Carbon dioxide insufflation for more comfortable endoscopic retrograde cholangiopancreatography: a randomized, controlled, double-blind trial

Background and study aims: The effect on abdominal pain of using carbon dioxide (CO₂) for insufflation during endoscopic retrograde cholangiopancreatography (ERCP) has not been investigated. The present study aimed to compare CO₂ insufflation with standard air insufflation with respect to the pain experienced during and after ERCP. In addition, we investigated the effect of CO₂ insufflation on the partial pressure of CO₂ (Pco₂).

Patients and methods: A total of 118 consecutive patients who were undergoing ERCP were randomized to CO₂ insufflation or to air insufflation during the procedure. Both the endoscopists and the patients were blinded with regard to the gas used. Patients rated the intensity of pain experienced on a 100-mm visual analogue scale (VAS) during ERCP and at 1 hour, 3 hours, 6 hours, and 24 hours after the procedure. Transdermal Pco₂ was measured continuously in all patients during the procedure.

Results: Altogether, 116 patients were eligible for analysis, 58 in each treatment group, and 91 patients responded to the questionnaire (78%). The mean severity of postprocedure pain was significantly reduced in the CO₂ group compared with the air group at 1 hour (5 mm vs. 19 mm on the VAS, \( P < 0.001 \)), at 3 hours (7 mm vs. 21 mm, \( P < 0.001 \)), at 6 hours (10 mm vs. 22 mm, \( P = 0.006 \)), and at 24 hours (4 mm vs. 20 mm, \( P < 0.001 \)) after the procedure. Radiographs taken 5 minutes after the procedure showed that abdominal distension was more pronounced in patients in the air insufflation group. There were no differences in Pco₂ values between the two treatment groups.

Conclusions: Carbon dioxide insufflation during ERCP significantly reduces postprocedural abdominal pain. No side effects were observed. Carbon dioxide should be the standard gas used for insufflation in ERCP.

Introduction

It has been shown in randomized controlled trials that carbon dioxide (CO₂) insufflation significantly reduces abdominal pain and discomfort in patients undergoing colonoscopy, flexible sigmoidoscopy, intraoperative endoscopy, and double-contrast barium enema [1–11]. Similarly, bowel distension after colonoscopy (demonstrated by plain abdominal radiography) has been shown to be significantly reduced after CO₂ insufflation compared with air insufflation [1,2]. Some of these trials also revealed that a considerable proportion of patients report significant abdominal symptoms caused by retained air after lower gastrointestinal endoscopy when air was used for insufflation [1–6].

Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used endoscopic procedure for visualizing the biliary tree and/or the pancreatic ducts. As in lower gastrointestinal endoscopy, gas is insufflated into the bowel during ERCP to optimize the endoscopic view in the duodenum. Air is usually used for this purpose, and painful abdominal distension would be the expected result. There is, however, limited knowledge on the frequency of abdominal pain occurring during and after ERCP. The few published trials indicate that a majority of patients undergoing ERCP suffer from abdominal pain during the procedure itself and that it may last for several hours after the procedure [12]. To our knowledge, no research has been performed investigating the use of CO₂ in ERCP.

It has been shown that the use of CO₂ has no side effects in colonoscopy [3,7]. In contrast to the practice reported in published colonoscopy trials, ERCP is often performed in heavily sedated patients, however, and sedation itself can cause a rise in the body Pco₂ [13]. Nelson et al. [14] re-
cently reported a moderate increase in Pco₂ during ERCP using air insufflation. The present trial aimed to evaluate whether CO₂ insufflation can reduce the incidence of abdominal pain during and after ERCP compared with standard air insufflation. As secondary end points, we investigated Pco₂ levels during ERCP, comparing CO₂ and air insufflation, to detect any rise in Pco₂ levels due to CO₂ insufflation, and also the degree of bowel distension occurring after procedures (determined by postprocedure radiographs), again comparing the two gases.

Patients and methods

Consecutive patients scheduled for ERCP at two Norwegian centers were eligible for participation unless they fulfilled one of the following exclusion criteria: age under 18 years, severe mental disorder (so unable to understand information on the trial), pregnancy, impaired cardiovascular status (New York Heart Association classes III–IV), known chronic obstructive pulmonary disease (COPD) with known CO₂ retention and refusal to participate. After written informed consent was obtained, participants were randomly assigned to either CO₂ insufflation or air insufflation during their ERCP procedure. Individual randomization to the two treatment groups (1 : 1) was performed by a computer program that generated the allocation sequence, and sealed envelopes were used for on-scene concealment and were administered by the endoscopy assistant. The patients and the endoscopists were all blinded with regard to the type of gas used. The study protocol was approved by the regional ethics committee (Regional Ethics Committee No: s-02-047).

Carbon dioxide was administered using a commercially available CO₂ regulator designed for use in endoscopy procedures (ECR; Olympus KeyMed Ltd., Southend, United Kingdom). The endoscopy assistant was responsible for switching the CO₂ device on and off. To prevent unblinding, the CO₂ device was placed behind the endoscopy rack and the air inlet button on the endoscopy rack was concealed to hide it from the endoscopist’s view. Patients were examined with standard ERCP video endoscopes (Olympus Europa, Hamburg, Germany). Midazolam and/or pethidine were used for sedation at the discretion of the endoscopist.

Evaluation of pain and discomfort

A questionnaire with 100-mm visual analog scales (VAS) was used to quantify abdominal pain experienced during and at 1 hour, 3 hours, 6 hours, and 24 hours after the procedure, as validated in recent studies [3, 4, 7]. The scales were labelled at the far left end with “no pain” and at the far right end with “very heavy pain.” The questionnaire was handed out to every patient after the procedure, to be filled in the next day and mailed back to the respective center in prepaid envelopes.

Evaluation of bowel distension

A dedicated gastroradiologist (S.A.) is present at the majority of ERCP procedures at Rikshospitalet University Hospital, although there is no radiology service when the dedicated radiologist is busy with other examinations or is not present at the hospital. ERCPs are performed without any routine radiology service at the Telemark center. Radiologic evaluation of bowel distension was therefore only performed at Rikshospitalet.

Plain abdominal radiographic images were taken 5 minutes after the end of the endoscopic procedure in every patient when the radiologist was available. The X-ray apparatus at the center has a 12-inch image intensifier. To minimize patients’ radiation exposure, four separate frame grabs (one in each of the four abdominal quadrants) were performed for the evaluation of bowel distension. These frame grabs were then put together to make up an image of the whole abdomen (Figure 1, 2). As there were no studies in the literature evaluating bowel distension after ERCP, we developed the following scoring system for gas in the gastrointestinal tract visible on the radiographic images, following the scoring system used for colonoscopy as far as possible [1, 2]:

- Grade 1: no distension (only traces of gas)
- Grade 2: light distension (traces of gas, slightly greater than physiologic amounts)
- Grade 3: moderate distension (moderate meteorism of the small bowel and/or colon)
- Grade 4: severe distension (heavy meteorism with marked distension of large portions of the small bowel and/or marked colonic meteorism)

The degree of bowel distension was evaluated after completion of the study by one dedicated radiologist (S.A.) who was blinded with regard to the insufflation gas used.

Pco₂ measurements

Direct measurement of arterial Pco₂ is an invasive procedure, and was considered impractical in our setting. However, it is known that transcutaneous measurement of Pco₂ correlates well with arterial Pco₂ in adults without severe lung disease [13]. Transcutaneous Pco₂ was measured continuously in the first 62 participants at the Oslo center, using a capnograph (TCM 30; Radiometer Inc., Copenhagen, Denmark) connected to a probe on the patient’s forearm. The standard reference range for Pco₂ in spontaneously breathing adults is 4.5–6.3 kPa. To prevent any severe adverse effects, a rise in Pco₂ above 8.5 kPa or to more than 3.5 kPa above the pre-examination level qualified for unblinding according to the protocol. If CO₂ insufflation had been used in such a patient, then insufflation would have to be changed to air. As only one capnograph was available for the study and it was considered sufficient to test this end point in 62 patients according to data from earlier trials (see below), only the first 62 patients at the Oslo center had their Pco₂ measured. The Telemark center only started to include patients in the study (without Pco₂ measurements) after analysis of the Oslo data had confirmed that CO₂ insufflation did not lead to a rise in the Pco₂. All procedure parameters of interest (e.g., duration of the examination, use of sedatives) were recorded by the endoscopist and the endoscopy assistant immediately after the examination, using existing gastrointestinal lab databases. Oxygen saturation, pulse rate, and arterial blood pressure were recorded routinely in all patients.

Statistical analysis

Differences in mean VAS scores were analyzed by ANOVA for repeated measurements. The proportion of individuals reporting no discomfort on the VAS was compared at each time point using the chi-squared test. Statistical significance was defined as a P value of less than 0.05. Two-sided tests were used. The relationship between the duration of the examination and the outcome variables of interest (pain and Pco₂) was analyzed by recoding the duration variable into three appropriate categories...
Below the 25th percentile, from the 25th to the 75th percentiles, and above the 75th percentile), computed for those patients where all data of interest were available. The statistical analysis was performed using SPSS 12.0 software (SPSS Inc., Chicago, Illinois, USA). Data are given as means ± standard deviation (SD) unless stated otherwise.

**Study power analysis**

The primary end point of this study was the pain and discomfort experienced by the patient. This outcome was therefore used for the power analysis. A 10% reduction in mean VAS score for abdominal pain in the CO₂ group compared with the air group was considered to be a clinically important difference. As there were no studies available, a pilot study was performed to estimate the number of individuals that would be required to detect predefined differences. The results of this study showed that we would need 48 patients in each group to detect a 10% reduction (mean pain score with air, 30 mm) on a VAS with 80% power and a significance level of 0.05.

With regard to Pco₂ values, it was considered that a rise in Pco₂ of > 1 kPa was clinically significant. Based on the results of our study on the use of CO₂ in colonoscopy [6], we calculated that a total of 62 patients were required to detect this difference with a statistical power of 80%. The first 62 consecutive patients were therefore included in this part of the study.

**Results**

During the 6-month study period, 118 patients were found to be eligible for inclusion in the study and were randomized, 101 at the Oslo center and 17 at the Telemark center. Two patients were excluded from the analyses (both from the Oslo center), one patient (who had been allocated to the CO₂ group) because he accidentally received air insufflation during the first 15 minutes of the ERCP, and one patient (allocated to the air insufflation group) because the ERCP was cancelled after allocation. A total of 116 patients were therefore included in the final analyses (78 men, 38 women; mean age 55 years).

Table 1 summarizes the baseline characteristics in the two treatment groups. The mean dose of pethidine used was reduced by nearly 10 mg in the CO₂ group compared with the air group (P = 0.17).

One 87-year-old patient in the CO₂ group at the Telemark center died suddenly 3 days after the ERCP. He had been operated on for a femoral neck fracture 1 week prior to the ERCP and died during his stay at a rehabilitation clinic. No autopsy was performed. The death was not related to the ERCP procedure or the gas insufflated according to the judgment made by the local investigators and the physicians at the rehabilitation clinic. Two patients

<table>
<thead>
<tr>
<th></th>
<th>CO₂ group</th>
<th>Air group</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Sex, M/F</td>
<td>16/42</td>
<td>22/36</td>
<td>–</td>
</tr>
<tr>
<td>Mean age ± SD, years</td>
<td>57 ± 16</td>
<td>54 ± 18</td>
<td>–</td>
</tr>
<tr>
<td>Mean length of examination ± SD, minutes</td>
<td>43 ± 27</td>
<td>48 ± 25</td>
<td>–</td>
</tr>
<tr>
<td>Mean dose of sedation/ analgesic ± SD, mg</td>
<td>6.3 ± 3.6</td>
<td>6.4 ± 2.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Midazolam</td>
<td>35.2 ± 27.9</td>
<td>44.0 ± 37.3</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 1 Patient characteristics and features of the endoscopic procedures in the group receiving air insufflation and in the group receiving carbon dioxide (CO₂) insufflation

SD, standard deviation.
were diagnosed with post-ERCP pancreatitis (one in each of the treatment groups). These patients were both treated conservatively and made a full recovery within a few days. No other complications were observed in either of the treatment groups.

Pain during and after the procedure
Overall, 91 patients (78%) responded to the questionnaire, 39 (67%) in the CO₂ group and 52 (89%) in the air group. As shown in Figure 3, mean pain scores were significantly reduced in the CO₂ group compared with the air group at all time points after the examination (P < 0.001 at 1 hour, 3 hours, and 24 hours). There was no difference observed between the two groups with regards to pain experienced during the examination (see Figure 4).

Bowel distension
There was a marked difference in the severity of bowel distension between the two groups (Table 2): 61% of patients in the air group showed moderate or severe gastrointestinal tract distension after ERCP, compared with only 29% in the CO₂ group (P = 0.06). An increasing amount of pain was observed with increasing duration of the examination in the air group, but this occurred to a lesser extent in the CO₂ group (Table 2). None of the differences observed within the treatment groups reached statistical significance (Table 2).

PcO₂ measurements
The PcO₂ was successfully measured in the first 62 patients included in the trial (28 in the CO₂ group, 34 in the air group). Figure 5 shows the mean PcO₂ values in the CO₂ and air groups. Several measurements of the PcO₂ were made during the procedures, but only the maximum PcO₂ level for each patient was used for analysis and the values shown in Figure 5 are the mean maximum values recorded during the examination in the CO₂ and air groups. A rise in PcO₂ level was observed in both groups. The rise was more pronounced in the air group, with a PcO₂ level slightly above the reference range during the procedure. No clinically or statistically significant differences were observed between the groups. No patient dropped below 92% oxygen saturation. In patients who underwent the longest...
Table 3  Degree of bowel distension observed on postprocedure abdominal radiographic images after ERCP using CO₂ and air insufflation

<table>
<thead>
<tr>
<th>CO₂ group n = 30</th>
<th>Air group n = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal appearance (grade 1), n (%)</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>Light distension (grade 2), n (%)</td>
<td>13 (42%)</td>
</tr>
<tr>
<td>Moderate distension (grade 3), n (%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Severe distension (grade 4), n (%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

* P for overall difference between the treatment groups: 0.06

Discussion

This is the first study to investigate the effect of CO₂ insufflation on abdominal pain caused by ERCP. The results clearly show that CO₂ is superior to air insufflation, significantly reducing the intensity of postprocedure abdominal pain. The effect was obvious at all the observed time points after the ERCP, up to 24 hours after the examination.

As shown in Figure 3, patients in the air group experienced moderate postprocedure pain with scores in the 20–25-mm range on a 100-mm VAS. In the CO₂ group, mean pain scores were less than 10 mm and so could be regarded as only minor.

The majority of patients in the CO₂ group, however, did not experience any pain at all after the procedure (scored 0 on the VAS). In this situation, mean values may not give an adequate estimate of the difference between treatment groups. We therefore computed the percentage of patients scoring 0 on the VAS in the CO₂ and air groups (Figure 4). The superiority of CO₂ when compared with air is clearly visible in this analysis.

No difference between the two treatment groups was observed in abdominal pain experienced during the procedure. There was, however, a trend noticed of reduced use of pethidine in patients in the CO₂ group compared with the air group. This may indicate a possible beneficial effect of CO₂ insufflation during the procedure itself, although this was not confirmed by the patient questionnaire data. It would be likely that lengthy procedures might benefit more from using CO₂.

The degree of bowel distension was markedly different in the two groups, with a clinically significant, 50% reduction in the number of patients with moderate or severe gastrointestinal distension after ERCP in the CO₂ group. To minimize radiation exposure, we used frame-grab fluoroscopy for radiographic imaging rather than ordinary abdominal radiographs. Using this technique, however, we were not able to quantify bowel distension on a centimeter scale. In addition, in contrast to the studies on bowel distension after colonoscopy [1,2], evaluation of both the small bowel and the colon was necessary in the present study. The scoring system used in this trial was therefore based on the subjective impression of the radiologist reading the images. However, by blinding the radiologist with regard to the gas used, bias towards either group in assessing the degree of bowel distension should have been excluded.

Unfortunately we were only able to perform radiologic imaging in 59 out of the 116 patients included in the trial. This was a result of the limited availability of this radiology service at our centers. The patients included in this part of the study should be a representative sample, however, and not biased in any way. However, because of the relatively small number of patients included in this analysis, the P value for the difference in gas distension between the two groups did not reach statistical significance. The radiographic images in our study were taken only 5 minutes after the end of the procedure, while the radiographs in the two studies on bowel distension after colonoscopy [1,2] were taken 1 hour after examination. Because of limited resources and for logistical reasons, it was not possible for us to postpone the taking of radiographs to more than 5 minutes after the end of the procedure. This may limit the comparability of the data. However, the results are very similar to those reported in the

Ernst et al. CO₂ insufflation for more comfortable ERCP... Endoscopy 2007; 39: 58–64

Brethauer M et al. CO₂ insufflation for more comfortable ERCP... Endoscopy 2007; 39: 58–64

![Figure 3](https://example.com/figure3.png)

![Figure 4](https://example.com/figure4.png)
literature, with a marked reduction of distension with the use of CO$_2$ during endoscopy. Moreover, Nakajima et al. [10] recently reported complete disappearance of bowel distension within 20 minutes after endoscopy after CO$_2$ insufflation, which is consistent with our results.

Carbon dioxide insufflation has been shown in several randomized trials to reduce pain and discomfort during both colonoscopy and flexible sigmoidoscopy [1 - 7]. ERCP is similar to lower gastrointestinal endoscopy in that significant amounts of gas have to be insufflated into the bowel to ensure good visualization. ERCP procedures can often last longer than colonoscopies, and therefore probably involve the use of greater amounts of gas. In addition, air insufflated into the duodenum needs more time to pass through the entire bowel system before being released per rectum in comparison with gas insufflated during colonoscopy. Therefore, theoretically, pain caused by retained air may be more pronounced and last longer after ERCP than after colonoscopy. Indeed, the present data confirm these assumptions. Judging from the data from the colonoscopy trials, more patients complained of abdominal pain after ERCP than after colonoscopy and the pain lasted for longer [3, 5]. Our data show that the degree of abdominal pain is quite constant during the first 24 hours after ERCP, while it is reduced over time after colonoscopy. This effect was observed in both our groups, but at a significantly lower level in the CO$_2$ group.

The intensity and duration of pain after air insufflation is a particularly unfavorable feature in ERCP because the procedure carries a high risk of complications, the first signs of which will often be pain. Pain related to insufflation may therefore mask other causes of pain and delay the diagnosis of complications and the implementation of adequate therapeutic measures. Carbon dioxide insufflation could therefore offer an advantage in this respect. Interestingly, patients in the air group reported more pain after the procedure than during the procedure. Pain after the procedure may be a more important factor in terms of patient complaints and anxiety as well as in their reluctance to undergo follow-up investigations than was previously thought. This emphasizes the importance of questioning patients not only with regard to their experience during endoscopic examinations but also about the hours following the procedure.

A possible bias in the results of the present study might be the larger proportion of patients in the air group who responded to the questionnaire (89%), compared with the CO$_2$ group (78%). Patients who did not experience any notable pain due to the ERCP could be less motivated to answer a questionnaire focusing significantly lower level in the CO$_2$ colonoscopy.

In brief

Another randomized study on the use of carbon dioxide in gastrointestinal endoscopy, this time in the ERCP setting: Somewhat correlated with the duration of the procedure, the postprocedure bloating was much less marked in the CO$_2$ group.

We did not observe any side effects due to CO$_2$ insufflation. However, in both the CO$_2$ group and in the air group, mean Pco$_2$ values were elevated during ERCP. This is to be regarded as an effect of the sedation, as shown in the literature [14]. Two patients had disturbingly high Pco$_2$ values recorded during the procedure, despite having normal oxygen saturation values. Some investigators have focused on the inadequacy of using oxygen saturation for monitoring adequate ventilation in sedated patients and recommend routine measurement of Pco$_2$ during ERCP to screen more effectively for hypoventilation [14]. According to our data, this may be indicated in some patients. Acidosis due to hypercapnia has been reported during CO$_2$ pneumoperitoneum for laparoscopic surgery and also when CO$_2$ is used in intraoperative endoscopy procedures [9, 15]. Severe cases, however, are rare and only seen with high-pressure CO$_2$ insufflation, which is not used in endoscopy procedures [15]. No blood gas samples were taken in this study and so we have no data on patients’ pH levels during CO$_2$ insufflation.

Patients with COPD were excluded from the present trial. To our knowledge, no studies have been performed to evaluate the safety of using CO$_2$ insufflation in patients with COPD. Therefore, for the time being, we recommend extensive respiratory monitoring, including Pco$_2$ measurements, when using CO$_2$ insufflation during ERCP in all patients with COPD, to monitor for possible adverse effects.

The vast majority of endoscopy facilities around the world still use air insufflation for endoscopic procedures. A considerable body of evidence now exists, however, showing the superiority of CO$_2$ over air in lower gastrointestinal endoscopy [1 - 8]. This study adds to the evidence in favor of using CO$_2$ for ERCP. The only technical equipment required for CO$_2$ insufflation is a water bottle and a CO$_2$ insufflator, but these tools are only supplied by two manufacturers (Olympus and E & EM). For the present trial we used the Olympus insufflator during ERCP. To further promote CO$_2$ insufflation in gastrointestinal endoscopy, other companies need to design devices for CO$_2$ insufflation that are compatible with their equipment.

In conclusion, CO$_2$ insufflation significantly reduces the incidence of abdominal pain after ERCP. No side effects due to CO$_2$ insufflation have been observed. Carbon dioxide should be used as the standard insufflation gas in ERCP. However, caution is warranted in patients with COPD until further studies have excluded the occurrence of CO$_2$-related adverse effects in these patients.

Acknowledgments

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Competing interests: None
References

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