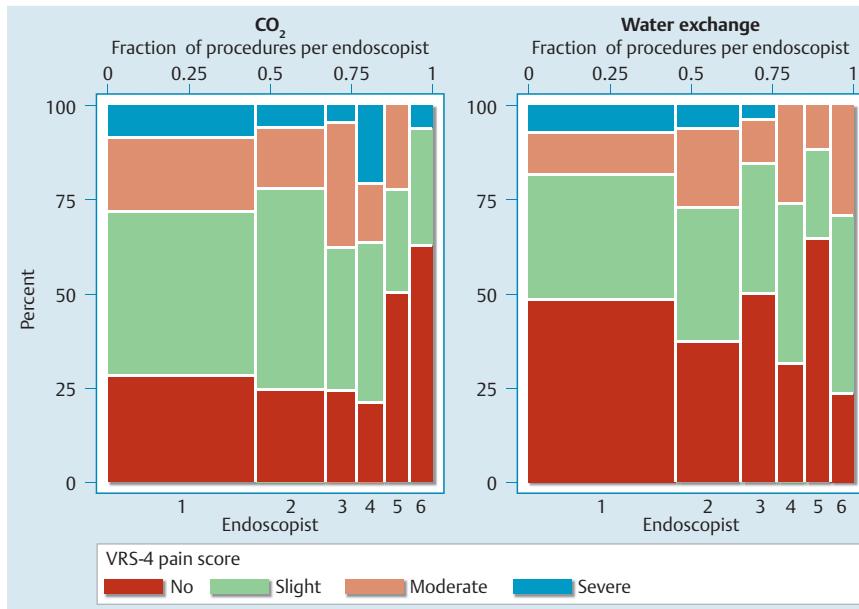


Fig. 3 Pain scores on a 4-point verbal rating scale in the water exchange and carbon dioxide groups for each endoscopist. Width of bars indicates fraction of procedures performed by each endoscopist.

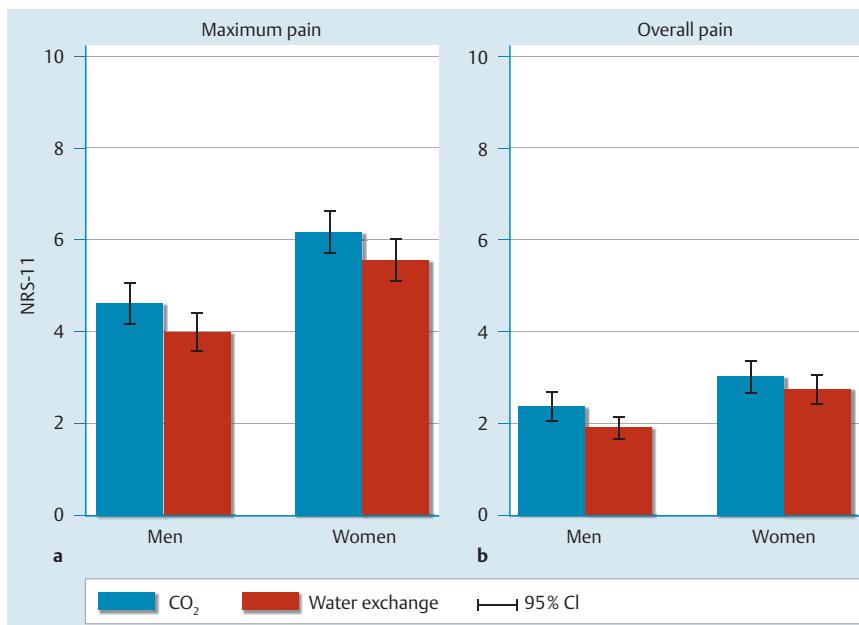


Fig. 4 Mean maximum (a) and overall (b) pain scores on an 11-point numeric rating scale (NRS-11) for men and women during colonoscopy insertion.

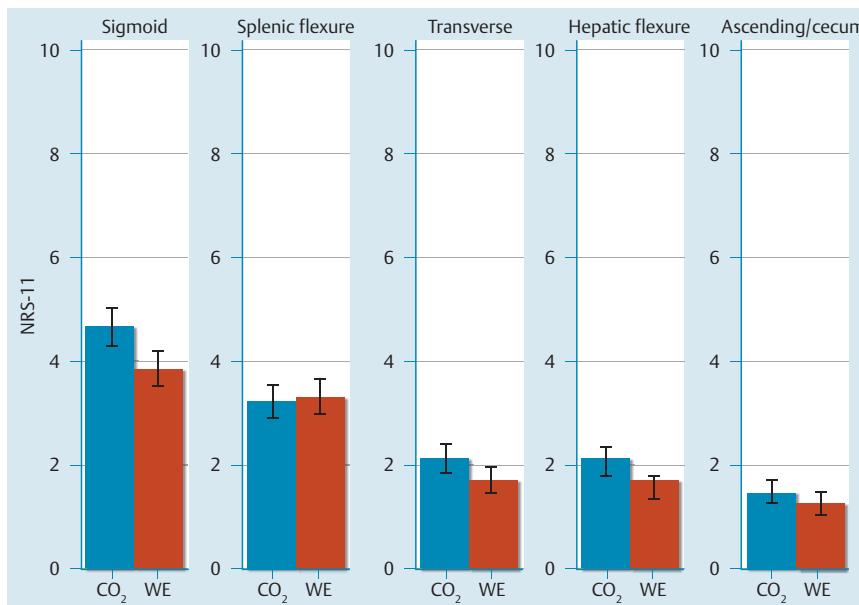


Fig. 5 Mean pain scores on an 11-point numeric rating scale (NRS-11) in five colonic segments with CO₂ or water exchange (WE) colonoscopy. Green error bars indicate 95 % confidence intervals.

smaller, but clinically meaningful, effect. Second, post hoc analyses showed higher VRS-4 pain scores overall in the CO₂ group than in the water exchange group, and a significantly larger proportion of patients experiencing no pain in the water exchange group than in the CO₂ group (► Fig. 2), findings that are clinically relevant.

As shown in ► Fig. 3, pain scores differed among endoscopists in our trial. Two of six endoscopists had higher VRS-4 scores with water exchange than with CO₂, one of whom also had higher NRS-11 scores (data not shown). Although we did not find a significant association between individual endoscopists and the primary end point, our data are not robust enough to draw firm conclusions, and the beneficial effect of water exchange on patient pain may not be universal among endoscopists. As an example, the performance of endoscopists who have very low pain scores with CO₂ may not improve with the water exchange technique. Maximum and overall pain on the NRS-11 was significantly lower with water exchange than with CO₂ (► Table 2); however, the effect was less pronounced than was hypothesized from results in the literature and less pronounced in women than in men (► Fig. 4). While study populations in previous trials with larger effect sizes were predominantly male, our results probably reflect an effect that is more generalizable to both sexes. The comparison of overall pain on the NRS-11 presented in ► Table 2 and ► Fig. 4 included only procedures completed to the cecum to avoid possible misjudgment resulting from incomplete data. Although already statistically significant, the difference between the groups was further increased in favor of water exchange in sensitivity analysis including available data from all procedures (data not shown). The extrapolation of pain scores from one rating scale to another is not straightforward, but the consistency of lower scores on different pain rating scales may support a conclusion that water exchange induced less pain than CO₂ insufflation. Previous trials with water exchange versus air insufflation have looked at the cecal intubation rate as the primary end point, with or without sedation dose as a concomitant primary end point [3, 5, 17]. The primary intention-to-treat analysis with such a design is the cecal intubation rate, and the need to switch on the air pump during intubation may be considered an intubation failure. In our trial, however, pain was the only primary end point, and the intention-to-treat analysis of interest was that of the pain scores according to group allocation. Although the CO₂ pump had to be turned on in 30 cases in the water exchange group, all procedures were completed to the cecum, resulting in a significantly higher overall cecal intubation rate in this group than in the CO₂ group (► Table 2). In all but 3 of these 30 procedures, the endoscopist had already reached beyond the sigmoid colon, which is the most painful segment (► Fig. 5). Pain was a significantly more frequent reason for cecal intubation failure in the CO₂ group than in the water exchange group. We therefore argue that the most relevant interpretation of the cecal intubation rate in the current trial is not whether CO₂ had to be used briefly in some water exchange procedures, but rather that an overall increase in the cecal intubation rate was observed with water exchange, probably in part as a result of less pain.

The cecal intubation time and total procedure time were significantly longer with water exchange than with CO₂ insufflation in the current trial (► Table 2). There were no fixed time limitations in the study protocol, and completing the water exchange procedures without switching on the CO₂ pump was generally prioritized, even if difficulties were encountered. In clinical practice, however, conversion to CO₂ insufflation is always possible if pro-

gress is slow. Because water exchange does not compromise the overall cecal intubation rate and seems to have a beneficial effect on pain scores in several colonic segments (► Fig. 5), there is no apparent reason to discourage this practice. Published learning curves with water exchange colonoscopy indicate that the cecal intubation rate and intubation time approach baseline after 100 to 300 cases [18, 19].

The detection rate of adenomas was well within the recommended target in colorectal cancer screening by colonoscopy in both study groups (► Table 2) [20, 21]. Although the detection rates for adenomas and sessile serrated adenomas were slightly higher in the water exchange group than in the CO₂ group, the difference did not reach statistical significance. The significantly higher detection rate for polyps, including all histologic subtypes, suggests that a relevant difference may exist, but larger trials are necessary to evaluate this hypothesis.

The major limitation of this study is that the endoscopists and assisting nurses could not be blinded to the colonoscopy technique used. In particular, the patients undergoing rescue procedures with ultrathin colonoscopes because of pain constitute a possible source of bias in the interpretation of the primary outcome. However, because all these procedures were aborted in the sigmoid colon with the allocated method, with a mean sigmoid colon NRS-11 score of 8.9, our approach to define these in the severe pain category on the VRS-4 seems reasonable. Also, fewer than half of all patients made the correct guess about which method had been used, and the primary end point was reported to a blinded assistant, so that adequate blinding for the main outcome is plausible. NRS-11 pain scores were, on the other hand, reported to the unblinded assisting nurse, and although the methods were standardized, these are more prone to bias. Furthermore, in between obvious anatomical landmarks, the recognition of which colonic segment has been reached may be subjective. Thus, the segmental pain scores may be biased. However, the magnetic endoscope imager provides reliable real-time information about colonoscope position and advancement. Another limitation is the endoscopists' relative inexperience with the water exchange technique compared with CO₂ insufflation. Although the endoscopists were required to reach an intention-to-treat cecal intubation rate of 90% or higher with water exchange in the last 30 training cases before joining the trial, we did not define a minimum total number of practice cases. Considering that the intention-to-treat cecal intubation rate with water exchange observed in the trial was lower than the threshold set for trial participation, it is possible that the endoscopists' learning curves had not yet reached a stable plateau, and the trial results should be interpreted accordingly.

The study also has some strengths. First, the multicenter, multinational design strengthens the generalizability of the results. Second, the combination of different pain-scoring modalities provides detailed insight into the mechanisms of pain during colonoscopy. Finally, all endoscopists underwent supervised training to ensure similar practice in all centers.

In conclusion, we failed to detect a significant reduction in moderate or severe procedural pain with water exchange compared with CO₂ insufflation in patients undergoing unsedated colonoscopy. Secondary outcomes, however, revealed that water exchange was associated with a significant increase in the proportion of patients reporting no procedural pain, a significant but small reduction in real-time pain scores, and an improved overall cecal intubation rate compared with CO₂ insufflation. The longer procedure times observed with water exchange may be discour-

ging; however, switching to CO₂ is always possible if progress is slow. In summary, the current results indicate that water exchange is a good alternative to CO₂ insufflation for colonoscope insertion.

Competing interests: Kjetil Garborg has received travel support and research grants from Olympus Norway.

Institutions

- ¹ Department of Medicine, Sorlandet Hospital HF, Kristiansand, Norway
- ² Institute of Health and Society, University of Oslo, Oslo, Norway
- ³ Department of Gastroenterological Oncology, Medical Center for Post-graduate Education and Institute of Oncology, Warsaw, Poland
- ⁴ Department of Medicine, Sorlandet Hospital HF, Arendal, Norway
- ⁵ Department of Pathology, Sorlandet Hospital HF, Kristiansand, Norway
- ⁶ Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA
- ⁷ Department of Research, Telemark Hospital, Skien, Norway
- ⁸ Cancer Registry of Norway, Oslo, Norway
- ⁹ Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway

Acknowledgements



We thank Dr. Felix Leung for his most valuable contribution to the design of the trial and for supervising the training cases. We also thank Dr. Magnus Løberg and Siv Furholm for the randomization, and all study nurses and assistants for collecting the trial data.

References

- 1 Cohen LB, Ladas SD, Vargo JJ et al. Sedation in digestive endoscopy: the Athens international position statements. *Aliment Pharmacol Ther* 2010; 32: 425–442
- 2 Wu J, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. *Endoscopy* 2012; 44: 128–136
- 3 Leung JW, Mann SK, Siao-Salera R et al. A randomized, controlled comparison of warm water infusion in lieu of air insufflation versus air insufflation for aiding colonoscopy insertion in sedated patients undergoing colorectal cancer screening and surveillance. *Gastrointest Endosc* 2009; 70: 505–510
- 4 Leung FW, Harker JO, Jackson G et al. A proof-of-principle, prospective, randomized, controlled trial demonstrating improved outcomes in scheduled unsedated colonoscopy by the water method. *Gastrointest Endosc* 2010; 72: 693–700
- 5 Leung J, Mann S, Siao-Salera R et al. A randomized, controlled trial to confirm the beneficial effects of the water method on U.S. veterans undergoing colonoscopy with the option of on-demand sedation. *Gastrointest Endosc* 2011; 73: 103–110
- 6 Falt P, Liberda M, Smajstrla V et al. Combination of water immersion and carbon dioxide insufflation for minimal sedation colonoscopy: a prospective, randomized, single-center trial. *Eur J Gastroenterol Hepatol* 2012; 24: 971–977
- 7 Amato A, Radaelli F, Paggi S et al. Carbon dioxide insufflation or warm-water infusion versus standard air insufflation for unsedated colonoscopy: a randomized controlled trial. *Dis Colon Rectum* 2013; 56: 511–518
- 8 Rabenstein T, Radaelli F, Zolk O. Warm water infusion colonoscopy: a review and meta-analysis. *Endoscopy* 2012; 44: 940–951
- 9 Garborg KK, Løberg M, Matre J et al. Reduced pain during screening colonoscopy with an ultrathin colonoscope: a randomized controlled trial. *Endoscopy* 2012; 44: 740–746
- 10 Calderwood AH, Jacobson BC. Comprehensive validation of the Boston Bowel Preparation Scale. *Gastrointest Endosc* 2010; 72: 686–692
- 11 Hoff G, Brethauer M, Huppertz-Hauss G et al. The Norwegian Gastronet project: continuous quality improvement of colonoscopy in 14 Norwegian centres. *Scand J Gastroenterol* 2006; 41: 481–487
- 12 Kaminski MF, Brethauer M, Zauber AG et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. *Endoscopy* 2012; 44: 695–702
- 13 Leung FW, Leung JW, Mann SK et al. The water method significantly enhances patient-centered outcomes in sedated and unsedated colonoscopy. *Endoscopy* 2011; 43: 816–821
- 14 Brethauer M, Thiis-Evensen E, Huppertz-Hauss G et al. NORCCAP (Norwegian colorectal cancer prevention): a randomised trial to assess the safety and efficacy of carbon dioxide versus air insufflation in colonoscopy. *Gut* 2002; 50: 604–607
- 15 Brethauer M, Lyng AB, Thiis-Evensen E et al. Carbon dioxide insufflation in colonoscopy: safe and effective in sedated patients. *Endoscopy* 2005; 37: 706–709
- 16 Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. *Pain* 2011; 152: 2399–2404
- 17 Cadoni S, Gallitti P, Sanna S et al. A two-center randomized controlled trial of water-aided colonoscopy versus air insufflation colonoscopy. *Endoscopy* 2014; 46: 212–218
- 18 Ramirez FC, Leung FW. The water method for aiding colonoscope insertion: the learning curve of an experienced colonoscopist. *J Interv Gastroenterol* 2011; 1: 97–101
- 19 Fischer LS, Lumsden A, Leung FW. Water exchange method for colonoscopy: learning curve of an experienced colonoscopist in a U.S. community practice setting. *J Interv Gastroenterol* 2012; 2: 128–132
- 20 Rex DK, Bond JH, Winawer S et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2002; 97: 1296–1308
- 21 Kaminski MF, Regula J, Kraszewska E et al. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010; 362: 1795–1803