# Efficacy and safety of carbon dioxide insufflation versus air insufflation during endoscopic retrograde cholangiopancreatography in randomized controlled trials: a systematic review and meta-analysis

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ABSTRACT

**Background and study aims** Ambient air is the most commonly used gas for insufflation in endoscopic procedures worldwide. However, prolonged absorption of air during endoscopic examinations may cause pain and abdominal distension. Carbon dioxide insufflation ($CO_2$i) has been increasingly used as an alternative to ambient air insufflation (AAi) in many endoscopic procedures due to its fast diffusion properties and less abdominal distention and pain. For endoscopic retrograde cholangiopancreatography (ERCP), use of $CO_2$ for insufflation is adequate because this procedure is complex and prolonged. Some randomized controlled trials (RCTs) have evaluated the efficacy and safety of $CO_2$ as an insufflation method during ERCP but presented conflicting results. This systematic review and meta-analysis with only RCTs evaluated the efficacy and safety of $CO_2$i versus AAi during ERCP.

**Methods** A literature search was performed using online databases with no restriction regarding idiom or year of publication. Data were extracted by two authors according to a predefined data extraction form. Outcomes evaluated were abdominal pain and distension, complications, procedure duration, and $CO_2$ levels.

**Results** Eight studies (919 patients) were included. Significant results favoring $CO_2$i were less abdominal distension after 1 h (MD: −1.41 [−1.81; −1.0], 95 % CI, $I^2 = 15\%$, $P < 0.00001$) and less abdominal pain after 1 h (MD: −23.80 [−27.50; −20.10], 95 %CI, $I^2 = 9\%$, $P < 0.00001$) and after 6 h (MD: −7.00 [−8.66; −5.33]; 95 % CI, $I^2 = 0\%$, $P < 0.00001$).

**Conclusion** Use of $CO_2$i instead of AAi during ERCP is safe and associated with less abdominal distension and pain after the procedure.

## Introduction

The first gastroscope used bulb insufflators. In the 1960s, light sources began to be integrated with air pumps for insufflation, and that is still the most commonly used air insufflation method in endoscopic examinations [1]. At present, the main gases used for insufflation are ambient air and carbon dioxide ($CO_2$). Ambient air is the most commonly used gas for insufflation in endoscopic procedures worldwide [2] and it is the trapped unabsorbed air that leads to prolonged abdominal pain and distension [3].

$CO_2$ is the most commonly used gas in laparoscopic surgery because it is noninflammable and can be rapidly absorbed and excreted. It is absorbed by the intestine 160 times faster than nitrogen and 13 times faster than oxygen, which are the main atmospheric gases [1]. In 1953, use of $CO_2$ was proposed as an insufflating agent in rigid ureteroscopy to prevent explosions during endoscopic removal of polyps with electrical current [1], and it began to be used in the 1960s in colonoscopic examinations with positive results such as less abdominal pain and less flatulence after the procedure [4 – 7]. For endoscopic retrograde cholangiopancreatography (ERCP), use of $CO_2$ for insufflation is adequate because this procedure is complex and prolonged [8]. Use of some gases as insufflating agents, including helium, argon, nitrogen, and xenon, has been evaluated in laparoscopic surgeries; however, these gases are not suitable for endoscopic examinations because of their absorption properties and availability [9].

Since the 1960 s, ERCP has rapidly evolved and is now considered the gold standard for treatment of pathologies of the biliopancreatic system [9]. In addition, the procedure is usually prolonged due to its complexity and requires large amounts of insufflated air to enable adequate visualization of the duodenal papilla and manipulation of instruments [2].

Reported incidence of complications of ERCP varies in the literature, but reported morbidity and mortality rates are 5 % to 10 % and 0.1 % to 1.0 %, respectively [10]. The main complications related to the procedure are pancreatitis (5 % – 10 % cases), bleeding (1 % – 2 % cases), infections (1 % – 2 % cases), and perforations (0.5 % – 0.6 % cases); the latter is one of the most feared complications [10].

$CO_2$ is rapidly absorbed by the intestine and transported through the lungs into the bloodstream, where it can cause acidosis and hypercapnia [5, 11]. The high level of $CO_2$ absorption, particularly in older patients and in patients with lung disease, can lead to severe cardiopulmonary problems, including hypoxemia, pulmonary edema, arrhythmia, and tachycardia [11, 12].

Some randomized controlled trials (RCTs) have evaluated the efficacy and safety of $CO_2$ as an insufflation method during ERCP but presented conflicting results; therefore, an updated systematic review and meta-analysis is necessary to evaluate the same. Some studies have shown similar results regarding pain and abdominal distension between the groups receiving $CO_2$ and ambient air [13], whereas other studies have shown a difference in these outcomes between the groups. In addition, evaluation periods after ERCP differ between the study groups (1, 3, 6, or 24 hours after examination). The purpose of this systematic review and meta-analysis was to evaluate the efficacy and safety of $CO_2$ as an insufflator during and after ERCP examinations.

# Methods

## Protocol and registration

A protocol was established and documented prior to initiating the study to specify eligibility criteria and analytical methods for the studies included in this systematic review and meta-analysis. This protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017032812

## Information sources and search

A literature search was performed to access all RCTs that compared use of $CO_2$ and ambient air in ERCP that were published until November 2016 through the following electronic databases: MEDLINE, SCOPUS, LILACS and CENTRAL (BVS), and Cochrane Library. References of the searched articles ("gray literature search") were also accessed. The search terms were "(Cholangiopancreatography, Endoscopic Retrograde, OR ERCP) AND ($CO_2$ OR carbon dioxide)" in MEDLINE, "Endoscopic Retrograde Cholangiopancreatography and ERCP AND $CO_2$ and carbon dioxide" in SCOPUS and LILACS, and "Endoscopic Retrograde Cholangiopancreatography AND $CO_2$" in the Cochrane Library.

## Study selection

When selecting studies, there were no restrictions on language, year of publication, patient follow-up duration, or status of the publication. After reading the titles and abstracts of the articles from the initial selection, the articles were evaluated with respect to study design (RCTs), study population (patients submitted to ERCP), insufflation method ($CO_2$ and ambient air), and outcome (pain and abdominal distension after ERCP, total duration of the procedure, procedure-related complications, $CO_2$ levels during ERCP, and increase in waist circumference).

## Data extraction

Data were extracted by two independent reviewers, and all the selected studies were included in the meta-analysis. In case of a divergence of opinions during data extraction and analysis, the doubts were taken to a discussion group in scientific methodology to define the best conduct. The following data were extracted from the selected studies: first author, year of publication, country, sample size, population subgroups, patient characteristics, type of sedation, prognosis, and outcomes.

## Data items

The studies evaluated compared insufflation with $CO_2$ and ambient air, and the study populations included patients subjected to ERCP. Outcomes selected for systematic review were presence of abdominal pain, absence of abdominal pain, abdominal distension after ERCP, $CO_2$ levels during ERCP, procedure-related complications, and total duration of ERCP. For analysis of abdominal pain, questionnaires were administered to measure the intensity of abdominal pain at 1, 3, 6, and 24 hours after the procedure. The visual analog scale (VAS) was the most widely used pain scale, with a range of 0 to 10 mm or 0 to 100 mm, and one study used the Wong – Baker FACES Pain Rating

Scale (WBS). Three studies were excluded from the meta-analysis: two that did not have sufficient data and one that used a different pain scale (WBS).

VAS were normalized to enable comparison between studies for each outcome by revising every study to a scale range from 0 to 10 mm (dividing 0 – 100 values by 10) or to a scale range from 0 to 100 mm (multiplying 0 – 10 values by 10), depending on the outcome analyzed. For example, we changed the VAS from the 100-mm one employed in study by Luigiano et al. [14] to the 10-mm one. For the same, we divided the values by 10, which enabled adequate comparison between the study groups, which both ranged from 0 to 10 mm.

### Risk of bias

Risk of bias was individually assessed for each study based on the randomization method, allocation method, blinding method, description of losses, prognosis, outcomes, and execution of an analysis using the intention-to-treat protocol. The JADAD scale, which is the score used to assess the quality of clinical studies, was used. This scale analyzes RCTs using the following criteria: description and method of randomization, blinding method, and description of losses. The randomization method was considered appropriate when it was performed by a sequence of random numbers generated using a computer or tables. Software and opaque/sealed envelopes were found to be adequate allocation methods. Studies that presented losses of more than 20 % were excluded. The blinding method considered appropriate was double blinding.

### Analysis

Data were analyzed using the software program Review Manager version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The risk difference (RD) at 95 % confidence interval (CI) was calculated for dichotomous variables using the Mantel-Haenszel test, and the mean difference (MD) at 95 % CI was calculated for continuous variables using the reverse variance test.

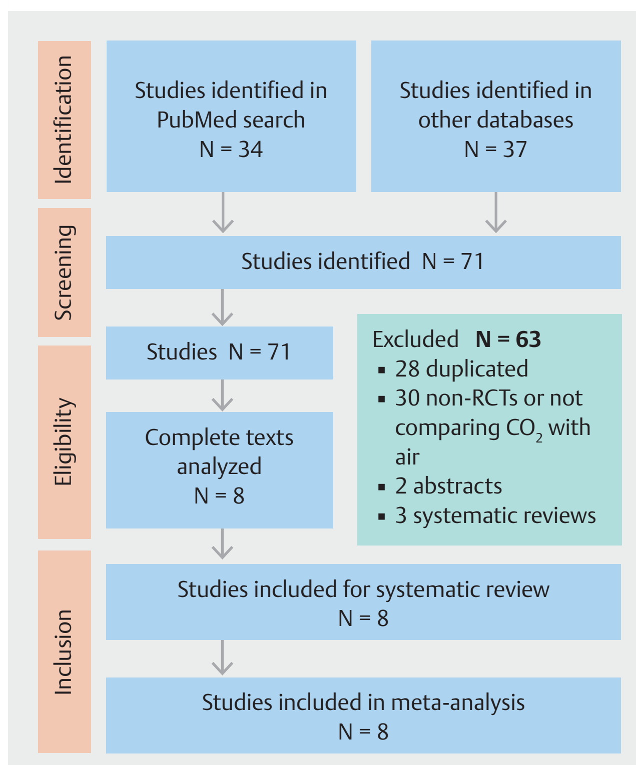
Heterogeneity was tested with the Q test for significance and with the inconsistency index ($I^2$), where a value > 50 % was considered as substantial heterogeneity between studies. A funnel plot was generated and linear regression tests were performed excluding the studies that were located outside the funnel plot (outliers). Next, another meta-analysis was performed without the outliers. True heterogeneity was presumed and the random effects model was applied in case of persistent high heterogeneity or if outliers could not be detected.

## Results

After screening the titles and abstract, 34 studies were selected from PUBMED and 37 studies from other databases [SCOPUS, LILACS, and CENTRAL (BVS), Cochrane Library, and gray literature search], resulting in selection of 71 studies. After this analysis, 63 articles were excluded: duplicates, nonrandomized studies, studies without complete texts [15 – 17], and systematic reviews [11, 18, 19]. Thus, eight studies [8, 13 ,14, 20 – 24] were included in the systematic review and meta-analysis, as shown in the flow chart below (▶ **Fig. 1**).

### Study identification and eligibility criteria

Eight RCTs [8, 13, 14, 20 – 24] involving 919 patients published between 2007 and 2016 were included. This population was divided into two groups: one group underwent insufflation with $CO_2$ and the other group received ambient air. The main symptoms of ERCP were choledocholithiasis, pancreatic and biliary tract neoplasms, dilated bile ducts, and benign and malignant stenosis of the biliary tract. All the procedures were performed under sedation; type of sedation varied between the studies, but most studies used a combination of sedatives. The main characteristics of the studies are shown in ▶ **Table 1**. One study [12] compared different types of insufflations under different sedation methods. Therefore, this study was divided into two subgroups: subgroup A (sedation with midazolam and propofol) and subgroup B (sedation only with propofol). Risk of bias is shown in ▶ **Table 2**. Outcomes of the selected studies were presence of abdominal pain, absence of abdominal pain,




▶ **Fig. 1** Search strategy.

▶ **Table 1** Characteristics of studies that used either $CO_2$ or ambient air as insufflating agents during endoscopic retrograde cholangiopancreatography.

| Author, year | Country | Center (N) | Participants ($CO_2$/Air) | Sedation |
|---|---|---|---|---|
| Bretthauer M et al. 2007 | Norway | 2 | 118 (58/58) | Midazolam and pethidine |
| Maple et al. 2009 | USA | 1 | 105 (50/50) | Propofol |
| Dellon et al. 2010 | USA | 1 | 78 (36/38) | Midazolam and fentanyl |
| Kuwatani et al. 2011 | Japan | 2 | 80 (40/40) | Fentanyl or pethidine and midazolam or diazepam |
| Luigiano et al. 2011 | Italy | 1 | 110 (37/39) | Propofol and remifentanil or fentanyl |
| Muraki et al. 2012 | Japan | 1 | 208 (106/102) | Midazolam and pentazocine |
| Nakamura et al. 2014 | Japan | 1 | 60 (30/30) | Midazolam and pethidine |
| Lee et al. 2015 | Korea | 1 | 160 (80/80) | Midazolam, fentanyl, and propofol |

▶ **Table 2** Risk of bias in included trials.

| Author | Randomization method | Allocation | Blinding | Withdrawals | Intention to treat | Score JADAD |
|---|---|---|---|---|---|---|
| Bretthauer M et al. | Computer-generated | Sealed envelopes | Double blind | Described | No | 5 |
| Maple et al. | Computer-generated | Opaque envelopes | Double blind | Described | No | 4 |
| Dellon et al. | Computer-generated | Opaque envelopes | Double blind | Described | No | 5 |
| Kuwatani et al. | Computer-generated | Not mentioned | Double blind | Described | Yes | 5 |
| Luigiano et al. | Computer-generated | Sealed envelopes | Double blind | Described | No | 5 |
| Muraki et al. | Computer-generated | Not mentioned | Double blind | Described | Yes | 5 |
| Nakamura et al. | Computer-generated | Not mentioned | Double blind | Described | Yes | 5 |
| Lee et al. | Computer-generated | Not mentioned | Double blind | Described | Yes | 5 |

abdominal distension, ERCP-related complications, total duration of ERCP, and $CO_2$ levels during ERCP.

## Abdominal pain

Abdominal pain after ERCP was evaluated in the eight studies included; however, not all the studies had comparable data. Only four studies were used to assess this outcome. The group that underwent insufflation with $CO_2$ experienced less pain than the one that received ambient air, with a significant difference at 1 hour after ERCP (MD: −23.80 [−27.50 to −20.10], 95 % CI, $I^2$ = 9 %, $P$ < 0.00001)(▶ **Fig. 2**) and 6 hours after ERCP (MD: −7.00 [−8.66 to −5.33]; 95 % CI, $I^2$ = 0 %, $P$ < 0.00001)(▶ **Fig. 3**). Sensitivity analysis was conducted for evaluation of pain at 1 hour after ERCP because of the high heterogeneity ($I^2$ = 90 %) observed, and one study [13] was excluded to reduce heterogeneity to 9 %. There was no significant difference in the pain levels at 3 and 24 hours after ERCP between these groups (▶ **Fig. 2**, ▶ **Fig. 3**, ▶ **Fig. 4**, ▶ **Fig. 5**).

## Absence of pain

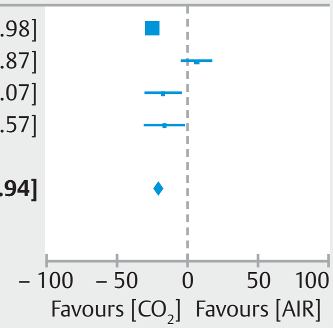
Absence of pain was evaluated in two studies at 1 hours and 3, 6, and 24 hours after ERCP using the 10-mm VAS pain questionnaire. There were sufficient data to perform a meta-analysis at two instances: 1 hour and 24 hours after ERCP (▶ **Fig. 6** and ▶ **Fig. 7**). $CO_2$ was better than ambient air based on the higher number of patients showing no pain after the procedure; however, a significant difference between the groups was found only 1 hour after ERCP (RD: 1.86 0.30 [0.17 – 0.43], 95 % CI, $I^2$ = 79 %, $P$ < 0.06).

## Abdominal distension

Four studies evaluated presence of abdominal distention after ERCP. The meta-analysis was conducted at 1 hour and 3 and 24 hours after ERCP. There was a significant difference between the groups, and the group that underwent insufflation with $CO_2$ had lesser distension than the one that received ambient air at 1 hour after ERCP (MD: −1.41 [−1.81 to −1.0], 95 % CI, $I^2$ = 15 %, $P$ < 0.00001)(▶ **Fig. 8**). Evaluation of abdominal distension at 3 and 24 hours after ERCP indicated no significant difference between the two groups (▶ **Fig. 9** and ▶ **Fig. 10**). Two studies (Maple et al [21]. and Dellon et al. [13]) evaluated the increase in abdominal circumference after ERCP in centimeters,

| Study or subgroup | $CO_2$ Mean | SD | Total | AIR Mean | SD | Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 10 | 4.4 | 37 | 35 | 12 | 39 | 74.8 % | – 25.00 [– 29.02, – 20.98] |
| E. Dellon, 2010 | 16.4 | 25.2 | 36 | 10.8 | 19.3 | 38 | 11.5 % | 5.60 [– 4.67, 15.87] |
| S. Lee a, 2015 | 11.8 | 22.5 | 40 | 29.5 | 34 | 40 | 7.6 % | – 17.70 [– 30.33, – 5.07] |
| S. Lee b, 2015 | 19.8 | 30.8 | 40 | 36.5 | 33.6 | 40 | 6.1 % | – 16.70 [– 30.83, – 2.57] |
| **Total (95 % CI)** | | | **153** | | | **157** | **100.0 %** | **– 20.42 [– 23.91, – 16.94]** |

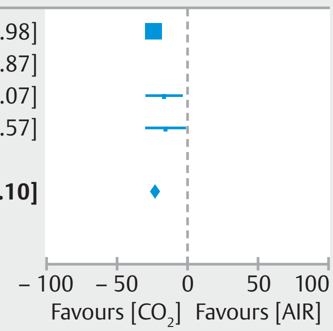
Heterogeneity: Chi² = 30.09, df = 3 ($P$ < 0.00001); I² = 90 %
Test for overall effect: Z = 11.50 ($P$ < 0.00001)



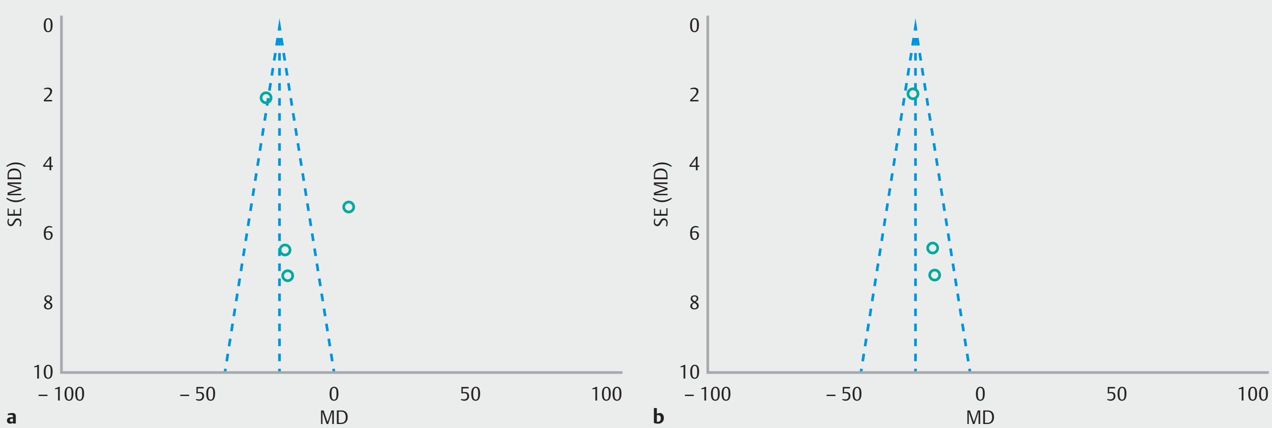

**a**

| Study or subgroup | $CO_2$ Mean | SD | Total | AIR Mean | SD | Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 10 | 4.4 | 37 | 35 | 12 | 39 | 84.6 % | – 25.00 [– 29.02, – 20.98] |
| E. Dellon, 2010 | 16.4 | 25.2 | 36 | 10.8 | 19.3 | 38 | 0.0 % | 5.60 [– 4.67, 15.87] |
| S. Lee a, 2015 | 11.8 | 22.5 | 40 | 29.5 | 34 | 40 | 8.6 % | – 17.70 [– 30.33, – 5.07] |
| S. Lee b, 2015 | 19.8 | 30.8 | 40 | 36.5 | 33.6 | 40 | 6.9 % | – 16.70 [– 30.83, – 2.57] |
| **Total (95 % CI)** | | | **117** | | | **119** | **100.0 %** | **– 23.80 [– 27.50, – 20.10]** |

Heterogeneity: Chi² = 2.21, df = 2 ($P$ = 0.33); I² = 9 %
Test for overall effect: Z = 12.61 ($P$ < 0.00001)




**b**




▶ **Fig. 2** Pain levels 1 hour after insufflation. **a** Pain levels 1 hour after insufflation. Funnel plot showing an outlier study **b** Pain levels 1 hour after insufflation. Funnel plot after withdrawn outlier study.

and both reported a more pronounced increase in abdominal circumference in patients who underwent insufflation with ambient air; however, one of the studies did not provide sufficient data to perform the meta-analysis.

## Procedure-related complications

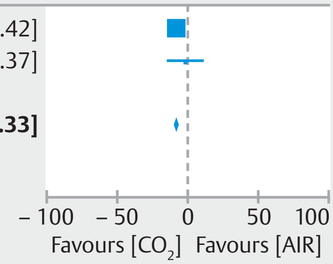
All the included studies evaluated ERCP-related complications. The main complications reported were pancreatitis and bleeding; no serious complications related to the procedure were reported. There was no significant difference between the $CO_2$ and ambient air groups (RD: −0.02 [−0.05 to 0.01], 95 % CI, $I^2 = 0\%$, $P = 0.15$)(▶ **Fig. 11**).

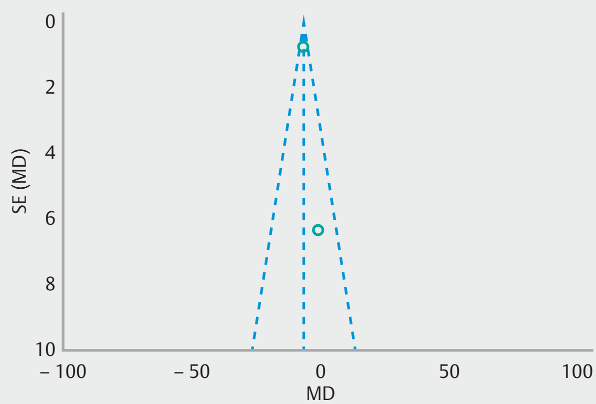
## Total duration of the procedure

All the included studies compared total length of ERCP between the two groups. Results of the meta-analysis indicated no significant difference between the two groups (MD: −0.10 [−2.75 to 2.54], 95 % CI, $I^2 = 0\%$, $P = 0.94$)(▶ **Fig. 12**).

| Study or subgroup | $CO_2$ Mean | SD | Total | AIR Mean | SD | Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 7 | 2.5 | 37 | 14.1 | 4.7 | 39 | 98.2 % | – 7.10 [– 8.78, – 5.42] |
| E. Dellon, 2010 | 18.3 | 25.4 | 32 | 19.5 | 26.7 | 34 | 1.8 % | – 1.20 [– 13.77, 11.37] |
| **Total (95 % CI)** | | | **69** | | | **73** | **100.0 %** | **– 7.00 [– 8.66, – 5.33]** |

Heterogeneity: Chi² = 0.83, df = 1 (*P* = 0.36); I² = 0 %
Test for overall effect: Z = 8.23 (*P* < 0.00001)




▶ **Fig. 3** Pain levels 3 hours after insufflation.

### $CO_2$ levels

Four studies reported changes in $CO_2$ levels during ERCP, but one study was excluded from the meta-analysis due to incomplete data. Thus, our meta-analysis included three studies and considered the peak $CO_2$ level during ERCP. This analysis indicated no significant differences but showed high heterogeneity between the groups (I² = 61 %, MD: 0.30 [−0.63 to 1.23], 95 % CI, I² = 61 % at *P* = 0.53](▶ **Fig. 13**).

## Discussion

ERCP is often a complex and prolonged examination; it requires large doses of medications for sedation and large volumes of insufflated air during the procedure. It may also cause some complications such as pancreatitis, hemorrhage, and perforations [23]. We included eight studies in this review to evaluate the efficacy and safety of this procedure using $CO_2$ or ambient air.

Evaluation of pain after ERCP was performed for all the included studies, showing that patients who underwent insufflation with $CO_2$ had less intense abdominal pain after the examination; however, this difference was only significant at 1 hour and 6 hours after the procedure. Four studies evaluated presence of abdominal distension and reported the superiority of $CO_2$ due to the lower levels of abdominal distension in this group, with statistical significance at 1 hour and 3 hours after the procedure. There was no significant difference between the two groups for the following outcomes: procedure-related complications, total duration of the procedure, $CO_2$ levels, and distension and pain at 24 hours after ERCP.

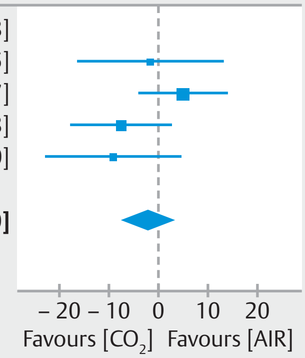
This systematic review and meta-analysis is the first to evaluate only RCTs [11, 18, 19]. Our results indicated the superiority of $CO_2$ over ambient air as an insufflation method because $CO_2$ improved patient comfort and decreased levels of pain and abdominal distension after the procedure.

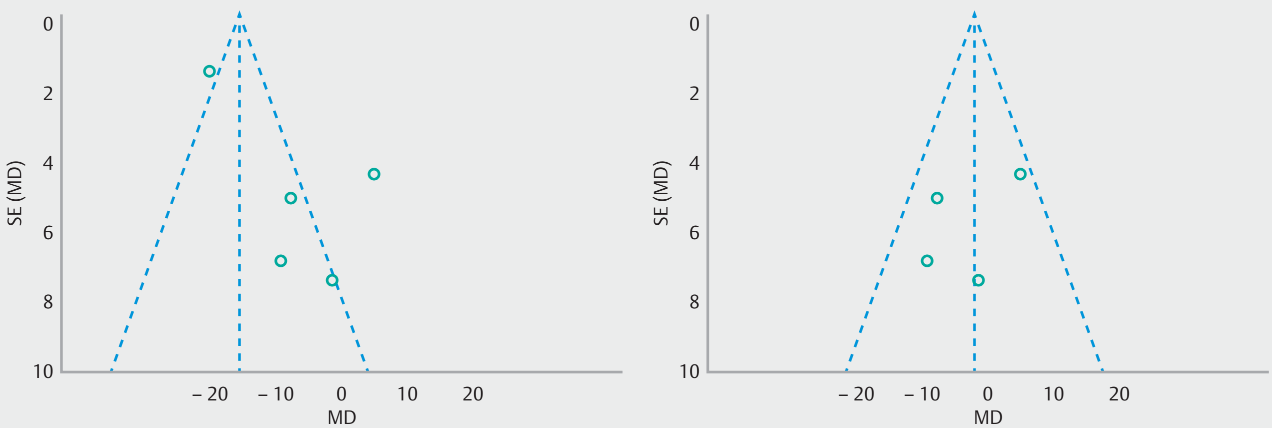
Most selected studies did not include older patients and patients with pulmonary disease, which raises concerns about the safety of use of $CO_2$ in these groups of patients, owing to the possibility of higher levels of hemodynamic complications after insufflation with large volumes of $CO_2$. Only the study by Nakamura et al [24]. included 60 patients older than 75 years who were subjected to ERCP. That study demonstrated the benefit of $CO_2$, with a significant difference in abdominal distension, nausea, and abdominal discomfort at 2 hours after ERCP between the two groups ($CO_2$ vs. ambient air), and it indicated no differences in $CO_2$ levels during the procedure between these groups, demonstrating the safety of using $CO_2$ in older patients.

The evaluated studies reported the type of sedation performed in patients, and most of them used a combination of sedatives. The diversity in types of sedation used may influence assessment of pain and discomfort during and after ERCP due to the different characteristics of each sedative in relation to degree of sedation and tolerance to stimuli. Only the study by Lee et al. [23] compared the two types of insufflation as a func-

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 8 | 2.5 | 37 | 28.1 | 9.6 | 39 | 0.0 % | – 20.10 [– 23.22, – 16.98] |
| E. Dellon, 2010 | 20.8 | 32.2 | 32 | 22.3 | 27.8 | 34 | 14.3 % | – 1.50 [– 16.05, 13.05] |
| M. Kuwatani, 2011 | 14 | 20 | 40 | 9 | 20 | 40 | 39.4 % | 5.00 [– 3.77, 13.77] |
| S. Lee a, 2015 | 11 | 19.7 | 40 | 18.5 | 25.9 | 40 | 29.7 % | – 7.50 [– 17.58, 2.58] |
| S. Lee b, 2015 | 19.1 | 30.3 | 40 | 28.3 | 31.3 | 40 | 16.6 % | – 9.20 [– 22.70, 4.30] |
| **Total (95 % CI)** | | | **152** | | | **154** | **100.0 %** | **– 2.00 [– 7.50, 3.50]** |

Heterogeneity: $Chi^2 = 4.69$, df = 3 ($P = 0.20$); $I^2 = 36\ \%$
Test for overall effect: Z = 0.71 ($P = 0.48$)

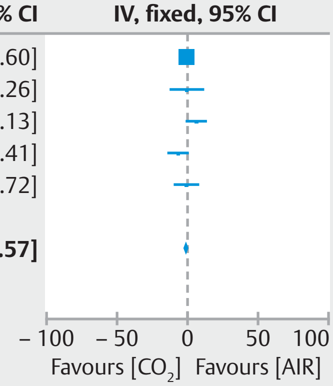



► **Fig. 4** Pain levels 6 hours after insufflation.

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 4.2 | 3.4 | 37 | 5 | 2.8 | 39 | 89.4 % | – 0.80 [– 2.20, 0.60] |
| E. Dellon, 2010 | 15 | 24.7 | 32 | 15.5 | 24 | 34 | 1.3 % | – 0.50 [– 12.26, 11.26] |
| M. Kuwatani, 2011 | 11 | 19 | 40 | 5 | 13 | 40 | 3.5 % | 6.00 [– 1.13, 13.13] |
| S. Lee a, 2015 | 3.5 | 10.8 | 40 | 10.3 | 20.6 | 40 | 3.4 % | – 6.80 [– 14.01, 0.41] |
| S. Lee b, 2015 | 9.3 | 17 | 40 | 10 | 21.2 | 40 | 2.5 % | – 0.70 [– 9.12, 7.72] |
| **Total (95 % CI)** | | | **189** | | | **193** | **100.0 %** | **– 0.76 [– 2.09, 0.57]** |

Heterogeneity: $Chi^2 = 6.15$, df = 4 ($P = 0.19$); $I^2 = 35\ \%$
Test for overall effect: Z = 1.12 ($P = 0.26$)



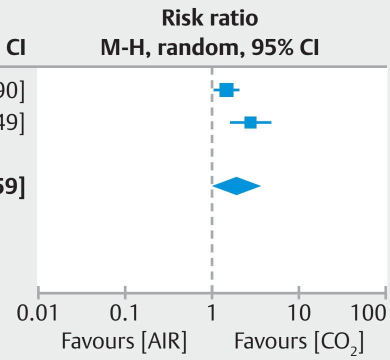

► **Fig. 5** Pain levels 24 hours after insufflation.

tion of two different methods of sedation: propofol alone vs. a combination of propofol and midazolam. This study demonstrated that the group that received a combination of sedatives and $CO_2$ insufflation had lower levels of pain, abdominal distension, and residual intra-abdominal gases as well as improved overall satisfaction with sedation.

| Study or subgroup | $CO_2$ Events | $CO_2$ Total | AIR Events | AIR Total | Weight | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| J. Maple, 2009 | 36 | 50 | 26 | 50 | 54.9 % | 1.38 [1.01, 1.90] |
| M. Bretthauer, 2007 | 26 | 39 | 13 | 52 | 45.1 % | 2.67 [1.58, 4.49] |
| **Total (95 % CI)** | | **89** | | **102** | **100.0 %** | **1.86 [0.97, 3.59]** |
| Total events | 62 | | 39 | | | |

Heterogeneity: Tau² = 0.18; Chi² = 4.68, df = 1 ($P$ = 0.03); I² = 79 %

Test for overall effect: Z = 1.86 ($P$ = 0.06)

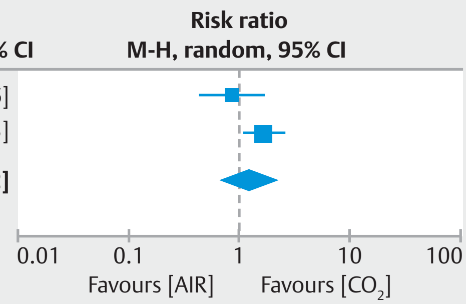



► **Fig. 6** Absence of pain 1 hour after insufflation.

| Study or subgroup | $CO_2$ Events | $CO_2$ Total | AIR Events | AIR Total | Weight | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| J. Maple, 2009 | 12 | 50 | 14 | 50 | 42.4 % | 0.86 [0.44, 1.66] |
| M. Bretthauer, 2007 | 18 | 39 | 20 | 52 | 57.6 % | 1.67 [1.10, 2.53] |
| **Total (95 % CI)** | | **89** | | **102** | **100.0 %** | **1.26 [0.65, 2.42]** |
| Total events | 37 | | 34 | | | |

Heterogeneity: Tau² = 0.15; Chi² = 2.87, df = 1 ($P$ = 0.09); I² = 65 %

Test for overall effect: Z = 0.68 ($P$ = 0.49)

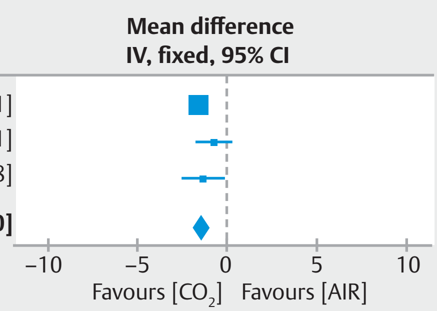



► **Fig. 7** Absence of pain 24 hours after insufflation.

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2015 | 0.72 | 0.36 | 37 | 2.31 | 1.5 | 39 | 69.8 % | −1.59 [−2.07, −1.11] |
| S. Lee a, 2015 | 0.75 | 1.43 | 40 | 1.5 | 2.76 | 40 | 17.7 % | −0.75 [−1.71, 0.21] |
| S. Lee b, 2015 | 1.05 | 1.95 | 40 | 2.38 | 3.14 | 40 | 12.5 % | −1.33 [−2.48, −0.18] |
| **Total (95 % CI)** | | | **117** | | | **119** | **100.0 %** | **−1.41 [−1.81, −1.00]** |

Heterogeneity: Chi² = 2.35, df = 2 ($P$ = 0.31); I² = 15 %

Test for overall effect: Z = 6.82 ($P$ < 0.00001)




► **Fig. 8** Abdominal distension 1 hour after endoscopic retrograde cholangiopancreatography.

Pain control during ERCP is of extreme importance to maintain patient comfort throughout the procedure. Less abdominal distension, which is expected with $CO_2$ insufflation due to faster gas diffusion through TGI into the bloodstream, is associated with less pain and therefore with lesser intravenous sedation usage, making it easier to achieve pain control.

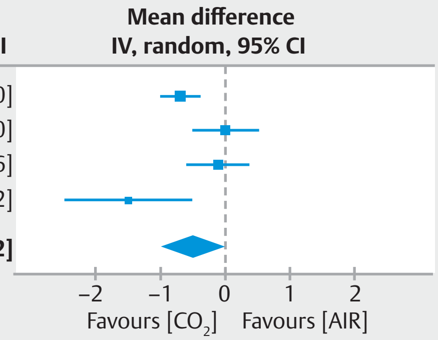
Many studies use different scales (VAS and WBS) to assess outcomes such as pain and distension. These scales, therefore, need to be standardized to enable proper comparison, inclusion of more studies in the meta-analysis, and reduction of selection bias.

Use of $CO_2$ for insufflation during ERCP was beneficial to patients because they presented with less discomfort during and after the procedure.

Analysis of procedure-related complications in patients who received $CO_2$ indicated that $CO_2$ had no benefits over ambient air. However, a possible advantage of $CO_2$ over air insufflation may be evident in case of ERCP-related perforation (i. e., following sphincter dilation or papillotomy procedures): the $CO_2$ absorption rate is faster than the air absorption rate, which could result in diminished abdominal distension, fewer ventilatory changes, and faster pneumoperitoneum or retropneumoperitoneum absorption, maintaining conservative treatment as a

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2015 | 0.61 | 0.21 | 37 | 1.31 | 0.92 | 39 | 31.7 % | −0.70 [−1.00, −0.40] |
| M. Kuwatani, 2011 | 0.6 | 1.2 | 40 | 0.6 | 1.1 | 40 | 26.2 % | 0.00 [−0.50, 0.50] |
| S. Lee a, 2015 | 0.33 | 1.23 | 40 | 0.45 | 0.93 | 40 | 26.9 % | −0.12 [−0.60, 0.36] |
| S. Lee b, 2015 | 0.43 | 1.43 | 40 | 1.93 | 2.81 | 40 | 15.1 % | −1.50 [−2.48, −0.52] |
| **Total (95 % CI)** | | | **157** | | | **159** | **100.0 %** | **−0.48 [−0.98, −0.02]** |

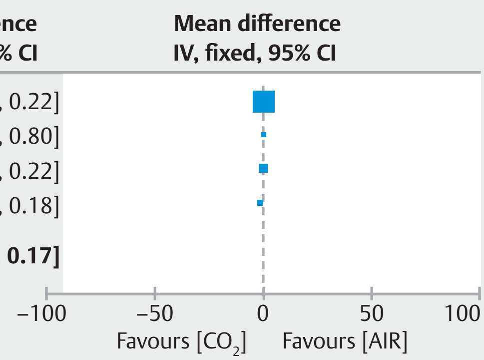
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 11.96$, df = 3 ($P = 0.008$); $I^2 = 75\ \%$
Test for overall effect: Z = 1.88 ($P = 0.06$)




▶ **Fig. 9** Abdominal distension 3 hours after endoscopic retrograde cholangiopancreatography.

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 0.31 | 0.25 | 37 | 0.22 | 0.32 | 39 | 73.1 % | 0.09 [−0.04, 0.22] |
| M. Kuwatani, 2011 | 0.6 | 1.6 | 40 | 0.4 | 1.1 | 40 | 3.3 % | 0.20 [−0.40, 0.80] |
| S. Lee a, 2015 | 0.13 | 0.56 | 40 | 0.15 | 0.53 | 40 | 21.2 % | −0.02 [−0.26, 0.22] |
| S. Lee b, 2015 | 0.28 | 1.34 | 40 | 0.83 | 1.93 | 40 | 2.3 % | −0.55 [−1.28, 0.18] |
| **Total (95 % CI)** | | | **157** | | | **159** | **100.0 %** | **0.06 [−0.05, 0.17]** |

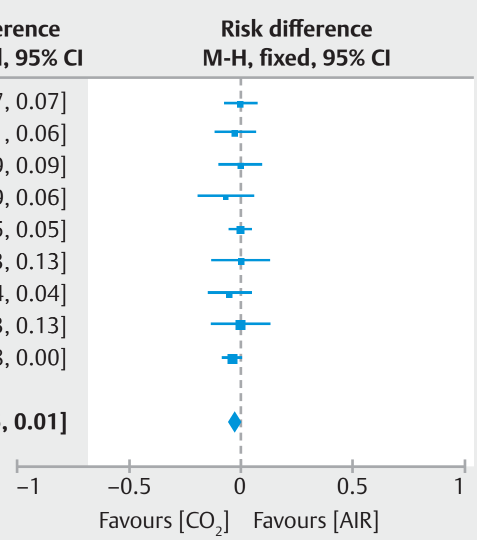
Heterogeneity: $Chi^2 = 3.54$, df = 3 ($P = 0.32$); $I^2 = 15\ \%$
Test for overall effect: Z = 0.99 ($P = 0.32$)




▶ **Fig. 10** Abdominal distension 24 hours after endoscopic retrograde cholangiopancreatography.

| Study or subgroup | $CO_2$ Events | $CO_2$ Total | AIR Events | AIR Total | Weight | Risk difference M-H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 1 | 37 | 1 | 39 | 8.7 % | 0.00 [−0.07, 0.07] |
| E. Dellon, 2010 | 1 | 36 | 2 | 38 | 8.5 % | −0.02 [−0.11, 0.06] |
| J. Maple, 2009 | 3 | 50 | 3 | 50 | 11.4 % | 0.00 [−0.09, 0.09] |
| K. Nakamura, 2014 | 1 | 30 | 3 | 30 | 6.9 % | −0.07 [−0.19, 0.06] |
| M. Bretthauer, 2007 | 1 | 58 | 1 | 58 | 13.3 % | 0.00 [−0.05, 0.05] |
| M. Kuwatani, 2011 | 4 | 40 | 4 | 40 | 9.2 % | 0.00 [−0.13, 0.13] |
| S. Lee a, 2015 | 1 | 40 | 3 | 40 | 9.2 % | −0.05 [−0.14, 0.04] |
| S. Lee b, 2015 | 4 | 40 | 4 | 40 | 9.2 % | 0.00 [−0.13, 0.13] |
| T. Muraki, 2013 | 0 | 106 | 4 | 102 | 23.8 % | −0.04 [−0.08, 0.00] |
| **Total (95 % CI)** | | **437** | | **437** | **100.0 %** | **−0.02 [−0.05, 0.01]** |
| Total events | 16 | | 25 | | | |

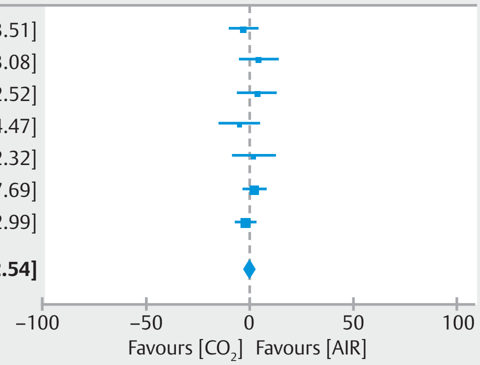
Heterogeneity: $Chi^2 = 3.13$, df = 8 ($P = 0.93$); $I^2 = 0\ \%$
Test for overall effect: Z = 1.43 ($P = 0.15$)




▶ **Fig. 11** Endoscopic retrograde cholangiopancreatography-related complications.

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 34.1 | 11.8 | 37 | 37.3 | 17.6 | 39 | 15.5 % | −3.20 [−9.91, 3.51] |
| E. Dellon, 2010 | 39.3 | 20.2 | 36 | 35.1 | 18.7 | 38 | 8.9 % | 4.20 [−4.68, 13.08] |
| K. Nakamura, 2014 | 43 | 19 | 30 | 39.6 | 17 | 30 | 8.4 % | 3.40 [−5.72, 12.52] |
| M. Bretthauer, 2007 | 43 | 27 | 58 | 48 | 25 | 58 | 7.8 % | −5.00 [−14.47, 4.47] |
| M. Kuwatani, 2011 | 45 | 24.75 | 40 | 43.03 | 22.41 | 40 | 6.5 % | 1.97 [−8.38, 12.32] |
| S. Lee a, 2015 | 27.53 | 14.01 | 40 | 25.23 | 10.32 | 40 | 24.0 % | 2.30 [−3.09, 7.69] |
| S. Lee b, 2015 | 23.07 | 10.77 | 40 | 25 | 11.68 | 40 | 28.8 % | −1.93 [−6.85, 2.99] |
| **Total (95 % CI)** | | | **281** | | | **285** | **100.0 %** | **−0.10 [−2.75, 2.54]** |

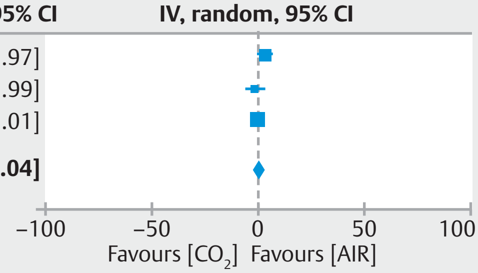
Heterogeneity: Chi² = 4.76, df = 6 (*P* = 0.57); I² = 0 %
Test for overall effect: Z = 0.08 (*P* = 0.94)




▶ **Fig. 12** Duration of endoscopic retrograde cholangiopancreatography.

| Study or subgroup | $CO_2$ Mean | $CO_2$ SD | $CO_2$ Total | AIR Mean | AIR SD | AIR Total | Weight | Mean difference IV, random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| C. Luigiano, 2011 | 46.3 | 8.3 | 37 | 43.1 | 2.3 | 39 | 30.8 % | 3.20 [0.43, 5.97] |
| E. Dellon, 2010 | 48.7 | 6.4 | 36 | 50 | 11.8 | 38 | 19.0 % | −1.30 [−5.59, 2.99] |
| K. Nakamura, 2014 | 43 | 2 | 30 | 43 | 2 | 30 | 50.2 % | 0.00 [−1.01, 1.01] |
| **Total (95 % CI)** | | | **103** | | | **107** | **100.0 %** | **0.74 [−1.56, 3.04]** |

Heterogeneity: Tau² = 2.49; Chi² = 5.08, df = 2 (*P* = 0.08); I² = 61 %
Test for overall effect: Z = 0.63 (*P* = 0.53)




▶ **Fig. 13** Maximum $CO_2$ levels.

more reliable option. This advantage was difficult to observe in our systematic review and meta-analysis because the outcome was uncommon (rate of less than 0.5 %); thus, further studies with a larger sample size are required.

Our main limitation was the non-standardization of evaluation of outcomes between the studies and non-inclusion of specific subgroups of the population such as elderly patients with pulmonary diseases. This may have limited certain analyses, but that is what we have available in the literature so far. Certainly, we need more large multicenter RCT studies with protocolized and standardized evaluations to better identify inferiority of use of ambient air supplied to ERCP.

# Conclusions

This systematic review and meta-analysis demonstrated that use of $CO_2$ as the insufflation method during ERCP was safer and better than use of ambient air because it decreased levels of pain and abdominal discomfort following the procedure.

## Competing interests

None

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