TITLE

Carbon dioxide vs air insufflation for elective colonoscopy: A meta-analysis and systematic review of randomized controlled trials

AUTHORS (EMAILS)

Muhammed Ashraf Memon, MBBS, MA Clin Ed, DCH, FRACS, FRCSI, FRCSEd, FRCSEng, FACS[1,2,3,4,5] (mmemon@yahoo.com)

Breda Memon, RGN, LLB, PGCEd[1] (bmemon@yahoo.com)

Rossita Mohamad Yunus, PhD[6] (rossita@um.edu.my)

Shahjahan Khan, PhD[5] (Shahjahan.khan@usq.edu.au)

DEPARTMENTS AND INSTITUTIONS

[1]South East Queensland Surgery (SEQS) and Sunnybank Obesity Centre, Suite 9, McCullough Centre, 259 McCullough Street, Sunnybank, Queensland, Australia

[2]Mayne Medical School, School of Medicine, University of Queensland, Brisbane, Queensland, Australia

[3]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia

[4]Faculty of Health and Social Science, Bolton University, Bolton, Lancashire, UK

[5]School of Agricultural, Computing and Environmental Sciences, International Centre for Applied Climate Sciences and Centre for Health Sciences Research, University of Southern Queensland, Toowoomba, Queensland, Australia

[6]Institute of Mathematical Sciences, University of Malaya, Kuala Lumpur, Malaysia

REPRINTS/CORRESPONDENCE

Professor M. A. Memon, FRCS, FRACS, AFACS Sunnybank Obesity Centre, Suite 9, McCullough Centre, 259 McCullough Street, Sunnybank, QLD 4109, Australia

Tel: +61 7 3345 6667 Fax: +61 7 3344 1752 Mobile: +61 448614170

Email: mmemon@yahoo.com

SECTION OF THE JOURNAL

Meta-analysis/Systematic Reviews

KEY WORDS

Colonoscopy; Carbon dioxide; Air; Randomized controlled trials; Human

Accepted for Oral Presentation at the American College of Surgeon's Clinical Congress 2015; McCormick Place, Chicago Illinois; Forum Colon and Rectal Surgery V; 8th October, 2015

STRUCTURED ABSTRACT:

Aims and objective: The aim was to conduct a meta-analysis and systematic review of RCTs comparing two methods of colonic insufflation for elective colonoscopy i.e. carbon dioxide or air and to evaluate their efficiency, safety and side effects.

Material and Methods: Prospective RCTs comparing carbon dioxide versus air insufflation for colonic distension during colonoscopy were selected by searching PubMed, Medline, Embase, Science Citation Index, Current Contents, and the Cochrane Central Register of Controlled Trials published between January 1980 and October 2014.The outcome variables analyzed included procedural and immediate post-procedural pain (during, end or within 15 min after procedure), early post-procedural pain (between 30-120 min), intermediate post-procedural pain (360 min) and late post-procedural pain (720-1140 min), cecal/ileal intubation rate, cecal/ileal intubation time, and total colonoscopy examination time. These outcomes were unanimously decided to be important since they influence the practical approach towards patient management within and outside of hospital. Random effects model was used to calculate the effect size of both binary and continuous data. Heterogeneity amongst the outcome variables of these trials was determined by the Cochran *Q* statistic and I^2 index. The meta-analysis was prepared in accordance with PRISMA guidelines.

Results: Twenty four RCTs totaling 3996 patients (CO_2=2017, Air=1979) were analyzed. Statistical significant differences for the pooled effect size were observed for procedural and immediate post-procedural pain (WMD 0.49, 95% CI 0.32, 0.73, p= 0.0005), early post-procedural pain between 30 and 120 minutes (WMD 0.25, 95% CI 0.12, 0.49, p=<0.0001), intermediate post-procedural pain i.e. 360 minutes post completion (WMD 0.35, 95% CI 0.23, 0.52, p=<0.0001) and late post-procedural pain, between 720 and 1440 minutes (WMD 0.53, 95% CI 0.34, 0.84, p=0.0061). Comparable effects were noted for cecal/ileal intubation rate (WMD 0.86, 95% CI 0.61, 1.22, p=0.3975), cecal/ileal intubation time (WMD -0.64, 95% CI -1.38, 0.09, p=0.0860) and total examination time (WMD -0.20, 95% CI -0.96, 0.57, p=0.6133).

Conclusions: On the basis of our meta-analysis and systematic review, we conclude that carbon dioxide insufflation significantly reduces abdominal pain during and following the procedure lasting up to 24 hours. There is no difference in the cecal/ileal intubation rate and time and total examination time between the two methods. Carbon dioxide retention with CO_2 insufflation during and after the colonoscopy shows inconsequential variation compared to air insufflation and has no adverse effect on patients. Carbon dioxide instead of air should be routinely utilized for colonoscopy.

INTRODUCTION:

Air insufflation is essential to distend the colonic lumen to obtain optimum visualization during colonoscopy. However this may result in the patient suffering from pain and nausea, both during and in the recovery phase following completion of the procedure. This is because trapped unabsorbed air can remain in the colon for prolonged period of time resulting in protracted bowel distension, which can lengthen the patient discomfort in the post-procedural period due to (a) of risk of bowel ischemia and (b) increased spasm. Some patients can experience substantial abdominal pain which can be confused with colonic perforation requiring unnecessary hospitalization and radiological investigations to rule out this complication. In 1953, Becker[1] recommended the use of carbon dioxide (CO_2) insufflation to eliminate the risk of electrocoagulation colonic gas explosion. In 1985, Coblentz et al[2] first described the beneficial effects of CO_2 instead of air during double contrast barium enema study. The authors found a significant reduction in the post procedural incidence of moderate to severe pain from 30% to 11% by the use of CO_2. They also demonstrated the rapid absorption of CO_2 from the gut, as evident from the abdominal radiographs at 1 hour. A similar study by Williams[3] in 1986 confirmed the superiority of CO_2 for double contrast barium enema. Roger[4] was the first to evaluate the feasibility of CO_2 insufflation during colonoscopy. Since then a number of studies[5,6] have shown the beneficial effect of CO_2 insufflation as fewer patients complained of abdominal pain during the procedure if they are not sedated, and following the completion of colonoscopy. This may be because of faster CO_2 absorption by the intestinal mucosa, up to 150 times faster than air[3]. However there remains the concern regarding temporary increase in CO_2 concentration in the blood with adverse respiratory consequences either during or after completion of colonoscopy.

Air insufflation still remains the standard method of colonic insufflation for colonoscopy in the vast majority of centers around the world. Until recently this was partly because of a lack of dedicated CO_2 insufflators adequately tailored for colonoscopy, cost issue and fear of respiratory complications especially in elderly patients. Nevertheless in the last 32 years a number of randomized controlled trials (RCTs) comparing air and CO_2 insufflation have been published analyzing various aspects of these two approaches. The objective of this meta-analysis and systematic review was to determine the

clinical outcomes, safety, effectiveness and side effects of these two methods of insufflation for colonoscopy.

MATERIALS AND METHODS:

Literature Search Strategy, Study Selection and Data Collection

Electronic databases (PubMed, Medline, Embase, Science Citation Index, Current Contents and the Cochrane Central Register of Controlled Trials) were search for RCTs published between January 1980 and October 2014 using medical subject headings (MeSH); "colonoscopy," "insufflation," "air," "carbon dioxide/CO_2," "abdominal pain," "comparative study," "prospective studies," "randomized/randomised controlled trial," "random allocation," 'clinical trial," "complications," and "human". A further search was undertaken of the bibliographies of all included primary studies and existing reviews and meta-analyses for additional citations. Data extraction, critical appraisal and quality assessment of the identified studies were carried out by two authors (BM, MAM). The authors were not blinded to the source of the document or authorship for the purpose of data extraction. Standardized data extraction form[7] was used by authors to independently and blindly summarize all the data available in the RCTs which was then entered directly into MS Word tables. Double data entry method was used in order to avoid errors in data extraction. The data were compared and discrepancies were addressed with discussion until consensus was achieved. The analysis was prepared in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement[8]. Random effects model was used for analysis of all the outcome variables.

Eligibility Criteria

Two reviewers (BM and MAM) individually considered the abstracts of the identified articles for potential eligibility. All the eligible full text articles were reviewed in detail and checked against our inclusion and exclusion criteria. Appropriateness was determined by these independent reviewers and by discussion in case of inconsistency. The RCTs must have reported on at least one clinically relevant outcome pertaining to the procedural and post-procedural period. Outcomes assessed were those considered to exert influence over practical aspects of medical/surgical practice and patient

management. All studies reporting on outcomes of this nature were considered and final analyses were run on outcome variables where numbers were sufficient to allow statistical analysis.

Inclusion Criteria

1. **Type of Study:** Only randomized controlled trials published in full in peer-reviewed journals between January 1980 and October 2014 were included for analysis.
2. **Language:** No language restriction was applied
3. **Types of Intervention:** Two different methods of colonic insufflation for elective full colonoscopy (i.e. from anus to caecum/terminal ileum), namely CO_2 versus air for the entire procedure were being assessed.
4. **Indications:** No restrictions on indications for colonoscopy were applied.
5. **Type of participants:** Only adult (>16 years) patients were the target population for this meta-analysis.

Exclusion Criteria

1. Prospective non-randomized controlled trials, retrospective and case controlled studies.
2. Ongoing unpublished RCTs and their abstracts
3. Duplicate publications
4. RCTs of CO_2 vs air insufflation for flexible sigmoidoscopy (and not full colonoscopy)[6]
5. RCTs comparing water immersion versus CO_2 insufflation
6. RCTs comparing CO_2 vs air insufflation where CO_2 was only used during withdrawal and not for the entire procedure[9]

Types of Outcome Measures Analyzed

1. Procedural and immediate post-procedural pain (during, end of procedure or within 15 min after completion)
2. Early post-procedural pain (between 30-120 min after completion)
3. Intermediate post-procedural pain (360 min after completion)

4. Late post-procedural pain (720-1140 min after completion)
5. Cecal/ileal intubation rate
6. Cecal/ileal intubation time
7. Total colonoscopy examination time

There were three other outcome variables, which although could not be quantitatively analyzed, were qualitatively analyzed and include:

8. CO_2 measurement during colonoscopy
9. CO_2 measurement post-procedural
10. CO_2 utilization during colonoscopy

Methodological Quality

The methodological quality of the identified RCTs was assessed using Jadad Scoring system[10]. Each study was allocated a score from zero to five, zero being the lowest quality and five being the highest quality based on reporting of randomization, blinding, and withdrawals reported during the study period.

Statistical Analysis and Risk of bias across Studies

Meta-analysis were performed using odds ratios (ORs) for binary outcome and weighted mean differences (WMDs) for continuous outcome measures. Data was pooled using the Mantel-Haenszel and the inverse variance method for binary and continuous outcomes respectively. The slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed counts in the calculation of the original OR[11]. DerSimonian and Laird random effects model was used to combine the data[12]. This is because in clinical practice, differences in patient demographics, health care practitioner skills etc. render the assumptions of the fixed effects model void when evaluating therapeutic or clinical interventions. Heterogeneity among studies was calculated using the Q statistic proposed by Cochran and I^2 index introduced by Higgins and Thompson[12-16]. If the observed value of Q was greater than the associated x^2 critical value at a given significant level, in this case 0.05, we conclude the presence of statistically significance between-studies variation. In order to pool

continuous data, mean and standard deviation of each study is required. However, some of the published clinical trials did not report the mean and standard deviation, but rather reported the size of the trial, the median and interquartile range. Using these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo et al[17]. Funnel plots were produced in order to determine the presence of publication bias in the present meta-analysis. Both total sample size and precision (reciprocal of standard error) were plotted against the treatment effects (OR for binary variables and WMD for continuous variables)[12,18-20]. All estimates were obtained using a computer program written in R[21]. All plots were obtained using the metafor-package[22]. In the case of tests of hypotheses, the paper reports p-values for different statistical tests on the study variables. In general, the effect is considered to be statistically significant if the p-value is small. If one uses a 5% significance level then the effect is significant only if the associated p-value is ≤5%.

RESULTS:

Included Studies

Cross searching of electronic databases yielded a total of 65 abstracts and hand searches of reference lists provided a further 7 citations. After exclusion of non-relevant citations, 32 unique citations of potential relevance were retrieved for review. The process by which these citations were excluded is described in Figure 1. There was almost perfect agreement (κ=0.99) between two authors (BM and MAM) regarding inclusion of these RCTs. No further potentially relevant unpublished studies were identified through a citation search of previous published reviews and meta-analyses on this subject. Twenty four randomized controlled trials met the inclusion criteria[23-46]. None of the RCTs were involved in the presentation of data beyond 24 hour follow-up and therefore duplication of data was not an issue (Fig 1). As no language restriction was applied, RCTs published on this subject in any language were included in our meta-analysis.

Methodological Quality

In general, the quality of RCTs demonstrated very good methodological quality based on Jadad scoring criteria with an average score of 4 (out of five), with a range of 1 to 5 (Table 1).

Heterogeneity

The *Q* test and I^2 Index are commonly used methods in meta-analysis for detecting heterogeneity. Significant heterogeneity i.e. I^2 index of 50% or more[16] was observed for a number of outcome variables (Table 2). This reflects differences in patient population, outcome measure, definition of variables, and follow-up of the individual RCTs included in this meta-analysis.

Publication Bias

A number of the funnel plots demonstrate asymmetry (dots outside the triangle) suggesting the presence of publication bias based on a large number of studies included in this meta-analysis (Fig 2).

Clinical Outcomes

Twenty four RCTs totaling 3996 patients (CO_2=2017, Air=1979) were analyzed[23-46]. For four out of the seven analyzable outcomes, the pooled effect size favored CO_2 insufflation over air with statistically significant reduction for procedural and immediate post-procedural pain (WMD 0.49, 95% CI 0.32, 0.73, p= 0.0005) (Fig 3, Table 2), early post-procedural pain between 30 and 120 minutes (WMD 0.25, 95% CI 0.12, 0.49, p=<0.0001) (Fig 4, Table 2), intermediate post-procedural pain i.e. 360 minutes post completion (WMD 0.35, 95% CI 0.23, 0.52, p=<0.0001) (Fig 5, Table 2) and late post-procedural pain, between 720 and 1440 minutes (WMD 0.53, 95% CI 0.34, 0.84, p=0.0061) (Fig 6, Table 2). Comparable effects were noted for cecal/ileal intubation rate (WMD 0.86, 95% CI 0.61, 1.22, p=0.3975) (Fig 7, Table 2), cecal/ileal intubation time (WMD -0.64, 95% CI -1.38, 0.09, p=0.0860) (Fig 8 Table 2) and total examination time (WD -0.20, 95% CI -0.96, 0.57, p=0.6133) (Fig 9, Table 2).

Brief description of various RCTs

Salient features of various RCTs comparing CO_2 vs air insufflation are detailed in Table 3. Ten RCTs[24,26,27,30,31,34,25,36,42,44] had more than 100 patients in both arms. Appraisal of post-procedural pain was undertaken subjectively at various time points depending on the study protocol. The vast majority

of studies used visual analogue scale (VAS) for this purpose. To appraise patients' pain experience, either telephone survey was carried out or patients were provided the questionnaire prior to their discharge and were requested to fill them up promptly the next day and mailed them back to their respective centers in a prepaid envelope. Routine sedation was not used in 9 RCTs[24,26,30,32,33,38,39,44,45]. Only three trials were multicenter[28,41,45] whereas the majority of them originated from a single center. Indications for colonoscopy varied i.e. diagnostic ± screening ± surveillance. Most of the colonoscopists participating in these RCTs seem to be quite experienced although the exact details are lacking. The shortest post-procedural follow-up was 10 minutes and longest being 1440 minutes. Complications were extremely rare (Table 4). Two RCTs[26,33] were designed to measure gas volumes between the groups. Two RCTs performed plain abdominal radiology to evaluate retention of bowel gas[23,25]. One RCT[46] specifically compared the toilet usage following colonoscopy between the two groups. Ten[24,28,30,32-35,39,41,43] and nine[24,28,30,32-34,39,41,43] RCTs respectively provided gas measurement during and after colonoscopy using various methodologies (Table 5).

DISCUSSION:

Effect of CO2 vs air insufflation on abdominal pain

With a total of 3996 patients (CO_2=2017, Air=1979), this is the largest body of comparative clinical data evaluated to date for CO_2 vs air insufflation for elective colonoscopy in adult patients. Based on the pooled effect size for various time points in relation to pain, CO_2 seems to have superiority over air. Sixteen RCTs[23-25,27-31,33-36,40,42,44,46] have reported on procedural and immediate post-procedural pain i.e. during, end or within 15 minutes following procedure. The pooled effect size showed a statistically significant larger number of patients, who were pain free following CO_2 insufflation versus air (947/1484 vs 700/1470, p=0.0005) (Fig 3). This trend continued to be observed (a) in the early post-procedural period i.e. between 30 minutes to 120 minutes reported by 13 studies consisting of 2196 patients[24,25,28-31,33,34,36,40,42,43,46] (Fig 4); (b) in the immediate post-procedural period i.e. 360 minutes reported by 11 studies consisting of 1666 patients[23-25,28,30,31,33,34,39,40,43] (Fig 5); and in the late post-procedural period i.e. between 720 to 1440 minutes reported by 12 studies consisting of 1909 patients[23-25,28,30,31,33,34,36,39,43,44] (Fig 6). Therefore it is evident that trapped unabsorbed colonic air

compared to CO_2 is the cause of the patient's abdominal discomfort due to prolonged bowel distension and accompanying rise in intraluminal pressure during and in the post-procedural period with consequent increase in the severity and extent of interference with colonic mucosal blood flow[47,48]. On the other hand rapid absorption of CO_2 via the intestinal mucosa into the blood and then being eliminated via respiration leads to significantly less bowel distension, abdominal pain and interference with colonic mucosal blood flow leading to quicker patient recovery. If one looks at the utility and effectiveness of treatment, when CO_2 is used instead of air for colonoscopy, the effectiveness is no different (see technical data below), the abdominal pain is significantly less, and the economic gain to patients and the employer if they return to work quicker favors the use of CO_2 although no such data is available in any of the RCTs. Newcomer et al[49] revealed post-colonoscopic pain results in missed work days in 4% of patients which has important financial implications both for the patients and the employers. As the prospect of widespread colonoscopic screening for colorectal cancer in the asymptomatic aging populations in the first world countries is gaining momentum and the demand for colonoscopy is becoming very high[50,51], it should therefore be a clinical priority to perform this procedure with least discomfort which leads to better acceptance and higher compliance by the population assuring the success of a mass colonoscopic screening program which will ultimately save lives.

Colonoscopy technical data

We further compared the technical data for colonoscopy performed using air and CO_2. Cecal/ileal intubation rates were reported by 13 (n=2281) RCTs[24,26,27,29-31,33,34,36,41,43-45] (Fig 7, Table 1). The pooled data showed comparable outcomes for CO_2 and air (p=0.3975). The cecal/ileal intubation time, reported by 16 RCTs[24,26,27,29,31-36,38,39,41,43,44,46], however the analyzable data was available for 14 RCTs (n=2331) and total examination time i.e. from the time of insertion of the scope until its withdrawal, was reported by 19 RCTs[25-27,30-36,38-46], however analyzable data was available for 17 RCTs (n=2905). Both of these variables showed no difference between the two groups (p=0.0860 and p=0.6133 respectively) (Fig 8 and 9, Table 2). Procedure related adverse effects or complications were reported by 11 RCTs[24,29,31-33,37,39,40,43,44,46]. They were extremely rare and no differences were noted between the

two groups (Table 4). It is entirely possible that the lack of any difference in technical data between the two groups may be related to experienced colonoscopists performing colonoscopy, however the exact description of "experience colonoscopists" is not provided by all of these trials and in others, the experience of colonoscopist was stated in years (e.g. 10 years) or number of scopes (e.g. 3000) performed by the them.

Safety and Effectiveness of CO_2 vs Air

Carbon dioxide is an end product of cellular respiration in organisms that obtain energy by breaking down sugars, fats and amino acids with oxygen as part of their metabolism. In humans, this CO_2 is carried through the venous system and is breathed out through the lungs. Therefore, the CO_2 content in the body is high in the venous system, and decreases in the respiratory system, resulting in lower concentrations along any arterial system. In concentrations up to 1% (10,000 ppm), it will make some people feel drowsy. Concentrations of 7% to 10% may cause suffocation, even in the presence of sufficient oxygen, manifesting as dizziness, headache, visual and hearing dysfunction, and unconsciousness within a few minutes to an hour. The physiological effects of acute CO_2 exposure are grouped together under the term hypercapnia, a subset of asphyxiation. Hypercapnia is generally caused by hypoventilation, lung disease (COPD), or diminished consciousness (sedated patients). It may also be caused by exposure to environments containing abnormally high concentrations of CO_2 or by rebreathing exhaled CO_2. Hypercapnia is generally defined as a blood gas CO_2 level over 45 mmHg. Since CO_2 is in equilibrium with carbonic acid in the blood, hypercapnia can drive serum pH down, resulting in a respiratory acidosis. The question whether exposure to CO_2 during colonoscopy produces undesirable effects such as high concentration of CO_2 in deeply sedated patients and especially in a group of patients suffering from pulmonary diseases? A number of previous studies have convincingly shown this not to be the case[24,28,52]. The end tidal CO_2 ($ETCO_2$) in unsedated patients will diminish because of hyperventilation[24], whereas in sedated or anaesthetized patients the $ETCO_2$ will increase slightly[28,52]. All these changes are transient and physiological and do not lead to any clinical consequences. We qualitatively analyzed the data from 10 RCTs (n=1471)[24,28,30,32-35,39,41,43] to see if the patients who were receiving CO_2 compared to air had higher CO_2 concentration measured

by various means (End tidal CO_2, processed transcutaneous CO_2, transcutaneous pCO_2 or using capnography) during and at the end of the procedure. Five RCTs[28,34,35,41,43] routinely sedated their patients. Even then, no significant rise in CO_2 was noted for the group insufflated with CO_2. The measured values for CO_2 for most patients remained within normal limits both during and at the end of colonoscopy (Table 5). Bretthauer et al[28] showed that in sedated patients in both the CO_2 and air groups, there was a slight increase in $ETCO_2$ values. The authors felt that it was sedation causing hypoventilation, which was the primary cause of CO_2 retention, rather than CO_2 insufflation. Other authors[33] feel that besides reduced rate of respiration during sedation, the positioning of the patients during colonoscopy i.e. left lateral position effects the movement of diaphragm, ribs and intercostal muscles, may lead to CO_2 retention even if air is insufflated for colonoscopy. Geyer et al[34] further showed that in sedated patients even who have pulmonary disorders including COPD, CO_2 insufflation did not produce any detrimental effects and they felt that "this makes it possible to transfer their data to a screening population without any restrictions". Similarly Singh et al[41] came to the same conclusion in their RCT as COPD patients were not excluded from their study and none of their patients suffered respiratory adverse effects even after receiving CO_2 for colonoscopy. They felt that the major limitation of their study was measurement of CO_2 via capnography which may not be very accurate. Our analysis therefore confirms the findings of previous RCTs that CO_2 does not produce detrimental side effects even in sedated patients during colonoscopy even when CO_2 is continuously pumped to inflate the colon (Table 5, Fig 10 & 11). However one can argue that CO_2 concentration measurement will be dependent on the volume insufflated during colonoscopy. Only two RCTs[26,33] have provided data on the volume of CO_2 used during the procedure. Bretthauer et al[26] measured the gas volumes in 218 out of 249 patients. The authors found comparable volumes of CO_2 and air were insufflated per minutes. However statistically significant differences in the volume of gas insufflation were noticed amongst some of the less experienced endoscopists, who utilized far more CO_2 during colonoscopy. However they did not correlate the volume findings with CO_2 concentration. Yamano et al[33] on the other hand analyzed their 120 patients and compared their finding to Bretthauer et al's study[26]. They observed that the mean gas volume and gas flow rate and the maximum gas

volume used in CO_2 cohort was much higher compared to Bretthauer et al's study[26]. However this did not lead to any abnormal increase in pCO_2 suggesting the safety of CO_2.

As far as the effectiveness of CO_2 insufflation is compared with air insufflation, cecal/ileal intubation rates, cecal/ileal intubation time, and total examination time i.e. from the time of insertion of the scope until its withdrawal were comparable with no differences in adverse effects. We further investigated the role of polyp/adenoma detection rates between the two insufflation types but there was insufficient data to comment on this issue. There are only three RCTs[27,31,36] which have provided us some details regarding polyps/adenoma detection rates which seems to be similar between the two insufflation methods although the details are lacking. We therefore strongly feel that as all the other colonoscopy quality indicators for both insufflation processes were similar, the issue of polyps/adenoma detection rate should remain similar for CO_2 and air insufflation. The polyp/adenoma detection rate depends on other factors such as operator experience, quality of bowel preparation, type of colonoscope, withdrawal time and previous history of colorectal polyps/cancer to name but a few[53].

Cost-effectiveness and Cost-benefit analysis of CO_2 vs Air

Cost-effectiveness is an important factor for patients and medical insurers. Cost effective analysis measure and compare the significant gains and losses associated with different methods of patients' management. This aspect of colonoscopy utilizing air versus CO_2 could not be analyzed due to lack of data across the board. Yamano et al[33] is the only study which has analyzed the cost difference between the two types of insufflation. According to these authors the total cost of endoscopy with CO_2 increases to 2.5% (about 400 yen) per endoscopy.

To the best of our knowledge the vast majority of day care and endoscopy facilities around the world are using air as the primary source for insufflation for endoscopy procedures due to (a) unawareness by the endoscopists that CO_2 can be substituted for air; (b) fear of CO_2 safety due to lack of knowledge; (c) unavailability of adequately tailored CO_2 insufflalators for endoscopy units especially for the older endoscopy stakes; and (d) ignorance regarding cost effectiveness and cost-benefit issues.

As none of the RCTs address the cost-effectiveness and cost-benefit issues (direct and indirect costs), it is imperative that future RCTs measure these two important aspects of clinical practice to determine the utility of treatment (i.e. benefit of treatment multiply by the probability of such benefit minus the cost).

LIMITATIONS:

There are a number of limitations both statistical and clinical in this paper. Firstly, heterogeneity was detected within several outcomes variables. (Table 2) Although some degree of heterogeneity is inevitable in a medical meta-analysis due to the realities of clinical practice, an I^2 index of 50% or more can be interpreted as describing significant heterogeneity which may undermine the quality and legitimacy of the results obtained (Table 2)[54,55]. Secondly, publication bias was detected on the funnel plots analysis for a number of outcomes[56] (Fig 2). Thirdly the inclusion of low quality RCTs based on Jadad score may impact the overall results. Fourthly, the correlation between the experienced vs novice colonoscopists and abdominal pain are not recorded or analyzed. Fifth, although the vast majority of RCTs have used visual analogue scale (VAS), this is a subjective measurement of abdominal pain during and in the post-procedural period and therefore caution is required when reporting such data. As VAS is highly subjective, it is valuable when looking at change within individuals, and is of less value for comparing across a group of individuals at one time point. Sixth, as this analysis has combined the pain score data (at various time points) in groups of individuals with no sedation, minimum sedation and conscious sedation, this will have some impact on overall results. Lastly most of the RCTs except for two have failed to analyze any correlation between the CO_2 or air volume and pain score, and therefore the impact of gas volume versus pain remains speculative.

CONCLUSIONS:

On the basis of this meta-analysis and systematic review, we conclude that CO_2 insufflation significantly reduces abdominal pain during and following the procedure lasting up to 24 hours. There is no difference in the cecal/ileal intubation rate and time and total examination time between the two methods. Significant CO_2 retention during and after the colonoscopy even in sedated patients with

pulmonary disease was no different with CO_2 insufflation compared to air insufflation and certainly has shown no detrimental effects. Therefore CO_2 instead of air should be routinely utilized for colonoscopy. In the future, however a number of other important issues need to be addressed which include the cost-effectiveness, cost-benefit analysis and utility of these two methods of insufflation for elective colonoscopy, correlation of experience of colonoscopist versus abdominal pain, the relationship between volume of gas and abdominal pain and the role of sedation vs non-sedation. This data will have a major impact over practical aspects of medical/surgical practice and patience management and policy decisions within institutions and health care insurers.

AUTHORS' CONTRIBUTIONS:

1. MAM and BM were responsible for the concept and design of this meta-analysis. Furthermore they take full responsibility for the integrity of the work as a whole, from the inception to published article.
2. MAM and BM were responsible for the acquisition and interpretation of the data.
3. RMY and SK were responsible for analyzing and interpretation of the data in depth from the statistical point of view.
4. All authors were involved in drafting the manuscript and revising it critically for important intellectual content and have given final approval of the version to be published. Furthermore all authors have participated sufficiently in the work to take public responsibility for its content.

DECLERATION OF CONFLICTS OF INTEREST:

MAM declares no conflict of interest

BM declares no conflict of interest

RMY declares no conflict of interest

SK declares no conflict of interest

REFERENCES:

1. Becker GL. The prevention or gas explosions in the large bowel during electrosurgery. Surg Gynecol Obstet. 1953; 97: 463-7.

2. Coblentz CL, Frost RA, Molinaro V, Stevenson GW. Pain after barium enema: effect of CO_2 and air on double-contrast study. Radiology 1985; 157: 35-6.

3. Williams CB. Who's for CO_2? Gastrointestinal Endosc 1986; 32: 365-7.

4. Rogers BH. CO2 during colonoscopy for safety and comfort. Surg Endosc 1985; 31: 108-9.

5. Hussein AM, Bartram CI, Williams CB. Carbon dioxide insufflation for more comfortable colonoscopy. Gastrointestinal Endosc 1984; 30: 68-70.

6. Bretthauer M, Hoff G, Thiis-Evensen E, Grotmol T, Thorp Holmsen S, Moritz V, Skovlund E. Carbon dioxide insufflation reduces discomfort due to flexible sigmoidoscopy in colorectal cancer screening. Scand J Gastroenterol 2002; 37: 1103-7.

7. Moher D, Cook D J, Eastwood S. Improving the quality of reports of meta- analyses of randomized controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896-1900.

8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA and PRISMA-P Group. Preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Review 2015; 4:1.

9. Chen PG, Li CH, Huang TY, Shih YL, Chu HC, Chang WK, Hsieh TY. Carbon dioxide insufflation does not reduce pain scores during colonoscope insertion in unsdeated patients: a randomized, control trial. Gastrointestinal Endosc 2013; 77: 79-89.

10. Jadad AR, Moore RA, Carroll D., Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.

11. Agresti A. An Introduction to Categorical Data Analysis. Wiley & Sons; New York 1996.

12. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for Meta-analysis in Medical Research. London: John Wiley; 2000.

13. Cochran WG. The combination of estimates from different experiments. Biometric 1954; 10: 101-29.

14. Hedges LV, Olkin I. Statistical Methods for Meta Analysis: Academic Press; Orlando, Florida 1985.

15. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539-1558.

16. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta analysis: Q Statistic or I^2 Index? Am Psychol Assoc 2006; 11: 193-206.

17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range and size of a sample. BMC Med Res Methodol 2005; 5: 13.

18. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997; 315: 629-34.

19. Tang JL, Liu JLY. Misleading funnel plot detection of bias in meta-analysis. J Clin Epidermiol 2000; 53: 477-484.

20. Span J, Carière E, Croockewitt S, Smits P. Publication bias, effects on the assessment of rosiglitasone. Br J Clin Pharmacol 2006; 62: 732.

21. R: A Language and Environment for Statistical Computing [Computer Program]. Version 1. Vienna: R Foundation for Statistical Computing; 2008.

22. Viechtbauer, W. Conducting Meta-Analyses in R with the metaphor Package, Journal of Statistical Software, 2010, http://www.metafor-project.org/doku.php/metafor

23. Stevenson GW, Wilson JA, Wilkinson J, Norman G, Goodacre RL. Pain following colonoscopy: elimination with carbon dioxide. Gastrointest Endosc. 1992; 38: 564-7.

24. Bretthauer M, Thiis-Evensen E, Huppertz-Hauss G, Gisselsson L, Grotmol T, Skovlund E, Hoff G. NORCCAP (Norwegian colorectal cancer prevention): a randomised trial to assess the safety and efficacy of carbon dioxide versus air insufflation in colonoscopy. Gut. 2002; 50: 604-7.

25. Sumanac K, Zealley I, Fox BM, Rawlinson J, Salena B, Marshall JK, Stevenson GW, Hunt RH. Minimizing postcolonoscopy abdominal pain by using CO_2 insufflation: a prospective, randomized, double blind, controlled trial evaluating a new commercially available CO_2 delivery system. Gastrointest Endosc. 2002; 56: 190-4.

26. Bretthauer M, Hoff GS, Thiis-Evensen E, Huppertz-Hauss G, Skovlund E. Air and carbon dioxide volumes insufflated during colonoscopy. Gastrointest Enodsc 2003; 58: 203-6.

27. Church J, Delaney C. Randomized, controlled trial of carbon dioxide insufflation during colonoscopy. Dis Colon Rectum. 2003; 46: 322-6.

28. Bretthauer M, Lynge AB, Thiis-Evensen E, Hoff G, Fausa O, Aabakken L. Carbon dioxide insufflation in colonoscopy: safe and effective in sedated patients. Endoscopy. 2005; 37: 706-9.

29. Wong JC, Yau KK, Cheung HY, Wong DC, Chung CC, Li MK. Towards painless colonoscopy: a randomized controlled trial on carbon dioxide-insufflating colonoscopy. ANZ J Surg. 2008; 78: 871-4.

30. Liu X, Liu D, Li J, Ou D, Zhou Z. Safety and efficacy of carbon dioxide insufflation during colonoscopy. J Cent Sout Univ (Med Sci) 2009; 34: 825-9.

31. Riss S, Akan B, Mikola B, Rieder E, Karner-Hanusch J, Dirlea D, Mittlböck M, Weiser FA. CO2 insufflation during colonoscopy decreases post-interventional pain in deeply sedated patients: a randomized controlled trial. Wien Klin Wochenschr. 2009; 121: 464-8.

32. Uraoka T, Kato J, Kuriyama M, Hori K, Ishikawa S, Harada K, Takemoto K, Hiraoka S, Fujita H, Horii J, Saito Y, Yamamoto K. CO2 insufflation for potentially difficult colonoscopies: efficacy when used by less experienced colonoscopists. World J Gastroenterol 2009; 15: 5186-92.

33. Yamano HO, Yoshikawa K, Kimura T, Yamamoto E, Harada E, Kudou T, Katou R, Hayashi Y, Satou K. Carbon dioxide insufflation for colonoscopy: evaluation of gas volume, abdominal pain, examination time and transcutaneous partial CO2 pressure. J Gastroenterol. 2010; 45:1235-40.

34. Geyer M, Guller U, Beglinger C. Carbon dioxide insufflation in routine colonoscopy is safe and more comfortable: results of a randomized controlled double-blinded trial. Diagn Ther Endosc. 2011; 2011: 378906.

35. Díez-Redondo P, Gil-Simón P, Alcaide-Suárez N, Atienza-Sánchez R, Barrio-Andrés J, De-la-Serna-Higuera C, Pérez-Miranda M. Comparison between insufflation with air or carbon dioxide during the colonoscopy in sedated patients with propofol. Rev Esp Enferm Dig. 2012;104: 411-7.

36. Falt P, Liberda M, Smajstrla V, Kliment M, Bártková A, Tvrdík J, Fojtík P, Urban O. Combination of water immersion and carbon dioxide insufflation for minimal sedation colonoscopy: a prospective, randomized, single-center trial. Eur J Gastroenterol Hepatol. 2012; 24: 971-7.

37. Fernández-Calderón M, Muñoz-Navas MÁ, Carrascosa-Gil J, Betés-Ibáñez MT, de-la-Riva S, Prieto-de-Frías C, Herráiz-Bayod MT, Carretero-Ribón C. Carbon dioxide vs. air insufflation in ileo-colonoscopy and in gastroscopy plus ileo-colonoscopy: a comparative study. Rev Esp Enferm Dig. 2012;104: 237-41.

38. Hsu WH, Sun MS, Lo HW, Tsai CY, Tsai YJ. Carbon dioxide insufflation during withdrawal of the colonoscope improved postprocedure discomfort: a prospective, randomized, controlled trial. Kaohsiung J Med Sci. 2012; 28: 265-9.

39. Imai A, Kato M, Ono S, Shimizu Y, Takeda H, Asaka M. Efficacy of carbon dioxide-insufflating colonoscopy in patients with irritable bowel syndrome: a randomized double-blind study. J Gastroenterol Hepatol. 2012; 27: 1623-8.

40. Mayr M, Miller A, Gauger U, Rösch T. CO_2 versus air insufflation for private practice routine colonoscopy: results of a randomized double blind trial. 25. Z Gastroenterol. 2012; 50: 445-8.

41. Singh R, Neo EN, Nordeen N, Shanmuganathan G, Ashby A, Drummond S, Nind G, Murphy E, Luck A, Tucker G, Tam W. Carbon dioxide insufflation during colonoscopy in deeply sedated patients. World J Gastroenterol. 2012; 18: 3250-3.

42. Cleland A, Carryer J, La Grow S. Carbon dioxide insufflation during colonoscopy: a randomised controlled trial. N Z Med J. 2013 13; 126: 87-94

43. Seo EH, Kim TO, Park MJ, Kim HJ, Shin BC, Woo JG, Heo NY, Park J, Park SH, Yang SY, Moon YS. The efficacy and safety of carbon dioxide insufflation during colonoscopy with consecutive esophagogastroduodenoscopy in moderately sedated outpatients: a randomized, double-blind, controlled trial. 18. J Clin Gastroenterol. 2013; 47: e45-9.

44. Amato A, Radaelli F, Paggi S, Baccarin A, Spinzi G, Terruzzi V. Carbon dioxide insufflation or warm-water infusion versus standard air insufflation for unsedated colonoscopy: a randomized controlled trial. Dis Colon Rectum. 2013; 56: 511-8.

45. Iida T, Okamura S, Kakizaki S, Sagawa T, Zhang Y, Kobayashi R, Masuo T, Mori M. Carbon dioxide insufflation reduces the discomfort due to colonoscopy as objectively analyzed by salivary stress markers. Acta Gastroenterol Belg. 2013; 76: 219-24.

46. Hsu WF, Hu WH, Chen YN, Lai HH, Chen MK, Chang LC, Tu CH, Chou CK, Wang HP, Wu MS, Chiu HM. Carbon dioxide insufflation can significantly reduce toilet use after colonoscopy: a double-blind randomized controlled trial. Endoscopy. 2014; 46: 190-5.

47. Brandt LJ, Boley sJ, Sammartano R. Carbon dioxide and room air insufflation of the colon: effects on colonic blood flow and intraluminal pressure in dog. Gastrointestin Endosc 1986; 32: 324-9.

48. Silva A, Ho HS, Mathiesen KA, Wolfe BM. Endoscopy during laparoscopy. Recduced post-procedural bowel distension with intraluminal CO2 insufflation. Surg Endosc 1999; 13: 662-7.

49. Newcomer MK, Shaw MJ, William DM, Jowell PS. Unplanned work absence following outpatient colonoscopy. J Clinical Gastroenterology 1999; 29: 76-8.

50. Stock C, Brenner H. Utilization of lower gastrointestinal endoscopy and fecal occult blood test in 11 European countries: evidence from the Survey of Health, Aging and Retirement in Europe (SHARE). Endoscopy 2010; 42: 546-556.

51. Centres for Disease Control and Prevention. Vital signs: Colorectal Cancer Screening, Incidence, and Mortality – United States, 2002-2010. MMWR Morb Mortal Wkly Rep; 60-884-890.

52. Nakajima K, Lee SW, Sonda T, Milsom JW. Intraoperative carbon dioxide colonoscopy: a safe insufflation alternative for locating colonic lesions during laparoscopic surgery; Surg Endosc 2005; 19: 321-32.

53. Adler A, Wegscheider K, Lieberman D, Aminalai A, Aschenbeck J, Drossel R, Mayr M, Mroß M, Scheel M, Schröder A, Gerber K, Stange G, Roll S, Gauger U, Wiedenmann B, Altenhofen L, Rosch T. Gut. 2013; 62:236-41. Factors determining the quality of screening colonoscopy: a prospective study on adenoma detection rates, from 12,134 examinations (Berlin colonoscopy project 3, BECOP-3).

54. Ng TT, McGory ML, Ko CY, et al. Meta-analysis in surgery: methods and limitations. *Arch Surg* 2006; 141: 1125-30.

55. Ioannidis J P, Patsopoulos N A, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007;335:914-916.

56. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455-463.

Figure 1: PRISMA flow diagram

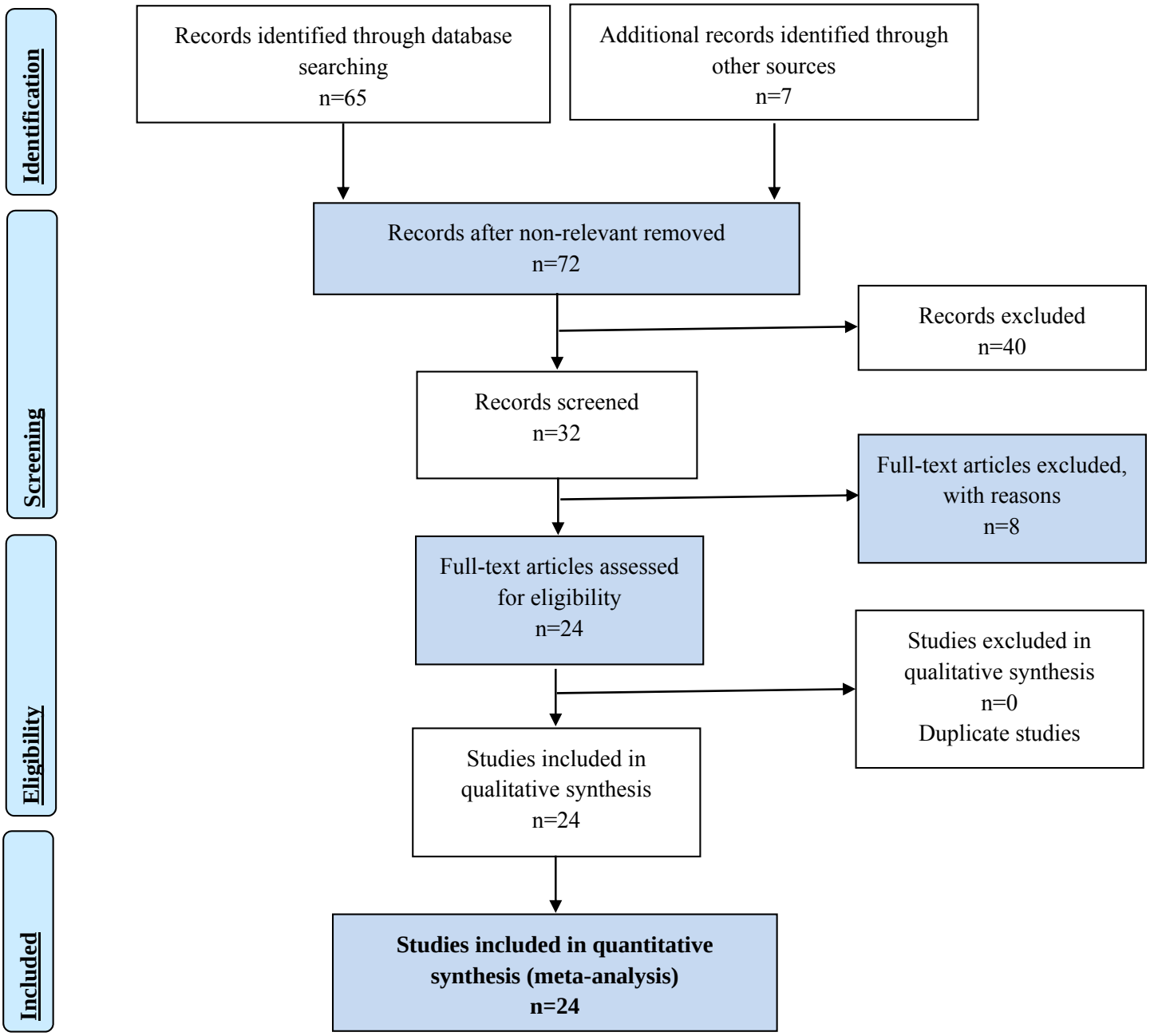

Figure 2: Funnel plots

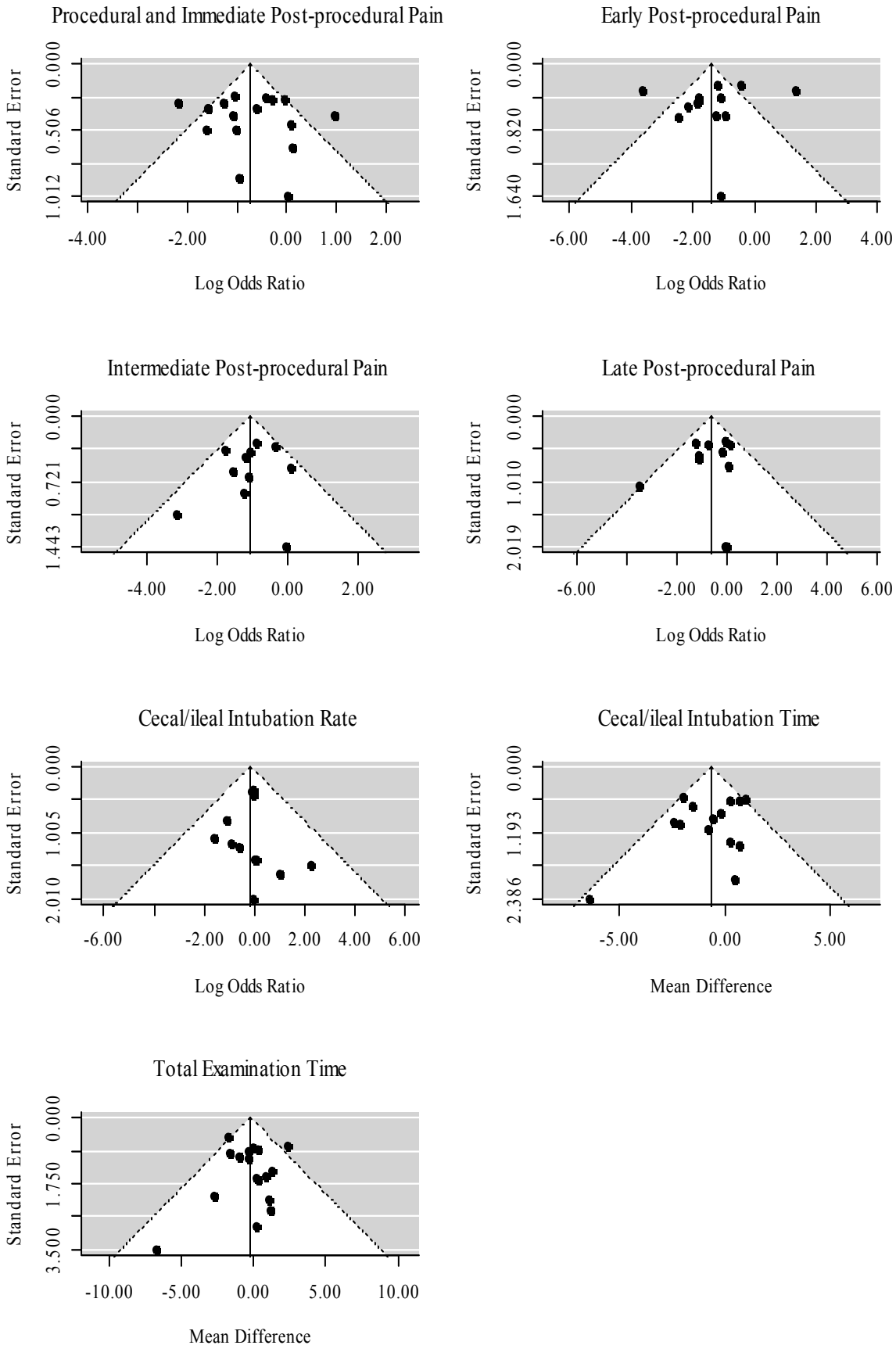

Figure 3: Procedural and immediate post-procedural pain (during, end or within 15min after procedure)

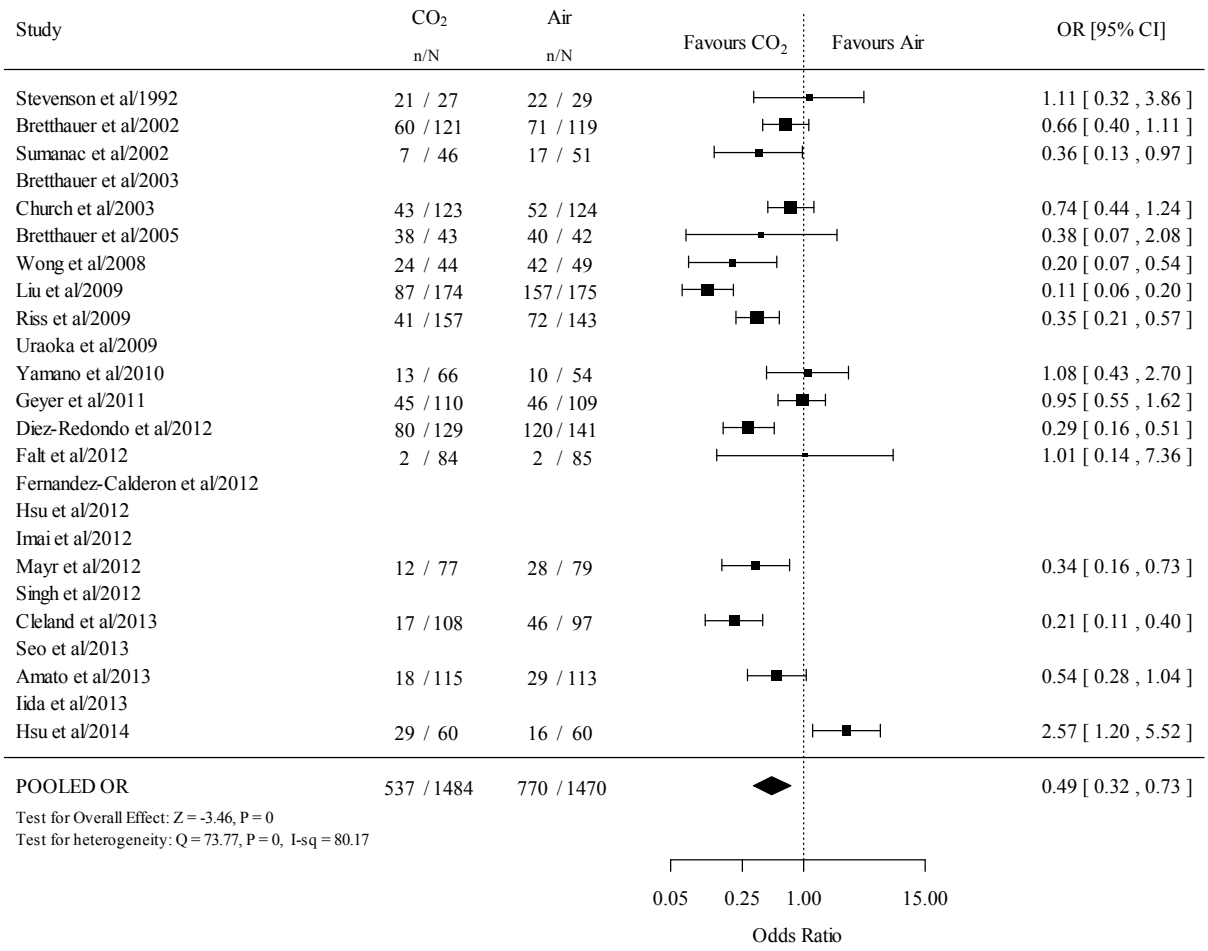

Figure 4. Early post-procedural pain (between 30-120 minutes)

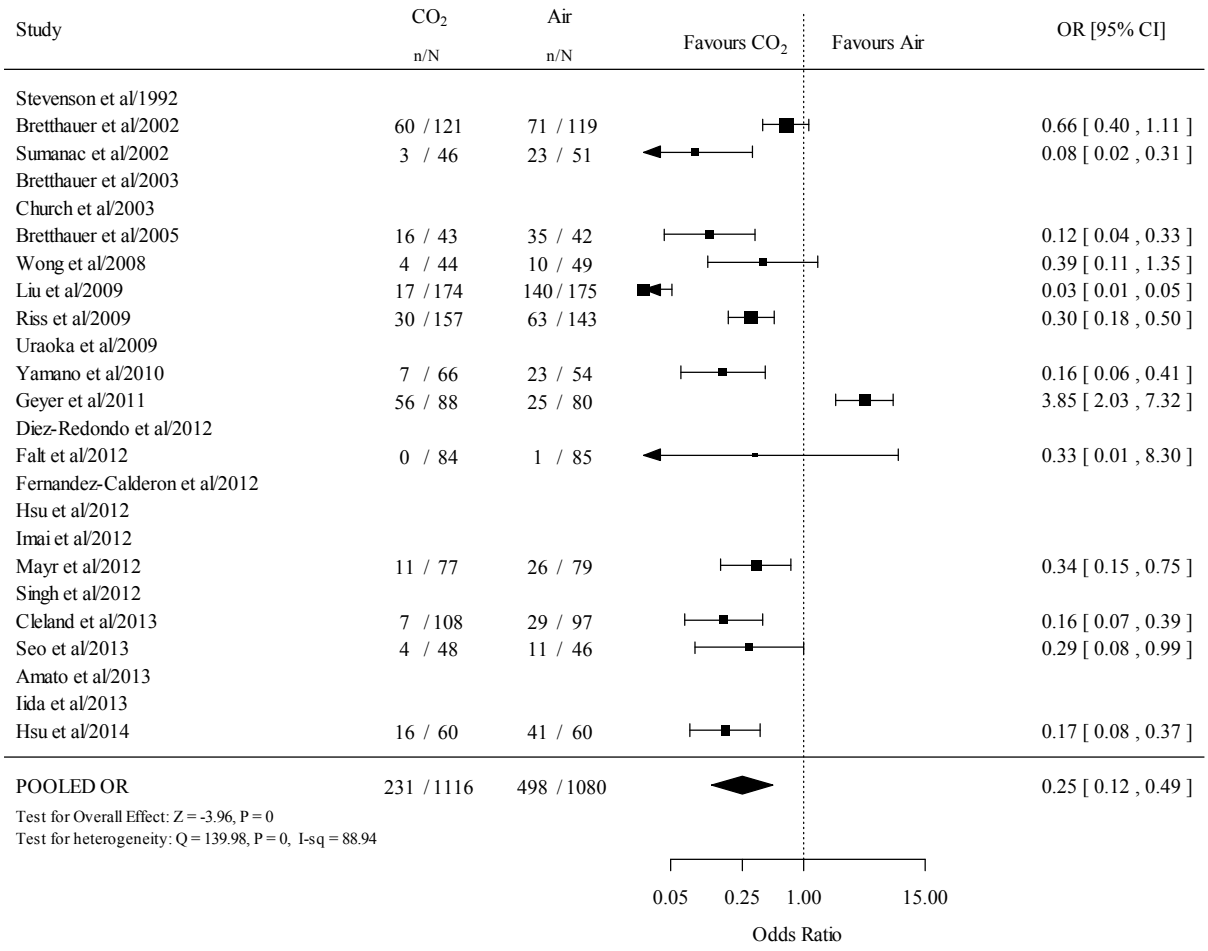

Figure 5: Intermediate post-procedural pain (360 minutes)

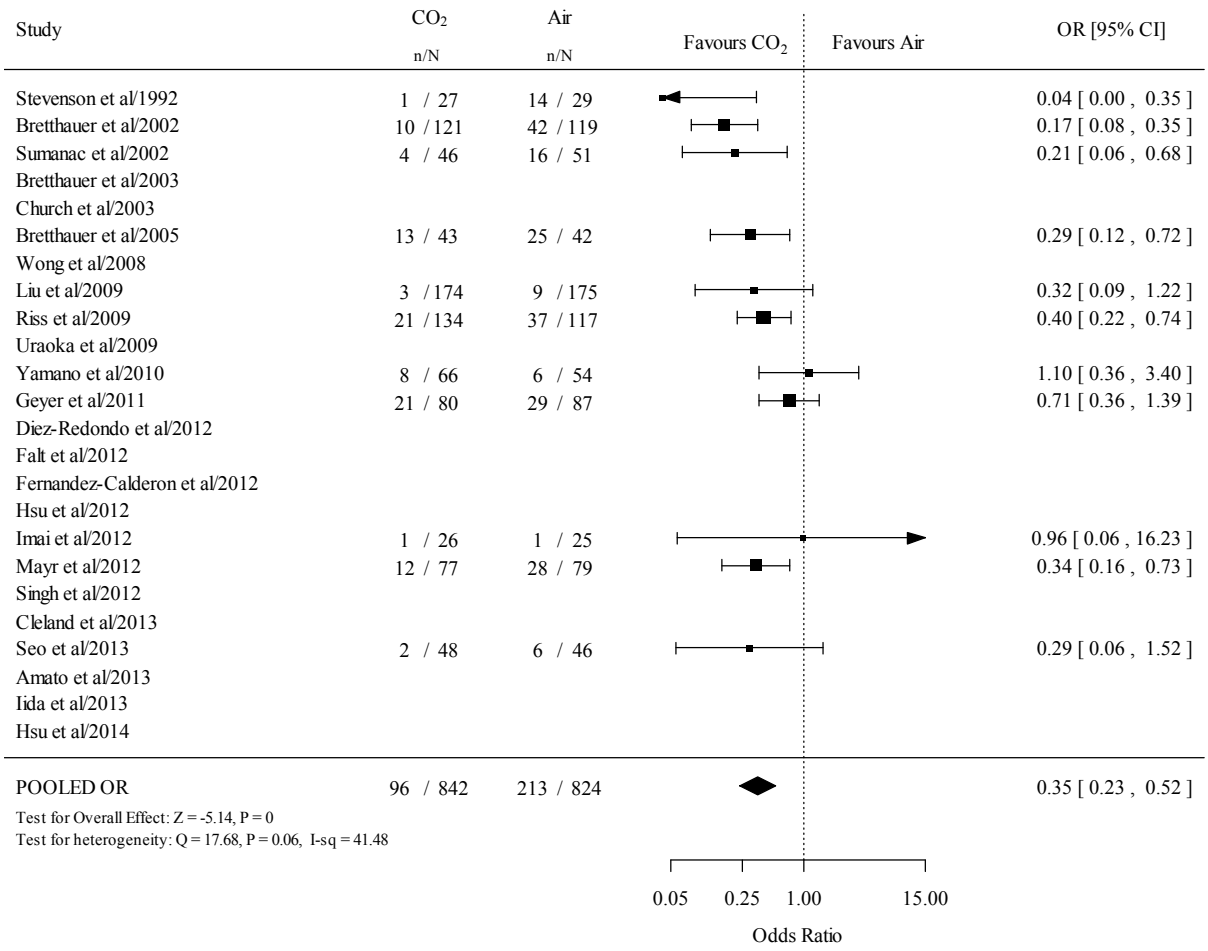

Figure 6. Late post-procedural pain (720-1440 minutes)

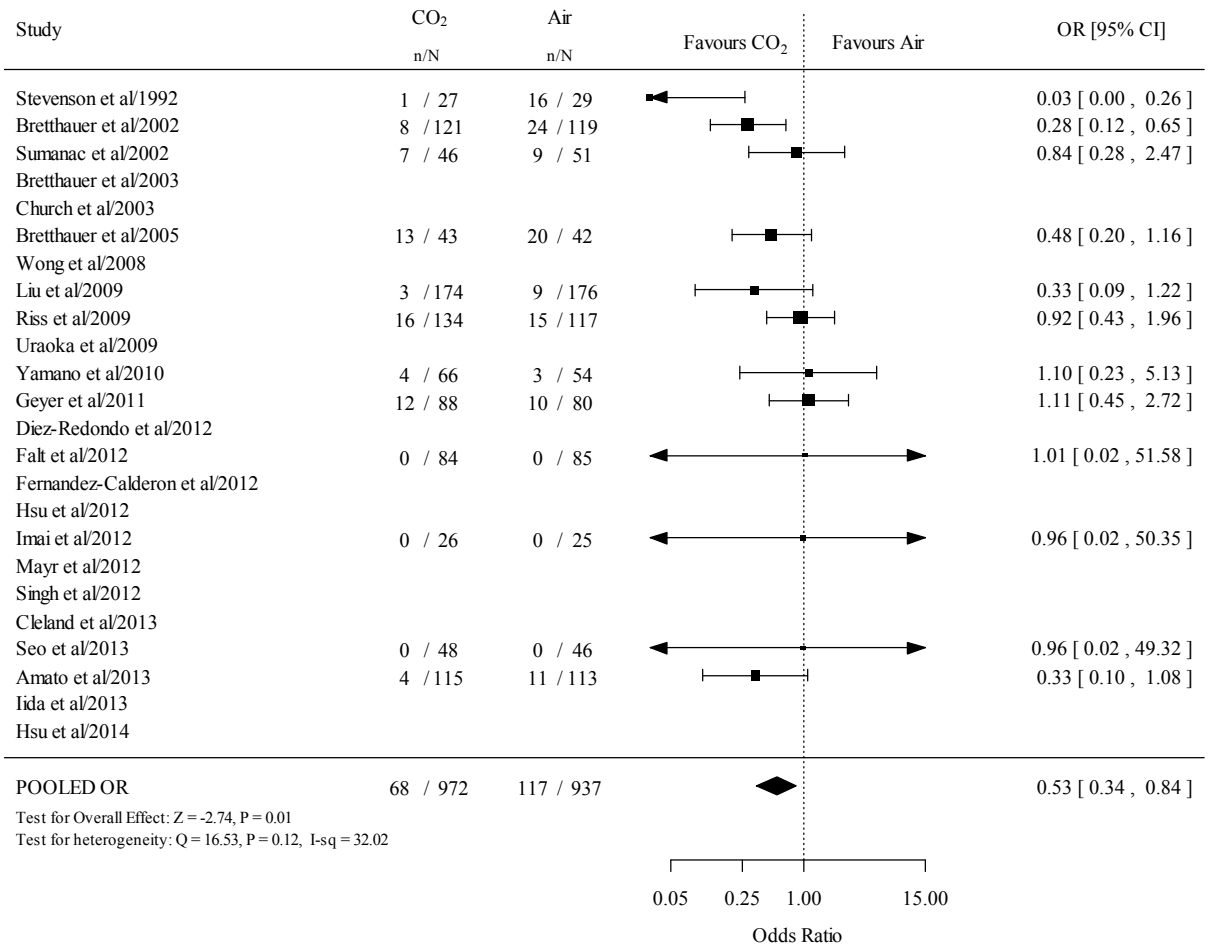

Figure 7: Cecal/ileal intubation rate

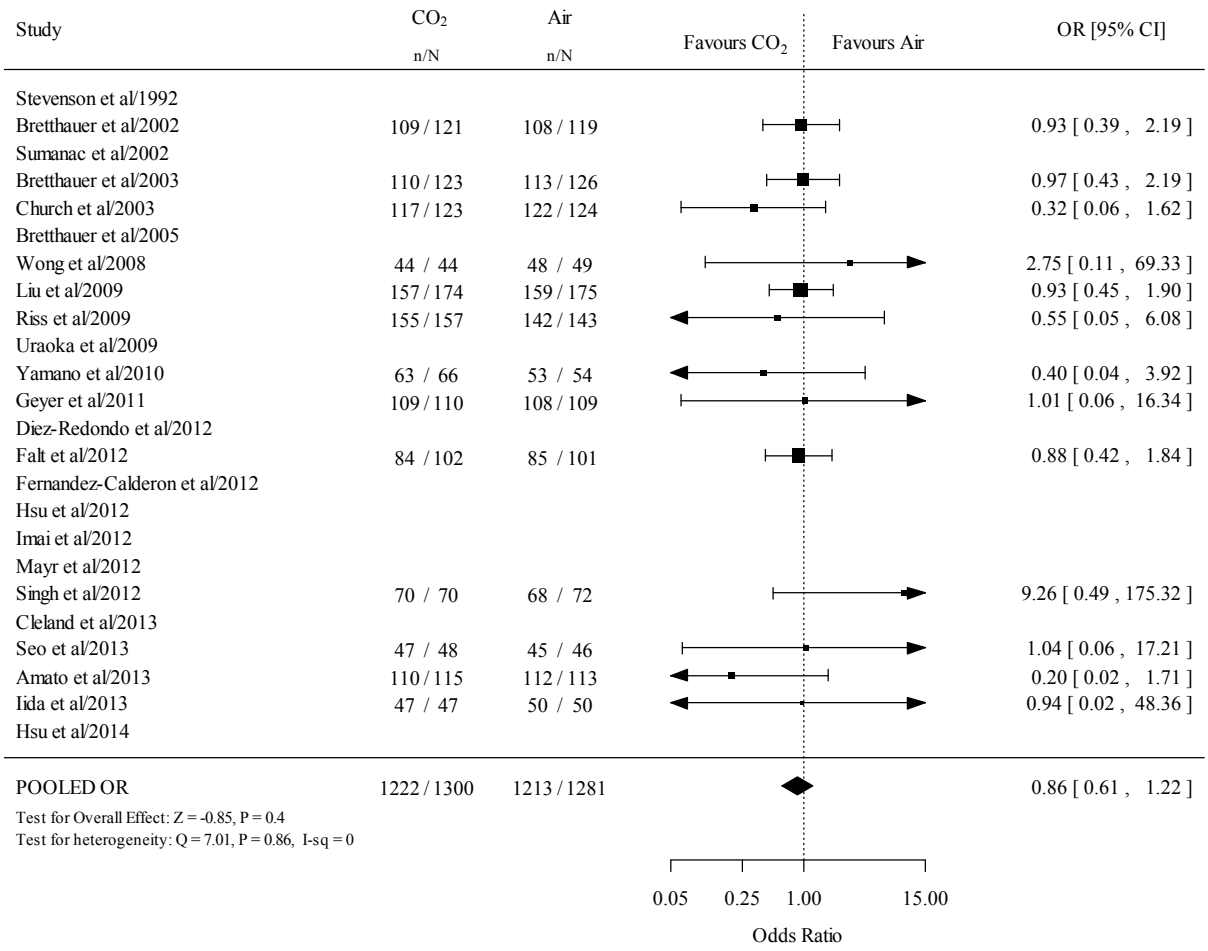

Figure 8. Cecal/ileal intubation time

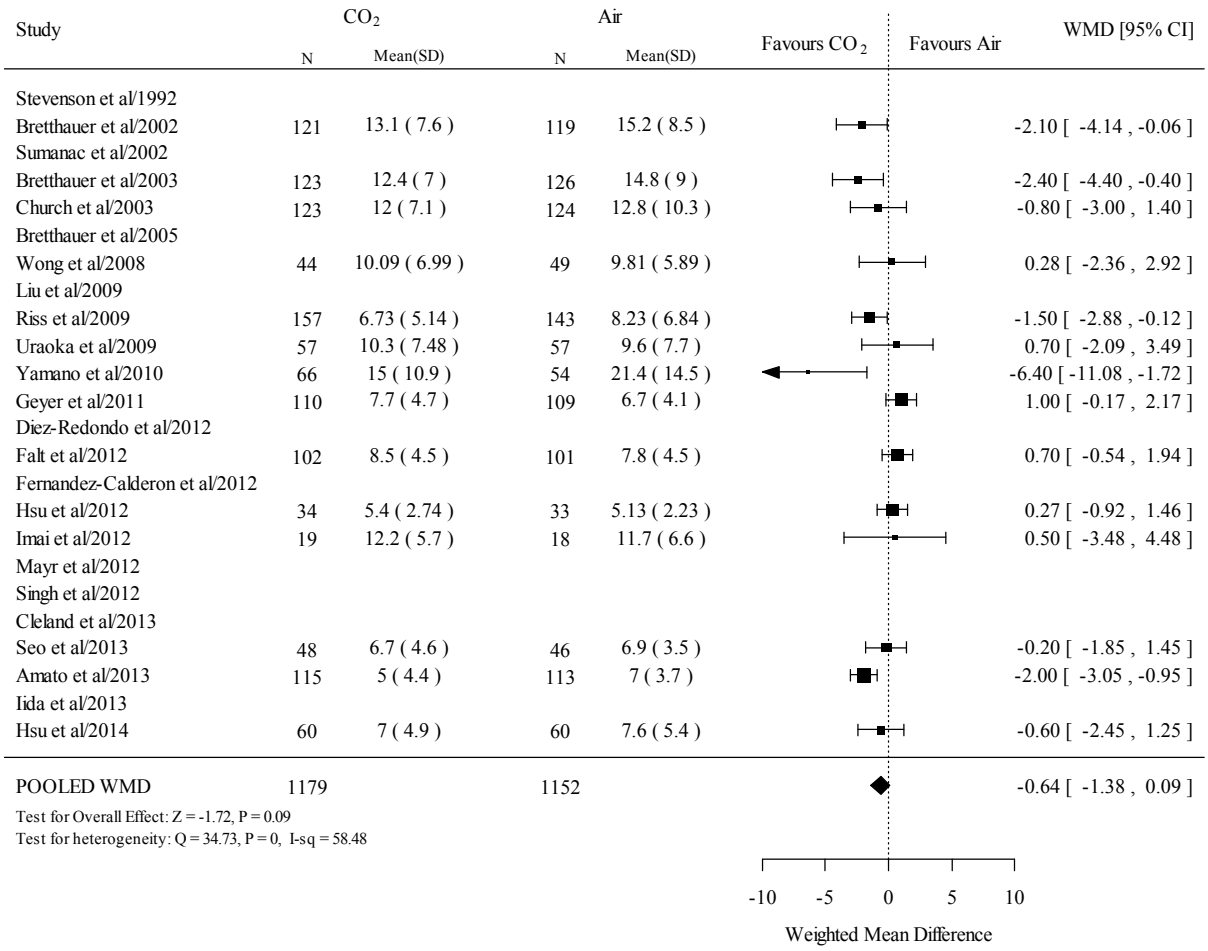

Figure 9: Total examination time

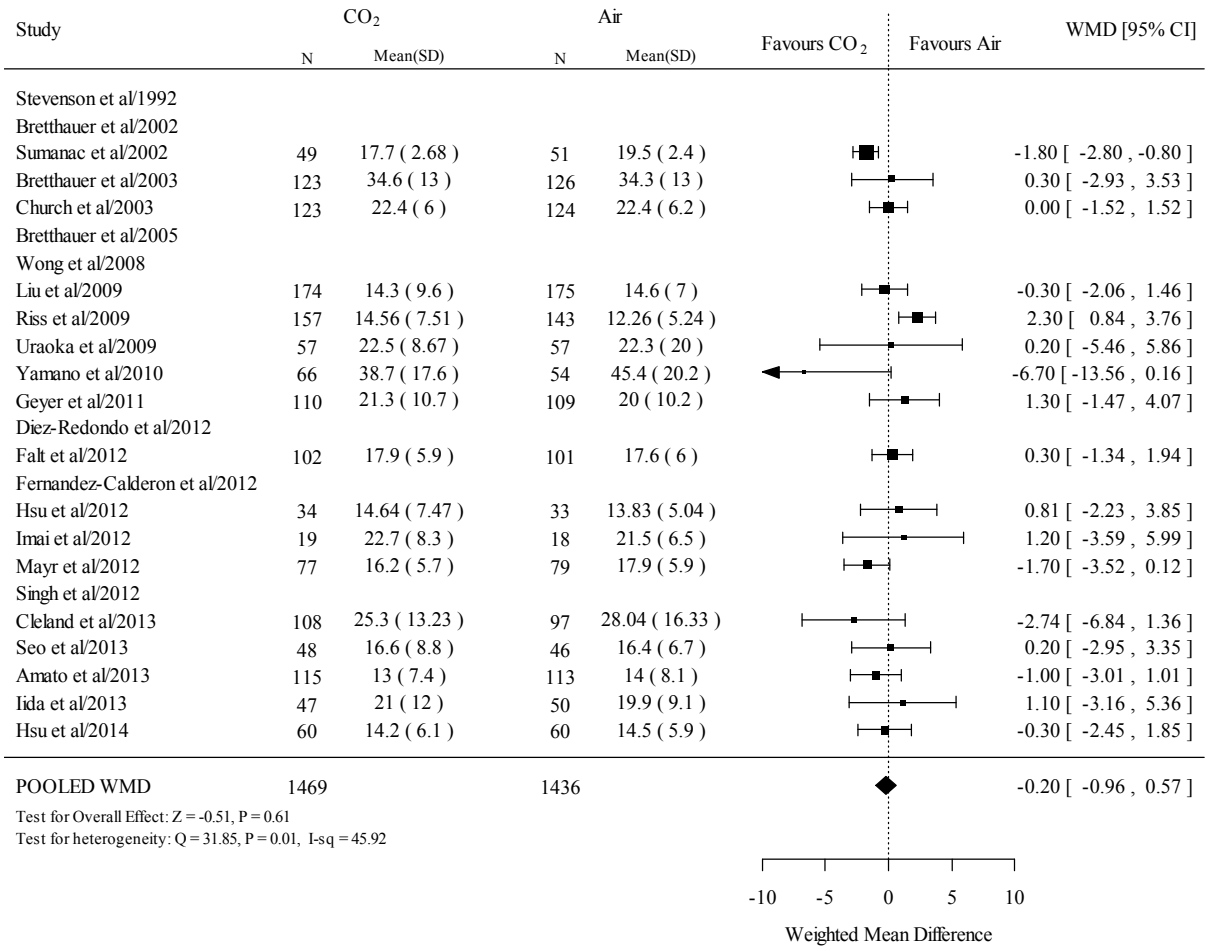

Table 1: Jadad Score

Author/Year	Jadad Score					
	Randomization		Blinding		Withdrawal/dropouts	Total score
	Randomized	Appropriate method	Double blinding	Appropriate method		
Stevenson GW et al/1992	1	1	0	1	1	4
Bretthauer M et al/2002	1	1	1	1	1	5
Sumanac K et al/2002	1	1	1	1	1	5
Bretthauer M et al/2003	1	1	1	1	1	5
Church J et al/2003	1	0	0	0	0	1
Bretthauer M al/2005	1	1	1	1	1	5
Wong JCH et al/2008	1	1	1	1	1	5
Liu X et al/2009	1	1	1	1	1	5
Riss S et al/2009	1	1	0	0	1	3
Uraoka T et al/2009	1	1	1	0	1	4
Yamano HO et al/2010	1	0	1	0	1	3
Geyer M et al/2011	1	1	1	1	1	5
Diez-Redondo P et al/2012	1	1	1	0	1	4
Falt P et al/2012	1	1	0	0	1	3
Fernandez-Calderon M et al/2012	1	0	0	0	0	1
Hsu WH et al/2012	1	0	0	0	1	2
Imai A et al/2012	1	1	1	1	1	5
Mayr M et al/2012	1	1	1	1	1	5
Singh R et al/2012	1	1	1	1	1	5
Cleland A et al /2013	1	1	1	1	1	5
Seo EH et al/2013	1	1	1	1	1	5
Amato A et al/2013	1	1	0	0	0	2
Iida T et al/2013	1	0	1	1	1	4
Hsu WF et al/2014	1	1	1	1	1	5

Jadad Score

The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding, and the flow of patients. There are 7 items. The last 2 attract a negative score, which means that the range of possible scores is 0 (bad) to 5 (good):

1. Was the study described as randomized (this includes words such as randomly, random, and randomisation)? (+1 Point)

2. Was the method used to generate the sequence of randomisation described and appropriate (table of random numbers, computer-generated, etc)? (+1 Point)

3. Was the study described as double blind? (+1 Point)

4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)? (+1 Point)

5. Was there a description of withdrawals and dropouts? (+1 Point)

6. Deduct one point if the method used to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to

date of birth, hospital number, etc)
7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).

Table 2: Summary statistics of pooled data

Clinical variables	k	N	Pooled OR/WMD (95% CI)	Test for Overall Effect	Test for Heterogeneity	
				Z (p-value)	Q (p-value)	I^2 (95% CI)
Procedural and immediate post-procedural Pain (during, end or within 15min after procedure)	16	2954	0.49 (0.32,0.73)^{o}	-3.46 (0.0005)	73.77(<0.0001) df=15	80.17 (60.78,91.48)
Early post-procedural pain (between 30-120 min)	13	2196	0.25 (0.12,0.49)^{o}	-3.96 (<0.0001)	139.98(<0.0001) df=12	88.94 (76.90,95.45)
Intermediate post-procedural pain (360 minutes)	11	1666	0.35 (0.23,0.52)^{o}	-5.14 (<0.0001)	17.68 (0.0606) df=10	41.48 (0.00,87.50)
Late post-procedural pain (720-1440 minutes)	12	1909	0.53 (0.34,0.84)^{o}	-2.74 (0.0061)	16.53 (0.1225) df=11	32.02 (0.00,83.61)
Cecal/ileal intubation Rate	13	2281	0.86 (0.61,1.22)^{o}	-0.85 (0.3975)	7.01 (0.8572) df=12	0.00 (0.00, 62.80)
Cecal/Ileal Intubation Time	14	2331	-0.64 (-1.38,0.09)^{w}	-1.72 (0.0860)	34.73 (<0.0001) df=13	54.48 (24.18,89.97)
Total Examination Time	17	2905	-0.20 (-0.96,0.57)^{w}	-0.51 (0.6133)	31.85 (0.0105) df=16	45.92 (4.64,77.66)

k represents number of studies, N represents number of patients, ^{o} represents pooled OR, ^{w} represents pooled WMD.

Table 3: Salient Feature of RCTs

Authors/Year/Ref	Country/ Language	RCT	Patients		Male		Female		Age		Routine Sedation	FU	Indications
			CO_2	Air	CO_2	Air	CO_2	Air	CO_2	Air			
			n	n	n	n	n	n	Mean or median	Mean or median	Yes or No = n	Min	
Stevenson GW et al/1992	Canada/Eng	SC	27	29	N/A	N/A	N/A	N/A	N/A	N/A	Yes = 56	1440	Elective - various
Bretthauer M et al/2002	Norway/Eng	SC	121	119	77	75	44	44	59.5	59.6	No=240	1440	Screening (NORCCAP)
Sumanac K et al/2002	Canada/Eng	SC	49	51	N/A	N/A	N/A	N/A	55.9 ± 1.9	53.1 ± 1.5	Yes= 100	1440	F/H of CC , Per/H polyp
Bretthauer M et al/2003	Norway/Eng	SC	123	126	77	78	46	48	59 (55-64)	59 (55-64)	No=249	N/A	Screening (NORCCAP)
Church J et al/2003	USA/Eng	SC	123	124	54	73	69	51	N/A	N/A	Yes = 247	10	Elective - various
Bretthauer M al/2005	Norway/Eng	MC	52	51	N/A	N/A	N/A	N/A	50 (22-94)	50 (22-94)	Yes = 52, No= 51	1440	Screening
Wong JCH et al/2008	Hong Kong/Eng	SC	44	49	21	23	23	26	59.9 (15.2)	58.5 (12.3)	Yes=93	120	Elective - various
Liu X et al/2009	China/Chinese	SC	174	175	100	101	74	74	48.5 (16.8)	48.1 (13.2)	Not routinely, Nos not available	1440	Elective - various
Riss S et al/2009	Austria/Eng	SC	157	143	N/A	N/A	N/A	N/A	N/A	N/A	Yes= 300	720	Elective - various
Uraoka T et al/2009	Japan/Eng	SC	57	57	18	39	19	38	65 (59-73)	62 (47-71)	Not routinely Nos not available	360	Screening, surveillance & diagnostic
Yamano HO et al/2010	Japan/Eng	SC	66	54	41	37	25	17	63.2 ± 8.5	61.7 ± 9.3	No = 120	1440	Screening
Geyer M et al/2011	Switzerland/Eng	SC	110	109	42	68	58	51	58 ± 13	62 ± 12	Yes= 219	1440	screening, surveillance & IBD
Diez-Redondo P et al/2012	Spain/Spanish &Eng	SC	129	141	59	63	70	78	56 (24-82)	56.7 (24-83)	Yes= 270	1440	Elective - various
Falt P et al/2012	Czech Republic/Eng	SC	102	101	50	54	52	51	59.4 ± 14.5	54 ± 53.5	Yes= 203	1440	Screening, surveillance & diagnostic
Fernandez-Calderon M et al/2012	Spain/Spaish & Eng	SC	132	82	79	52	53	30	59 (11.6)	59 (13.2)	Yes= 214	120	Elective
Hsu WH et al/2012	Taiwan/Eng	SC	34	33	20	19	14	14	47.9 ± 14.3	48.8 ± 11.3	No= 67	60	Elective - various
Imai A et al/2012	Japan/Eng	SC	19	18	9	8	10	10	55.7 ± 18.6	57.8 ± 17.7	No= 37	1440	Elective - IBS

Mayr M et al/2012	Germany/Eng	SC	77	79	35	32	42	47	62.4 ± 8.3 (39-83)	61 ± 10.9 (23-77)	Yes=124, No= 32	1440	Diagnostic & screening
Singh R et al/2012	Australia/Malaysia/Eng	MC	70	72	45	33	25	39	58.26 (22-84)	59.97 (22-88)	Yes= 142	N/A	Screening, polyp surveillance
Cleland A et al /2013	New Zealand/Eng	SC	108	97	51	43	57	54	61.33 ± 15.79	61.93 ± 12.75	Yes = 205	60	Elective - various
Seo EH et al/2013	Republic of Korea/Eng	SC	48	46	20	24	28	22	48.8 ± 9.0	49.9 ± 8.4	Yes= 94	1440	Screening, surveillance & diagnostic
Amato A et al/2013	Italy/Eng	SC	115	113	75	72	40	41	61.5 ± 14.0	60 ± 13.4	No=279 Yes=62	1440	Screening, surveillance & diagnostic
Iida T et al/2013	Japan/Eng	MC	47	50	36	38	11	12	58.9 ± 10.8	56.6 ± 12.2	No= 97	60	Elective
Hsu WF et al/2014	Taiwan/Eng	SC	60	60	37	31	23	29	54.7 ± 8.9	56.3 ± 9.6	Yes= 120	120	Screening

Eng= English, FU= Follow-up, IBD= Inflammatory bowel disease, MC= Multicenter, Min= Minutes, n= Number, N/A= Not available, NORCCAP= Norwegian colorectal cancer prevention, RCT= Randomized Controlled Trial, SC= Single Center,

Table 4: Adverse events during colonoscopy with CO2 and Air

Author/Year	Adverse Events	
	CO_2	Air
Stevenson GW et al/1992	N/A	N/A
Bretthauer M et al/2002	0	1 (perforation)
Sumanac K et al/2002	N/A	N/A
Bretthauer M et al/2003	N/A	N/A
Church J et al/2003	N/A	N/A
Bretthauer M al/2005	N/A	N/A
Wong JCH et al/2008	0	1 (late haemorrhage)
Liu X et al/2009	N/A	N/A
Riss S et al/2009	0	0
Uraoka T et al/2009	0	0
Yamano HO et al/2010	2 (headache)	1 (headache)
Geyer M et al/2011	N/A	N/A
Diez-Redondo P et al/2012	N/A	N/A
Falt P et al/2012	N/A	N/A
Fernandez-Calderon M et al/2012	0	0
Hsu WH et al/2012	N/A	N/A
Imai A et al/2012	N/A	N/A
Mayr M et al/2012	0	0
Singh R et al/2012	0	0
Cleland A et al /2013	N/A	N/A
Seo EH et al/2013	0	0
Amato A et al/2013	0	1 (perforation)
Iida T et al/2013	N/A	N/A
Hsu WF et al/2014	0	0

NA= Not available

Table 5: CO_2 measure during and after colonoscopy

Author/Year	Routine Sedation	CO_2 measurement during procedure and post-procedural				
		During Procedure		Post-procedural		CO_2 measurement
	Y or N/Total	Mean pressure CO_2 group Air group	Pts in normal range/Total pts	Mean pressure CO_2 group Air group	Pts in normal range/Total pts	
Stevenson GW et al/1992		N/A	N/A	N/A	N/A	
Bretthauer M et al/2002	N= 240 (T=240)	5.6kPa 5.4kPa	75/75 81/81	5.5kPa 5.4kPa	75/75 81/81	$ETCO_2$
Sumanac K et al/2002		N/A	N/A	N/A	N/A	
Bretthauer M et al/2003		N/A	N/A	N/A	N/A	
Church J et al/2003		N/A	N/A	N/A	N/A	
Bretthauer M al/2005	Y=52, N=51 (T=103)	4.3 kPa 4.2 kPa	49/52 51/51	4.4 kPa 4.2 KPa	52/52 51/51	
Wong JCH et al/2008		N/A	N/A	N/A	N/A	
Liu X et al/2009	Not routinely, numbers not available (T=349)	32.5 mmHg 32.1 mmHg	102/102 103/103	32.5 mmHg 32.5 mmHg	102/102 103/103	$ETCO_2$
Riss S et al/2009		N/A	N/A	N/A	N/A	
Uraoka T et al/2009		<60 mmHg <60 mmHg	57/57 57/57	<60 mmHg <60 mmHg	57/57 57/57	$PtcCO_2$
Yamano HO et al/2010	N= 120 (T=120)	42.5 mmHg 43 mmHg	66/66 54/54	40 mmHg 40 mmHg	66/66 54/54	$tcpCO_2$
Geyer M et al/2011	Y=219 (T=219)	37.3±5.2 mmHg 35.2±4.3 mmHg	110/110 109/109	37.0±5.2 mmHg 35.6±6.0 mmHg	110/110 109/109	$tcpCO_2$
Diez-Redondo P et al/2012	Y=270 (T=270)	<30 mmHg <30 mm Hg	72/141 59/129	<30 mmHg <30 mm Hg	N/A/141 N/A/129	CO2 via capnography
Falt P et al/2012		N/A	N/A	N/A	N/A	
Fernandez-Calderon M et al/2012		N/A	N/A	N/A	N/A	
Hsu WH et al/2012		N/A	N/A	N/A	N/A	$PtCO_2$
Imai A et al/2012	N=37 (T=27)	39.7 mmHg 38.5 mmHg	27/27 21/21	39.5 mmHg 38.3 mmHg	27/27 21/21	$PtCO_2$
Mayr M et al/2012		N/A	N/A	N/A	N/A	
Singh R et al/2012	Y=142 (T=142)	19.28 15.1	70/70 72/72	N/A N/A	70/70 72/72	Capnography readings
Cleland A et al /2013		N/A	N/A	N/A	N/A	
Seo EH et al/2013	Y=94 (T=94)	37.9 mmHg	48/48	38.6±3.14 mmHg	48/48	$ETCO_2$

		36.9 mmHg	46/46	37.2±2.40 mmHg	46/46	
Amato A et al/2013		N/A	N/A	N/A	N/A	
Iida T et al/2013		N/A	N/A	N/A	N/A	
Hsu WF et al/2014		N/A	N/A	N/A	N/A	

$ETCO_2$= End Tidal CO_2, N= No, N/A= Not available, $PtCO_2$= Transcutaneous partial pressure of CO_2, $PtcCO_2$= Processed Transcutaneous CO_2, T= Total, tcpCO2= Transcutaneous pCO_2, Y= Yes