

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

 OPEN ACCESS


Authors

Marina Lordello Passos, Igor Braga Ribeiro, Diogo Turiani Hourneaux de Moura, Nádia Korkischko, Gustavo Luis Rodela Silva, Tomazo Prince Franzini, Wanderley Marques Bernardo, Eduardo Guimarães Horneaux de Moura

Institution

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC/FMUSP, Gastrointestinal Endoscopy Unit, São Paulo, Brazil

submitted 25.7.2018

accepted after revision 6.12.2018

Bibliography

DOI <https://doi.org/10.1055/a-0854-3739> |
Endoscopy International Open 2019; 07: E487–E497
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 2364-3722

Corresponding author

Igor Braga Ribeiro, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Rua Paes Leme, 215. Ed. Thera Faria Lima, Torre Água, Ap 1206, Brazil
Fax: +55 11 30697579
igorbraga1@gmail.com

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 (CO₂i) 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 CO₂ for insufflation is adequate because this procedure is complex and prolonged. Some randomized controlled trials (RCTs) have evaluated the efficacy and safety of CO₂ 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 CO₂i 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 CO₂ levels.

Results Eight studies (919 patients) were included. Significant results favoring CO₂i were less abdominal distension after 1 h (MD: -1.41 [-1.81; -1.0], 95% CI, I²=15%, *P*<0.00001) and less abdominal pain after 1 h (MD: -23.80 [-27.50; -20.10], 95%CI, I²=9%, *P*<0.00001) and after 6 h (MD: -7.00 [-8.66; -5.33]; 95% CI, I²=0%, *P*<0.00001).

Conclusion Use of CO₂i 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 meth-

od in endoscopic examinations [1]. At present, the main gases used for insufflation are ambient air and carbon dioxide (CO₂). Ambient air is the most commonly used gas for insufflation in endoscopic procedures worldwide [2] and it is the trapped un-

absorbed air that leads to prolonged abdominal pain and distension [3].

CO₂ 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 CO₂ 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 CO₂ 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 1960s, 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].

CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 (CO₂ OR carbon dioxide)” in MEDLINE, “Endoscopic Retrograde Cholangiopancreatography and ERCP AND CO₂ and carbon dioxide” in SCOPUS and LILACS, and “Endoscopic Retrograde Cholangiopancreatography AND CO₂” 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 (CO₂ and ambient air), and outcome (pain and abdominal distension after ERCP, total duration of the procedure, procedure-related complications, CO₂ 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 CO₂ 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, CO₂ 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.

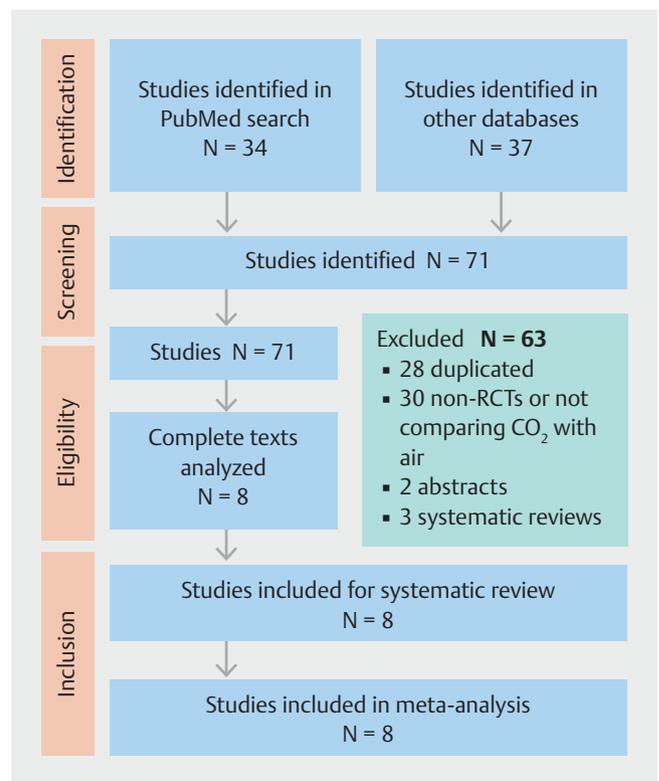
Heterogeneity was tested with the Q test for significance and with the inconsistency index (I^2), where a value >50% was considered as substantial heterogeneity between studies. A funnel plot was generated and linear regression tests were performed excluding the studies that were located outside the 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 CO₂ 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 CO₂ 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 remifentanyl 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 CO₂ levels during ERCP.

Abdominal pain

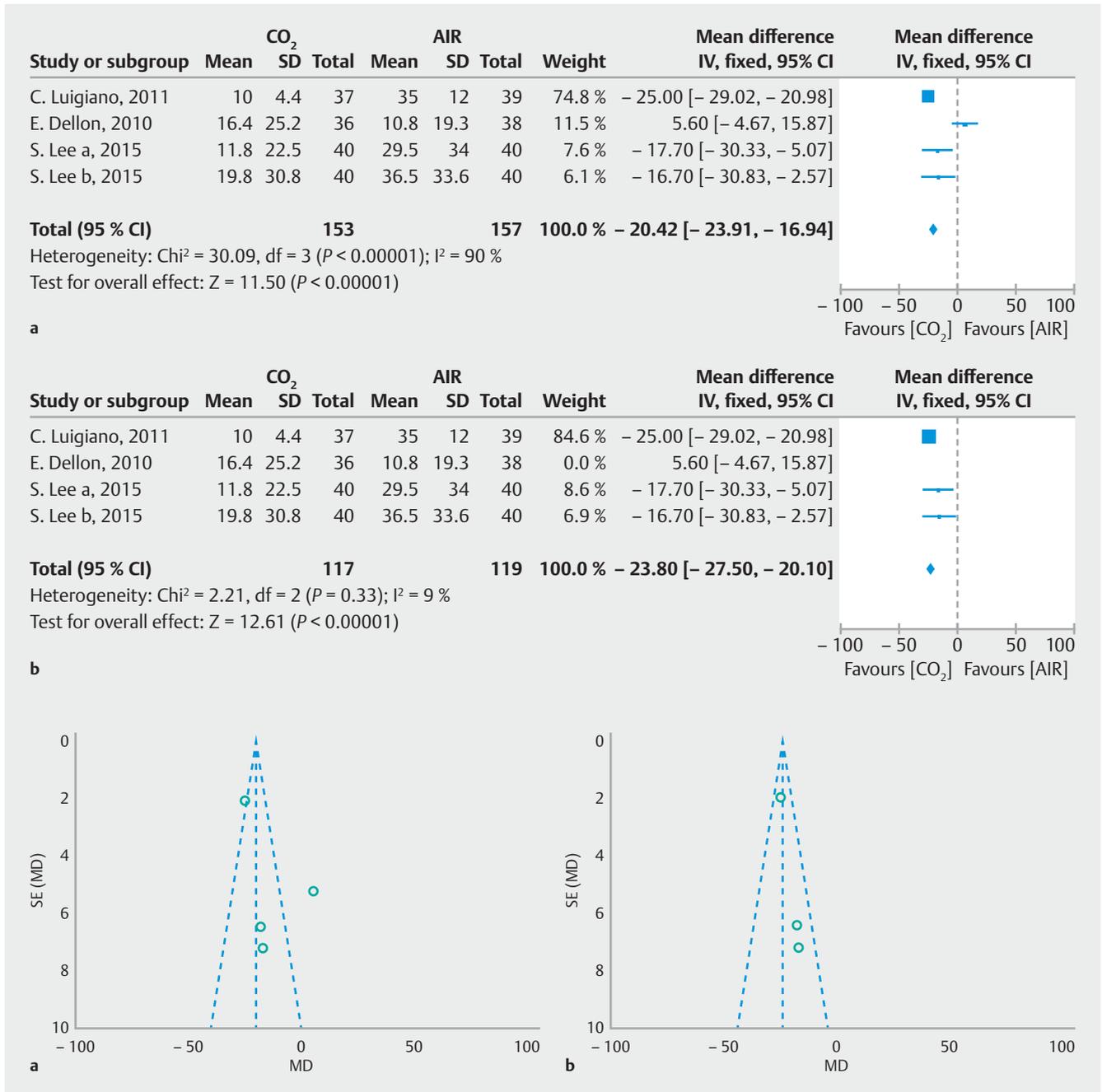
Abdominal pain after ERCP was evaluated in the eight studies included; however, not all the studies had comparable data. Only four studies were used to assess this outcome. The group that underwent insufflation with CO₂ experienced less pain than the one that received ambient air, with a significant difference at 1 hour after ERCP (MD: -23.80 [-27.50 to -20.10], 95% CI, I²=9%, *P*<0.00001) (► Fig. 2) and 6 hours after ERCP (MD: -7.00 [-8.66 to -5.33]; 95% CI, I²=0%, *P*<0.00001) (► Fig. 3). Sensitivity analysis was conducted for evaluation of pain at 1 hour after ERCP because of the high heterogeneity (I²=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 hour 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). CO₂ 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, I²=79%, *P*<0.06).

Abdominal distension

Four studies evaluated presence of abdominal distension 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 CO₂ 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, I²=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,



► **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.

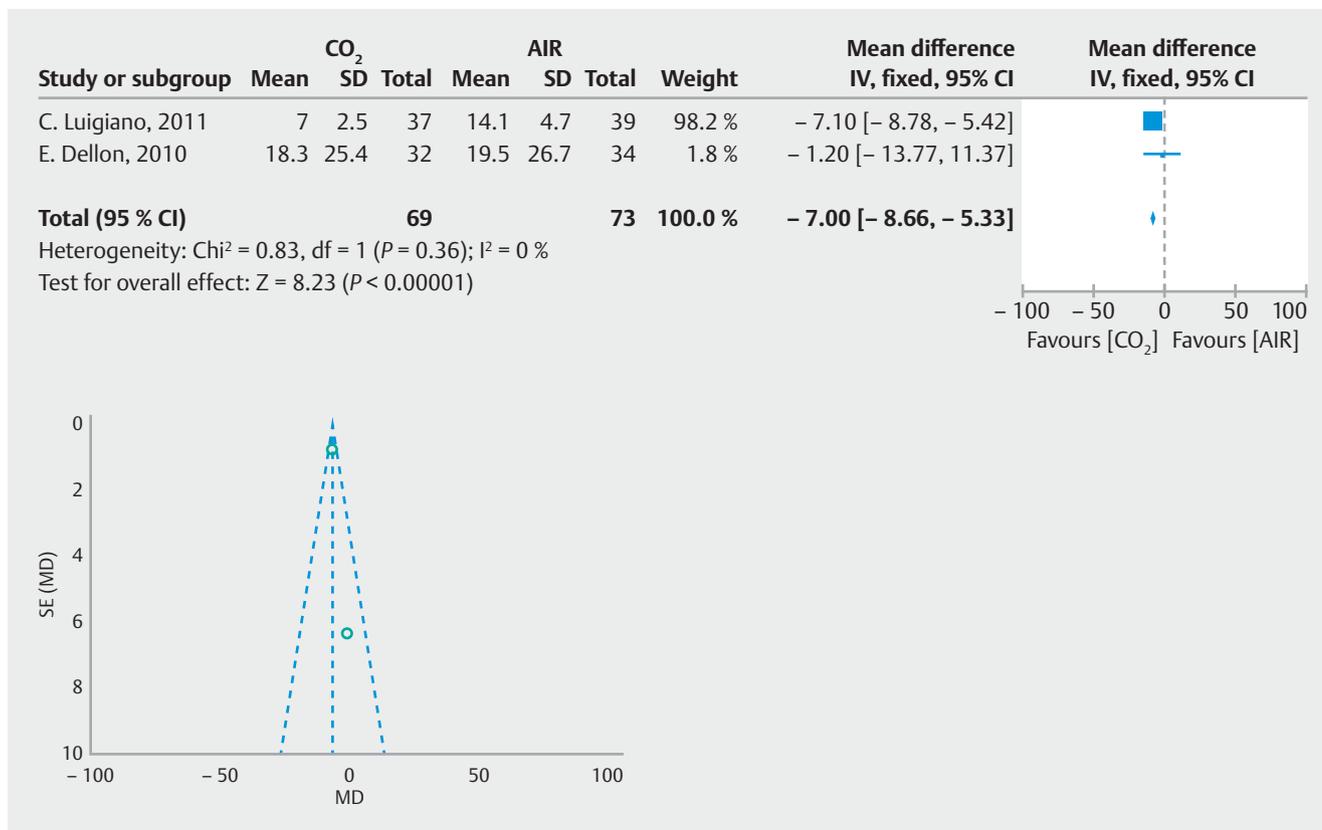
Procedure-related complications

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

CO₂ and ambient air groups (RD: -0.02 [-0.05 to 0.01], 95% CI, I² = 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, I² = 0%, P = 0.94) (► **Fig. 12**).



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

CO₂ levels

Four studies reported changes in CO₂ 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 CO₂ level during ERCP. This analysis indicated no significant differences but showed high heterogeneity between the groups ($I^2=61\%$, MD: 0.30 [-0.63 to 1.23], 95% CI, $I^2=61\%$ 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 CO₂ or ambient air.

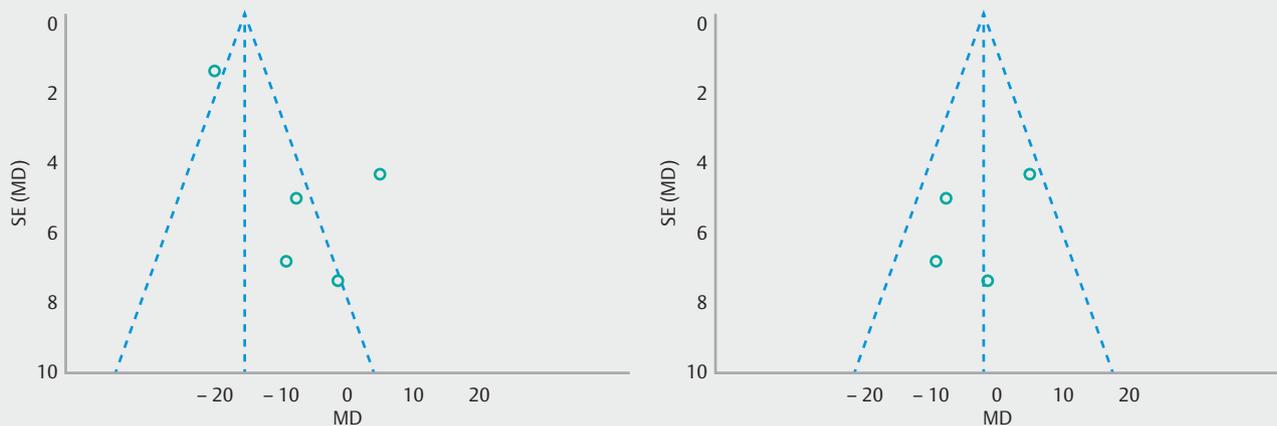
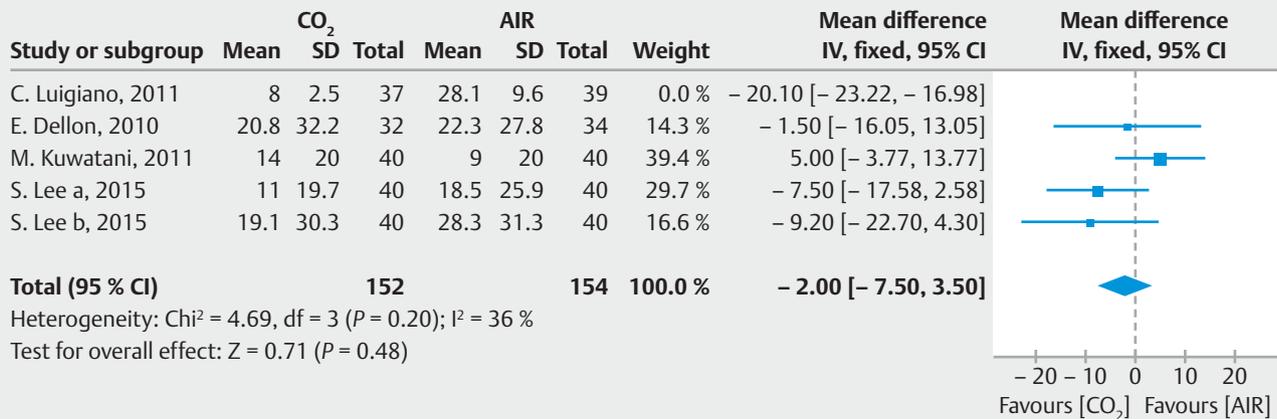
Evaluation of pain after ERCP was performed for all the included studies, showing that patients who underwent insufflation with CO₂ had less intense abdominal pain after the examination; however, this difference was only significant at 1 hour and 6 hours after the procedure. Four studies evaluated presence of abdominal distension and reported the superiority of CO₂ 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, CO₂ levels, and distension and pain at 24 hours after ERCP.

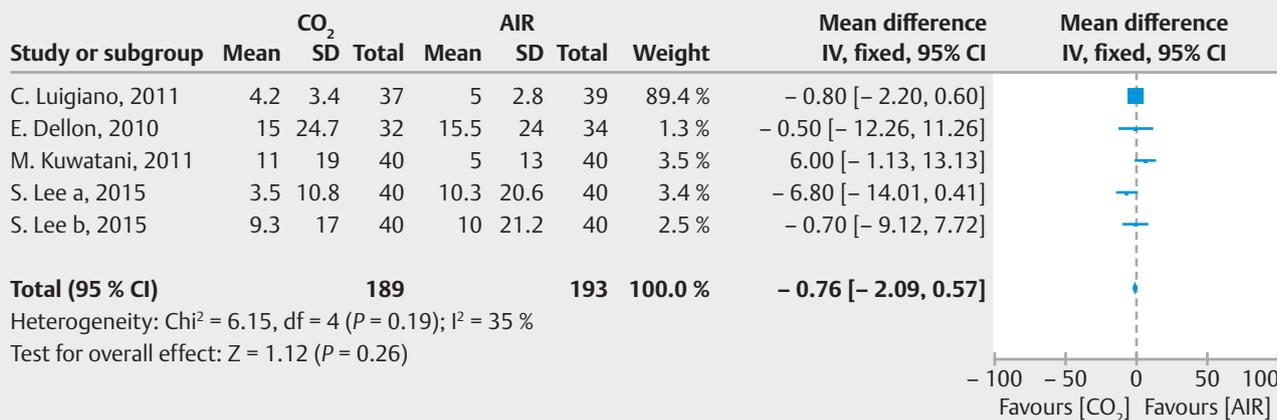
This systematic review and meta-analysis is the first to evaluate only RCTs [11, 18, 19]. Our results indicated the superiority of CO₂ over ambient air as an insufflation method because CO₂ improved patient comfort and decreased levels of pain and abdominal distension after the procedure.

Most selected studies did not include older patients and patients with pulmonary disease, which raises concerns about the safety of use of CO₂ in these groups of patients, owing to the possibility of higher levels of hemodynamic complications after insufflation with large volumes of CO₂. 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 CO₂, with a significant difference in abdominal distension, nausea, and abdominal discomfort at 2 hours after ERCP between the two groups (CO₂ vs. ambient air), and it indicated no differences in CO₂ levels during the procedure between these groups, demonstrating the safety of using CO₂ 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-



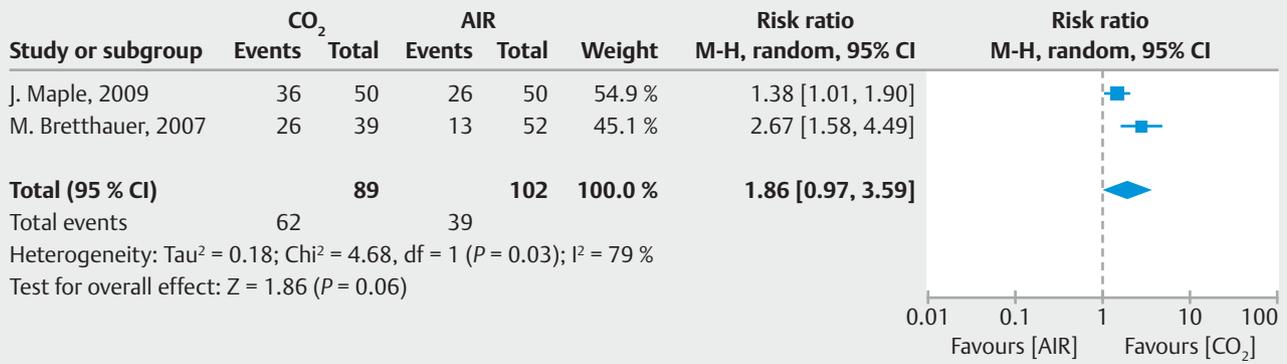
► Fig. 4 Pain levels 6 hours after insufflation.



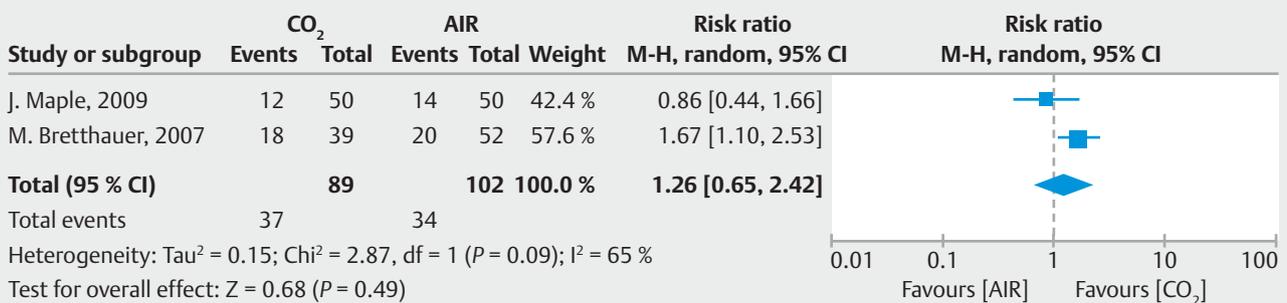
► Fig. 5 Pain levels 24 hours after insufflation.

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 CO₂ insufflation had lower levels of pain, abdominal disten-

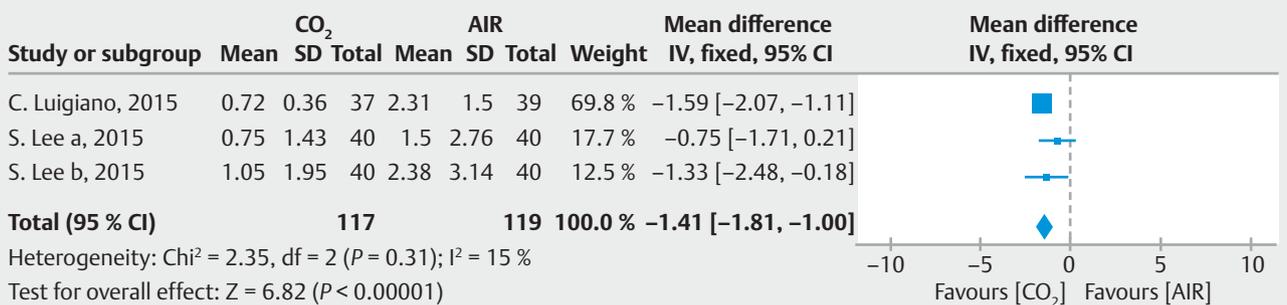
sion, and residual intra-abdominal gases as well as improved overall satisfaction with sedation.



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



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



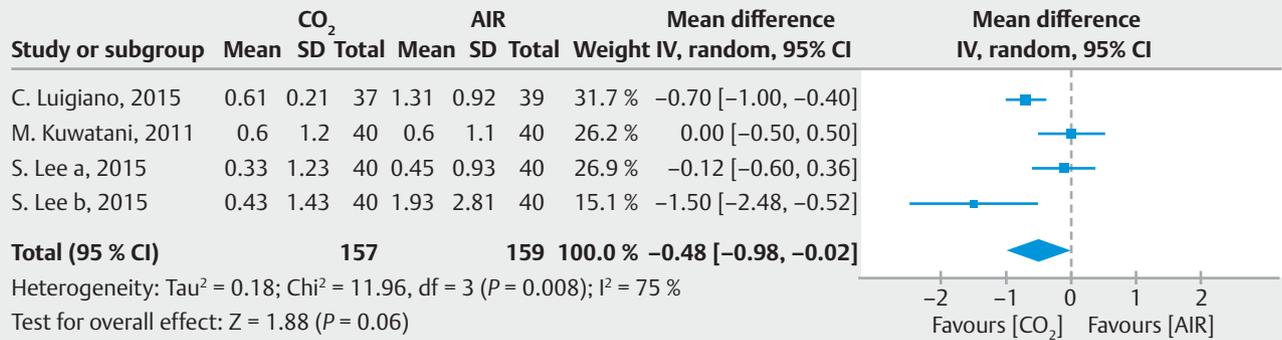
► Fig. 8 Abdominal distension 1 hour after endoscopic retrograde cholangiopancreatography.

Pain control during ERCP is of extreme importance to maintain patient comfort throughout the procedure. Less abdominal distension, which is expected with CO₂ 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.

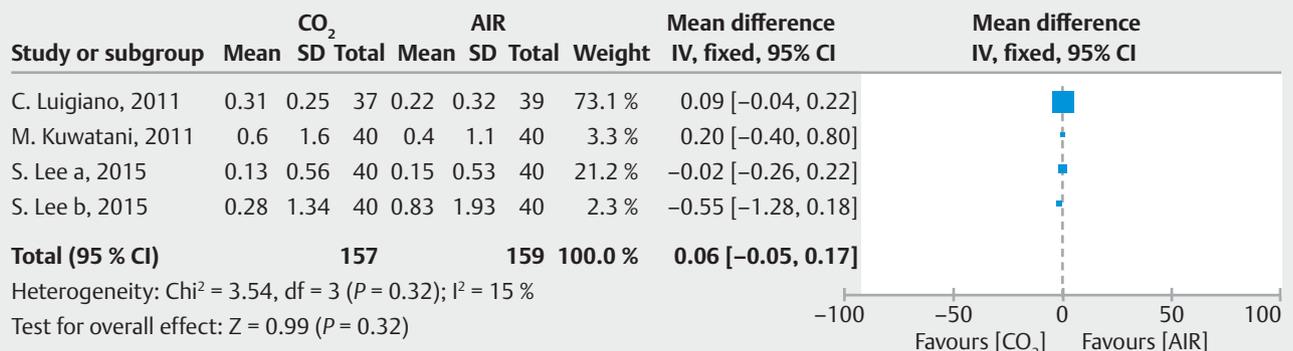
Many studies use different scales (VAS and WBS) to assess outcomes such as pain and distension. These scales, therefore, need to be standardized to enable proper comparison, inclusion of more studies in the meta-analysis, and reduction of selection bias.

Use of CO₂ for insufflation during ERCP was beneficial to patients because they presented with less discomfort during and after the procedure.

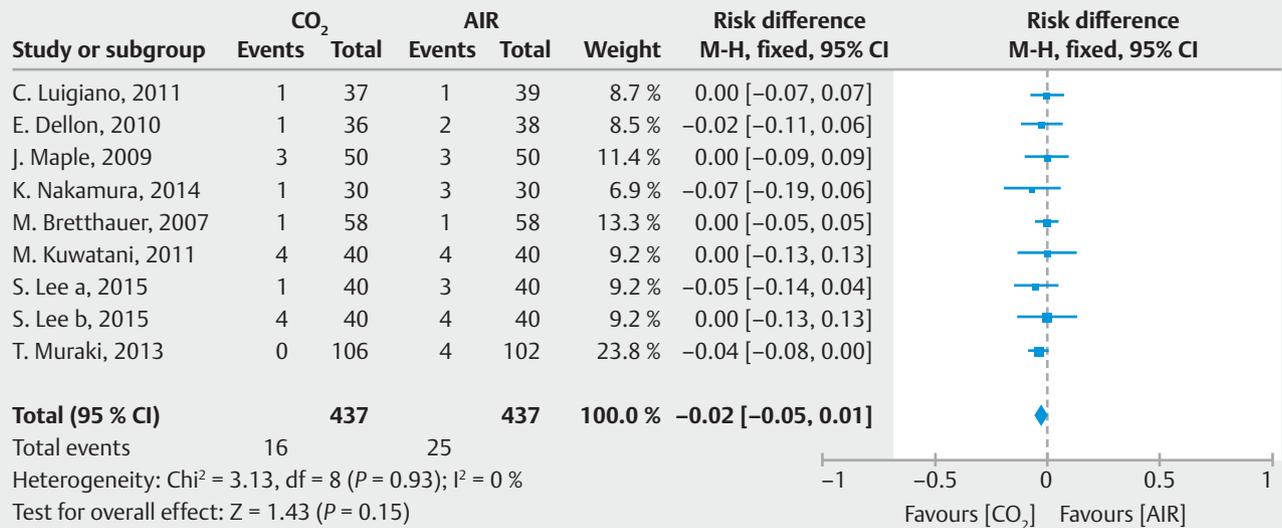
Analysis of procedure-related complications in patients who received CO₂ indicated that CO₂ had no benefits over ambient air. However, a possible advantage of CO₂ over air insufflation may be evident in case of ERCP-related perforation (i. e., following sphincter dilation or papillotomy procedures): the CO₂ absorption rate is faster than the air absorption rate, which could result in diminished abdominal distension, fewer ventilatory changes, and faster pneumoperitoneum or retroperitoneum absorption, maintaining conservative treatment as a



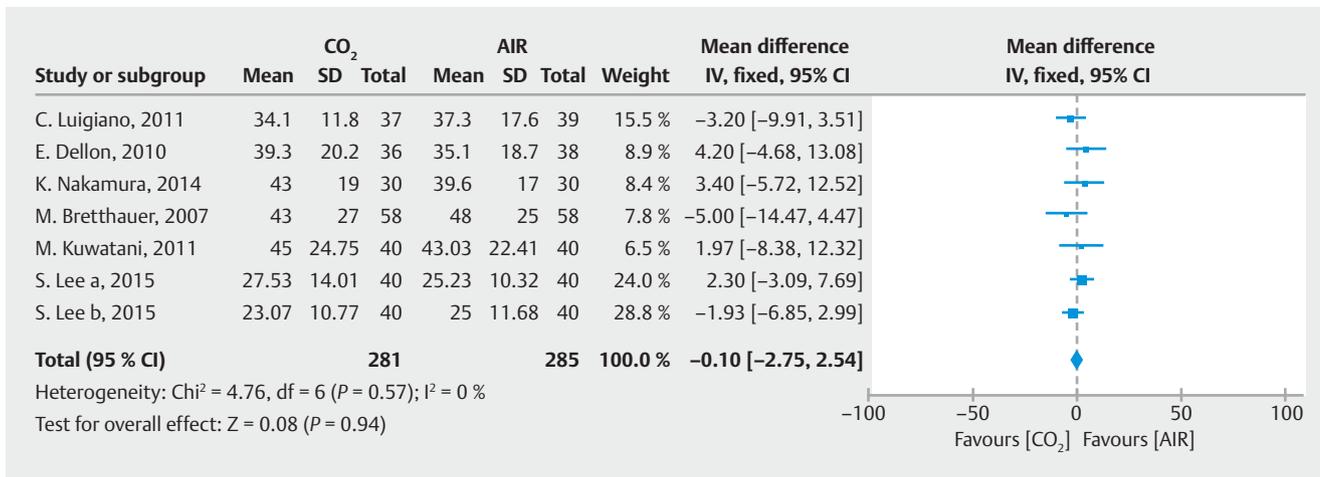
► Fig. 9 Abdominal distension 3 hours after endoscopic retrograde cholangiopancreatography.



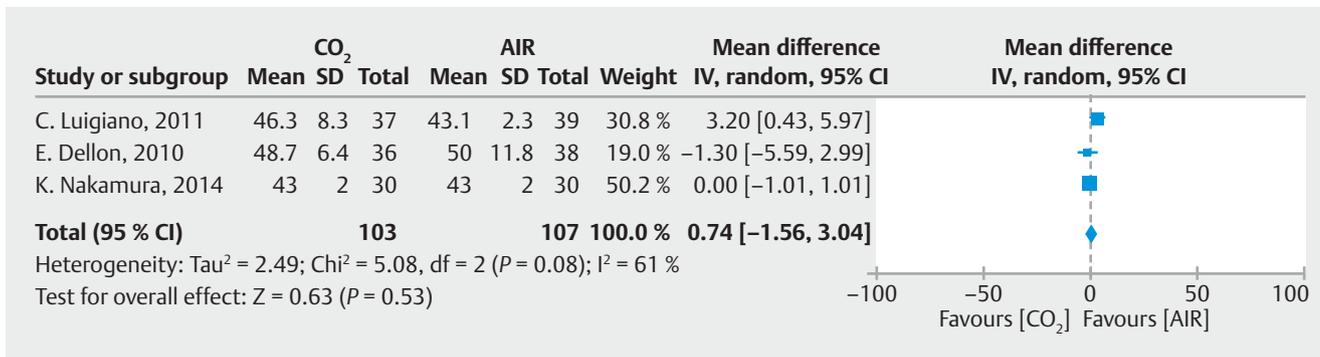
► Fig. 10 Abdominal distension 24 hours after endoscopic retrograde cholangiopancreatography.



► Fig. 11 Endoscopic retrograde cholangiopancreatography-related complications.



► Fig. 12 Duration of endoscopic retrograde cholangiopancreatography.



► Fig. 13 Maximum CO₂ 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 CO₂ 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

References

- [1] Maple JT, Banerjee S, Barth BA et al. Methods of luminal distention for colonoscopy. *Gastrointest Endosc* 2013; 77: 519–525
- [2] Isaacs P. Endoscopic retrograde cholangiopancreatography training in the United Kingdom: A critical review. *World J Gastrointest Endosc* 2011; 3: 30
- [3] Lord AC. Is the type of insufflation a key issue in gastro-intestinal endoscopy? *World J Gastroenterol* 2014; 20: 2193
- [4] Wu J, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. *Endoscopy* 2012; 44: 128–136
- [5] Janssens F, Deviere J, Eisendrath P et al. Carbon dioxide for gut distension during digestive endoscopy: Technique and practice survey. *World J Gastroenterol* 2009; 15: 1475
- [6] Coronel M, Korkischko N, Marques Bernardo W et al. Comparison between carbon dioxide and air insufflation in colonoscopy: a systematic review and meta-analysis based on randomized control trials. *J Gastroenterol Pancreatol Liver Disord* 2017: 1–11
- [7] Ribeiro IB, Bernardo WM, da Martins BC et al. Colonic stent versus emergency surgery as treatment of malignant colonic obstruction in the palliative setting: a systematic review and meta-analysis. *Endosc Int open* 2018; 6: E558–E567
- [8] Muraki T, Arakura N, Kodama R et al. Comparison of carbon dioxide and air insufflation use by non-expert endoscopists during endoscopic retrograde cholangiopancreatography. *Dig Endosc* 2013; 25: 189–196

- [9] Menes T, Spivak H. Laparoscopy Searching for the proper insufflation gas. *Surg Endosc* 2000; 14: 1050–1056
- [10] Enns R, Eloubeidi MA, Mergener K et al. ERCP-related perforations: risk factors and management. *Endoscopy* 2002; 34: 293–298
- [11] Cheng Y. Carbon dioxide insufflation for endoscopic retrograde cholangiopancreatography: A meta-analysis and systematic review. *World J Gastroenterol* 2012; 18: 5622
- [12] Kim BS, Kim I-G, Ryu BY et al. Management of endoscopic retrograde cholangiopancreatography-related perforations. *J Korean Surg Soc* 2011; 81: 195
- [13] Dellon ES, Velayudham A, Clarke BW et al. A randomized, controlled, double-blind trial of air insufflation versus carbon dioxide insufflation during ERCP. *Gastrointest Endosc* 2010; 72: 68–77
- [14] Luigiano C, Ferrara F, Pellicano R et al. Carbon dioxide insufflation versus air insufflation during endoscopic retrograde cholangiopancreatography under general anesthesia. *Minerva Med* 2011; 102: 261–269
- [15] Chen Yi Mei SL, Ashby A, George B et al. Mo1456 a prospective double blind randomised controlled trial of carbon dioxide versus air insufflation during ERCP: Is it worth the pain? *Gastrointest Endosc* 2011; 73: AB351
- [16] Arjunan S, Darishetty S, Tandan M et al. Randomized, double-blind, controlled trial showing carbon dioxide is superior to air insufflation during endoscopic retrograde cholangio pancreatography. *J Gastroenterol Hepatol* 2011; 26: 2
- [17] Huang Y, Gu HX, Guo ZH et al. A randomized controlled study on carbon dioxide insufflation during ERCP (in Chinese). *Chin J Dig Endosc* 2011; 28: 664–667
- [18] Shi H, Chen S, Swar G et al. Carbon dioxide insufflation during endoscopic retrograde cholangiopancreatography. *Pancreas* 2013; 42: 1093–1100
- [19] Wu J. Carbon dioxide insufflation versus air insufflation during endoscopic retrograde cholangiopancreatography: a meta-analysis. *J Interv Gastroenterol* 2013; 3: 37
- [20] Bretthauer M, Seip B, Aasen S et al. Carbon dioxide insufflation for more comfortable endoscopic retrograde cholangiopancreatography: a randomized, controlled, double-blind trial. *Endoscopy* 2007; 39: 58–64
- [21] Maple JT, Keswani RN, Hovis RM et al. Carbon dioxide insufflation during ERCP for reduction of postprocedure pain: a randomized, double-blind, controlled trial. *Gastrointest Endosc* 2009; 70: 278–283
- [22] Kuwatani M, Kawakami H, Hayashi T et al. Carbon dioxide insufflation during endoscopic retrograde cholangiopancreatography reduces bowel gas volume but does not affect visual analogue scale scores of suffering: a prospective, double-blind, randomized, controlled trial. *Surg Endosc* 2011; 25: 3784–3790
- [23] Lee SJ, Lee TH, Park S-H et al. Efficacy of carbon dioxide versus air insufflation according to different sedation protocols during therapeutic endoscopic retrograde cholangiopancreatography: prospective, randomized, double-blind study. *Dig Endosc* 2015; 27: 512–521
- [24] Nakamura K, Yamaguchi Y, Hasue T et al. The usefulness and safety of carbon dioxide insufflation during endoscopic retrograde cholangiopancreatography in elderly patients: a prospective, double-blind, randomized, controlled trial. *Hepatogastroenterology* 2014; 61: 2191–2195