

TITLE

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

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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 (CO₂=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 CO₂ 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, Becker¹ recommended the use of carbon dioxide (CO₂) insufflation to eliminate the risk of electrocoagulation colonic gas explosion. In 1985, Coblentz et al² first described the beneficial effects of CO₂ 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 CO₂. They also demonstrated the rapid absorption of CO₂ from the gut, as evident from the abdominal radiographs at 1 hour. A similar study by Williams³ in 1986 confirmed the superiority of CO₂ for double contrast barium enema. Roger⁴ was the first to evaluate the feasibility of CO₂ insufflation during colonoscopy. Since then a number of studies^{5,6} have shown the beneficial effect of CO₂ 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 CO₂ absorption by the intestinal mucosa, up to 150 times faster than air³. However there remains the concern regarding temporary increase in CO₂ 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 CO₂ 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 CO₂ 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/CO₂,” “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 form⁷ 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) statement⁸. 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 CO₂ 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 CO₂ vs air insufflation for flexible sigmoidoscopy (and not full colonoscopy)⁶
5. RCTs comparing water immersion versus CO₂ insufflation
6. RCTs comparing CO₂ vs air insufflation where CO₂ was only used during withdrawal and not for the entire procedure⁹

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. CO₂ measurement during colonoscopy
9. CO₂ measurement post-procedural
10. CO₂ utilization during colonoscopy

Methodological Quality

The methodological quality of the identified RCTs was assessed using Jadad Scoring system¹⁰. 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 OR¹¹. DerSimonian and Laird random effects model was used to combine the data¹². 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 Thompson¹²⁻¹⁶. If the observed value of Q was greater than the associated χ^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 al¹⁷. 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 R²¹. All plots were obtained using the metafor-package²². 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 $\leq 5\%$.

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 ($\kappa=0.99$) 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 criteria²³⁻⁴⁶. 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 more¹⁶ 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 (CO₂=2017, Air=1979) were analyzed²³⁻⁴⁶. For four out of the seven analyzable outcomes, the pooled effect size favored CO₂ 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 CO₂ 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 RCT⁴⁶ 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 (CO₂=2017, Air=1979), this is the largest body of comparative clinical data evaluated to date for CO₂ vs air insufflation for elective colonoscopy in adult patients. Based on the pooled effect size for various time points in relation to pain, CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 CO₂ although no such data is available in any of the RCTs. Newcomer et al⁴⁹ revealed post-colonoscopy 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 CO₂. 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 CO₂ 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 CO₂ 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 CO₂ is carried through the venous system and is breathed out through the lungs. Therefore, the CO₂ 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 CO₂ 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 CO₂ or by rebreathing exhaled CO₂. Hypercapnia is generally defined as a blood gas CO₂ level over 45 mmHg. Since CO₂ 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 CO₂ during colonoscopy produces undesirable effects such as high concentration of CO₂ 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 CO₂ (ETCO₂) in unsedated patients will diminish because of hyperventilation²⁴, whereas in sedated or anaesthetized patients the ETCO₂ 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 CO₂ compared to air had higher CO₂ concentration measured

by various means (End tidal CO₂, processed transcutaneous CO₂, transcutaneous pCO₂ 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 CO₂ was noted for the group insufflated with CO₂. The measured values for CO₂ for most patients remained within normal limits both during and at the end of colonoscopy (Table 5). Bretthauer et al²⁸ showed that in sedated patients in both the CO₂ and air groups, there was a slight increase in ET-CO₂ values. The authors felt that it was sedation causing hypoventilation, which was the primary cause of CO₂ retention, rather than CO₂ insufflation. Other authors³³ feel that besides reduced rate of respiration during sedation, the positioning of the patients during colonoscopy i.e. left lateral position affects the movement of diaphragm, ribs and intercostal muscles, may lead to CO₂ retention even if air is insufflated for colonoscopy. Geyer et al³⁴ further showed that in sedated patients even who have pulmonary disorders including COPD, CO₂ 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 al⁴¹ 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 CO₂ for colonoscopy. They felt that the major limitation of their study was measurement of CO₂ via capnography which may not be very accurate. Our analysis therefore confirms the findings of previous RCTs that CO₂ does not produce detrimental side effects even in sedated patients during colonoscopy even when CO₂ is continuously pumped to inflate the colon (Table 5, Fig 10 & 11). However one can argue that CO₂ concentration measurement will be dependent on the volume insufflated during colonoscopy. Only two RCTs^{26,33} have provided data on the volume of CO₂ used during the procedure. Bretthauer et al²⁶ measured the gas volumes in 218 out of 249 patients. The authors found comparable volumes of CO₂ 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 CO₂ during colonoscopy. However they did not correlate the volume findings with CO₂ concentration. Yamano et al³³ on the other hand analyzed their 120 patients and compared their finding to Bretthauer et al’s study²⁶. They observed that the mean gas volume and gas flow rate and the maximum gas

volume used in CO₂ cohort was much higher compared to Bretthauer et al's study²⁶. However this did not lead to any abnormal increase in pCO₂ suggesting the safety of CO₂.

As far as the effectiveness of CO₂ 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 CO₂ 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 few⁵³.

Cost-effectiveness and Cost-benefit analysis of CO₂ 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 CO₂ could not be analyzed due to lack of data across the board. Yamano et al³³ 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 CO₂ 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 CO₂ can be substituted for air; (b) fear of CO₂ safety due to lack of knowledge; (c) unavailability of adequately tailored CO₂ insufflators 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 outcomes⁵⁶ (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 CO₂ 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 CO₂ 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 CO₂ retention during and after the colonoscopy even in sedated patients with

pulmonary disease was no different with CO₂ insufflation compared to air insufflation and certainly has shown no detrimental effects. Therefore CO₂ 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 patient 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.

DECLARATION 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

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Figure 1: PRISMA flow diagram

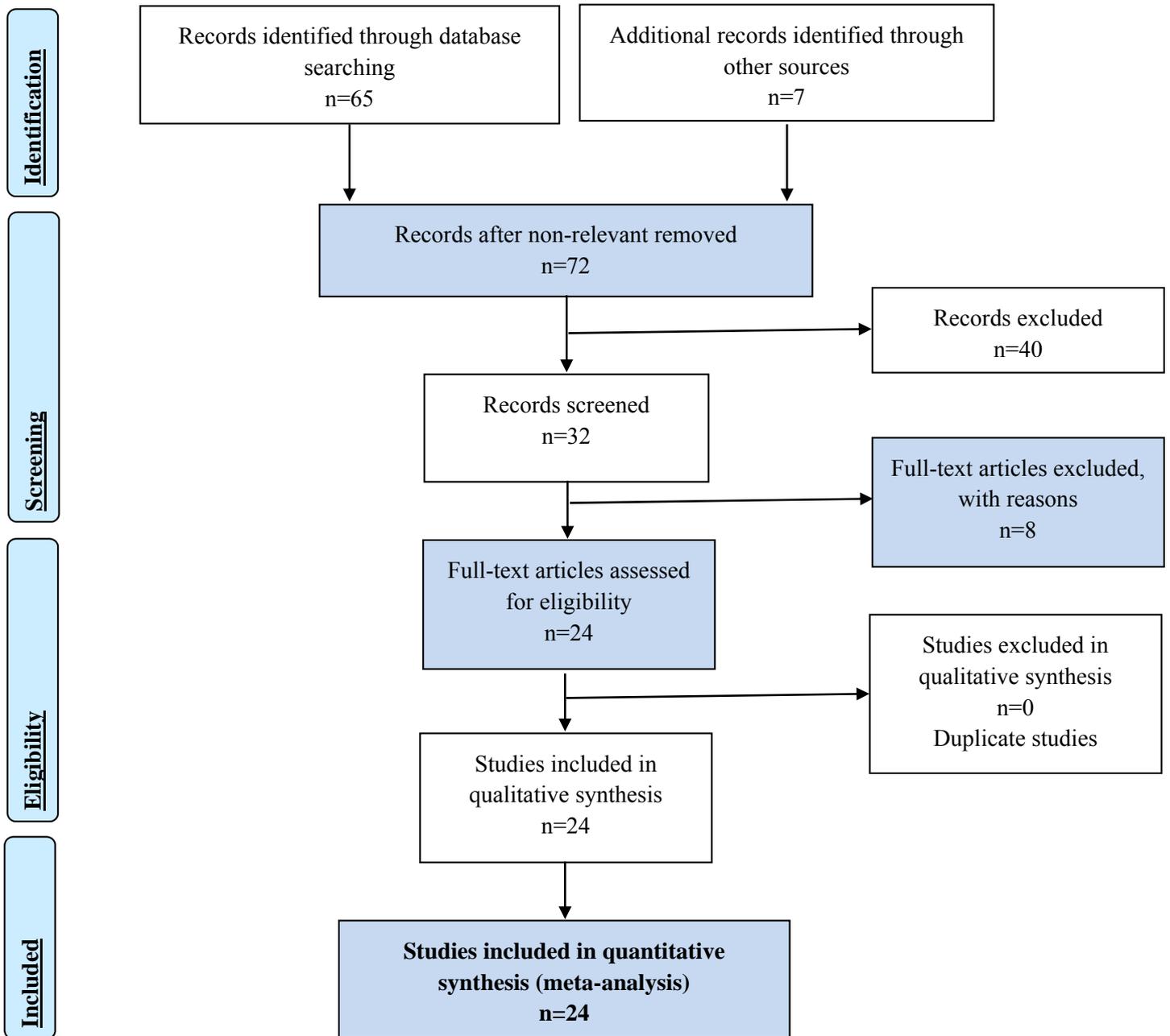


Figure 2: Funnel plots

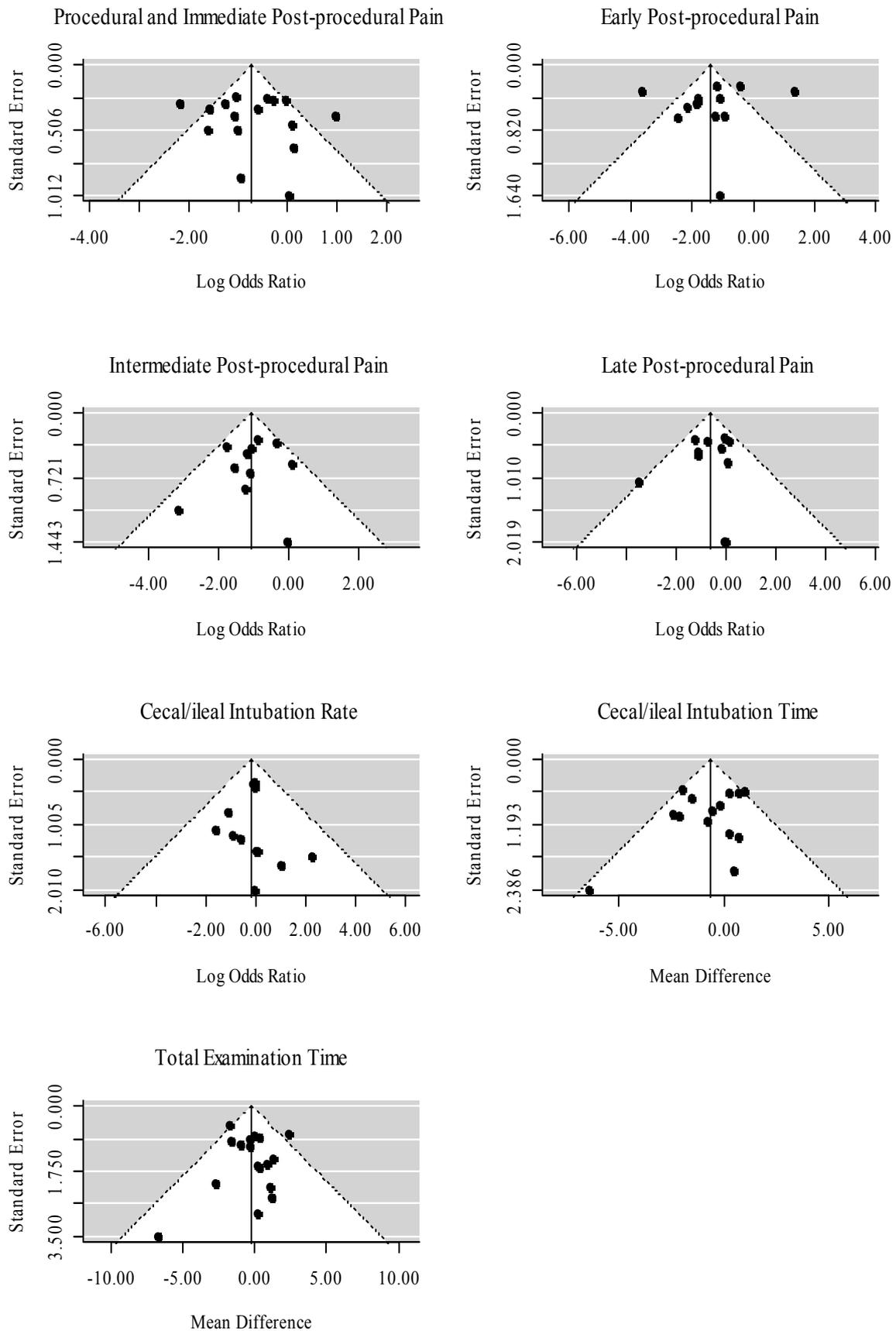


Figure 3: Procedural and immediate post-procedural pain (during, end or within 15min after procedure)

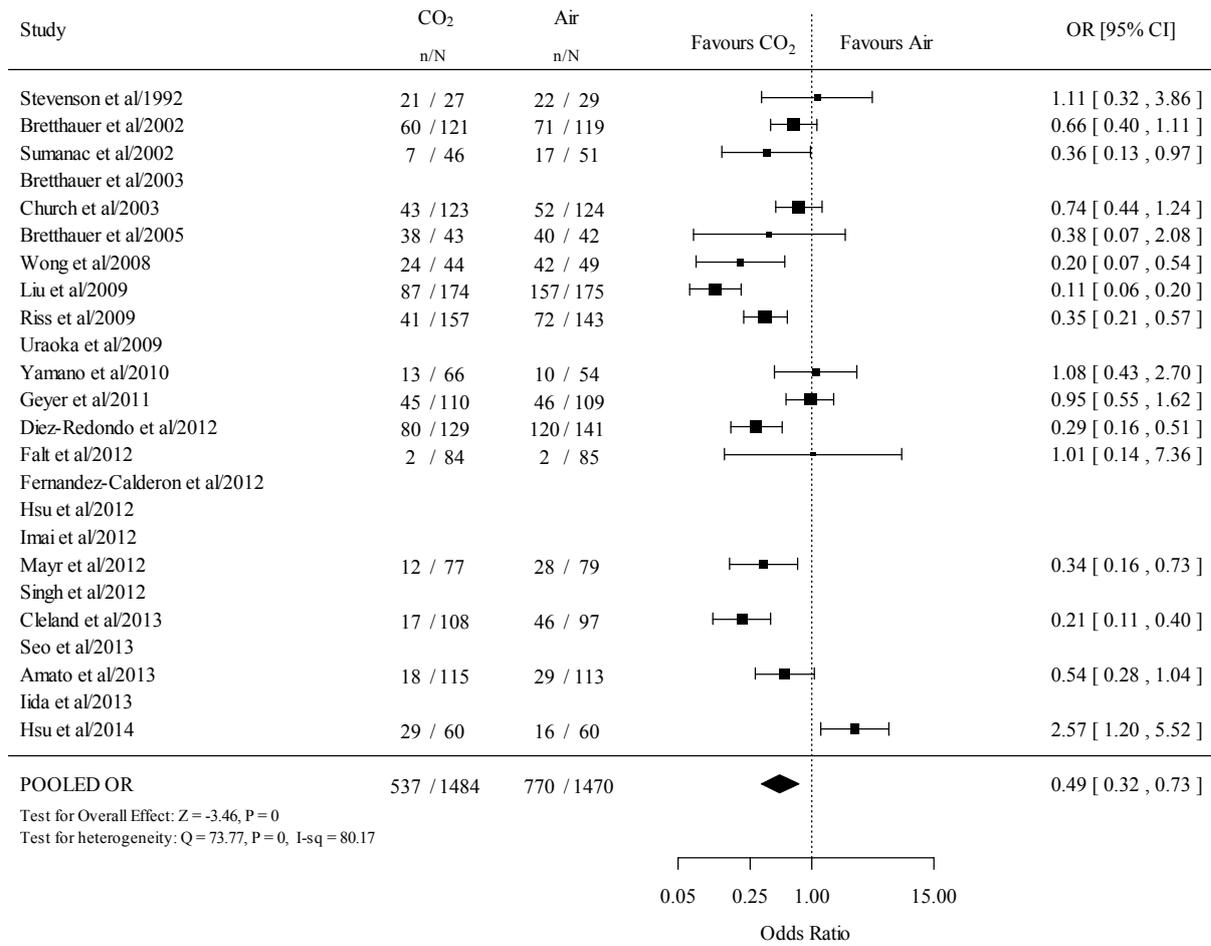


Figure 4. Early post-procedural pain (between 30-120 minutes)

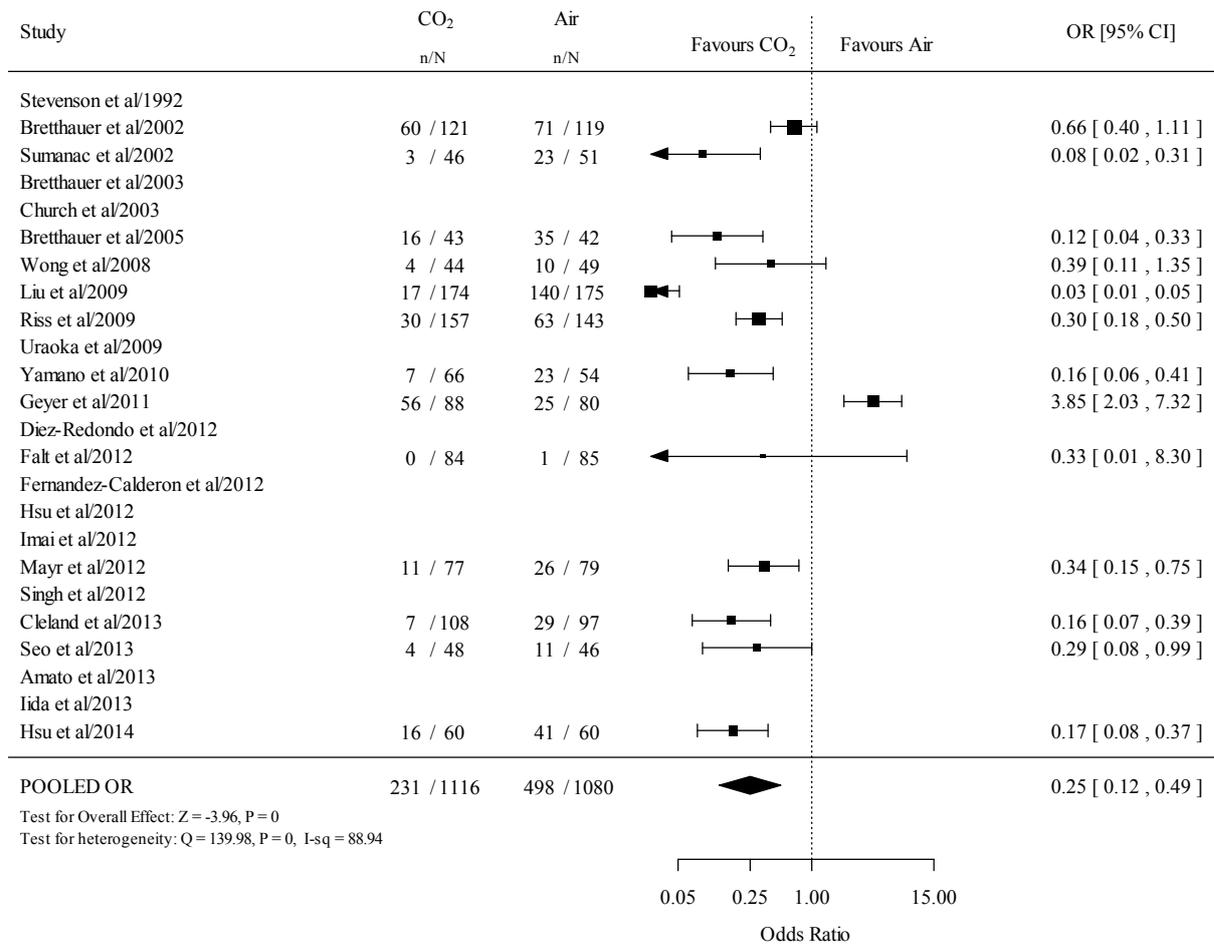


Figure 5: Intermediate post-procedural pain (360 minutes)

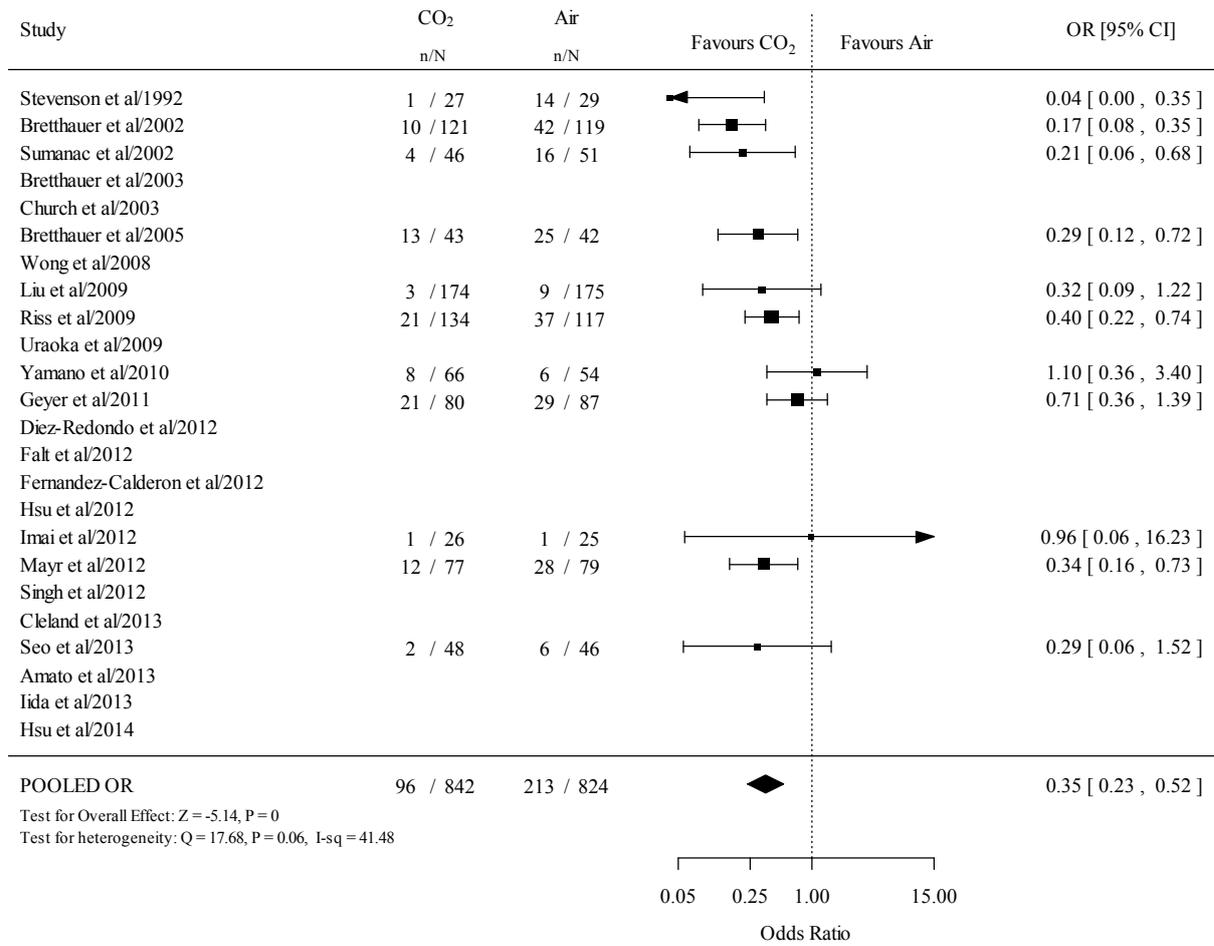


Figure 6. Late post-procedural pain (720-1440 minutes)

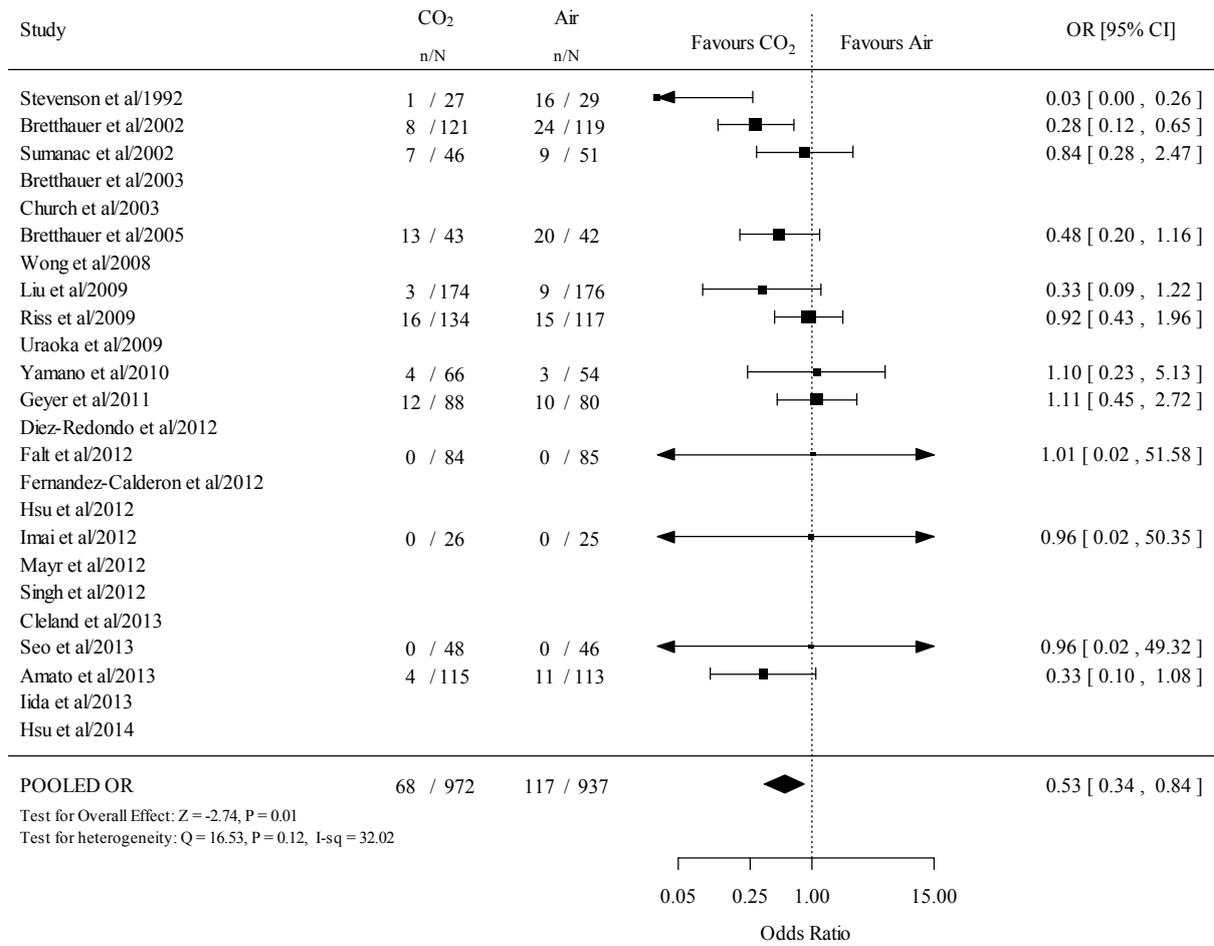


Figure 7: Cecal/ileal intubation rate

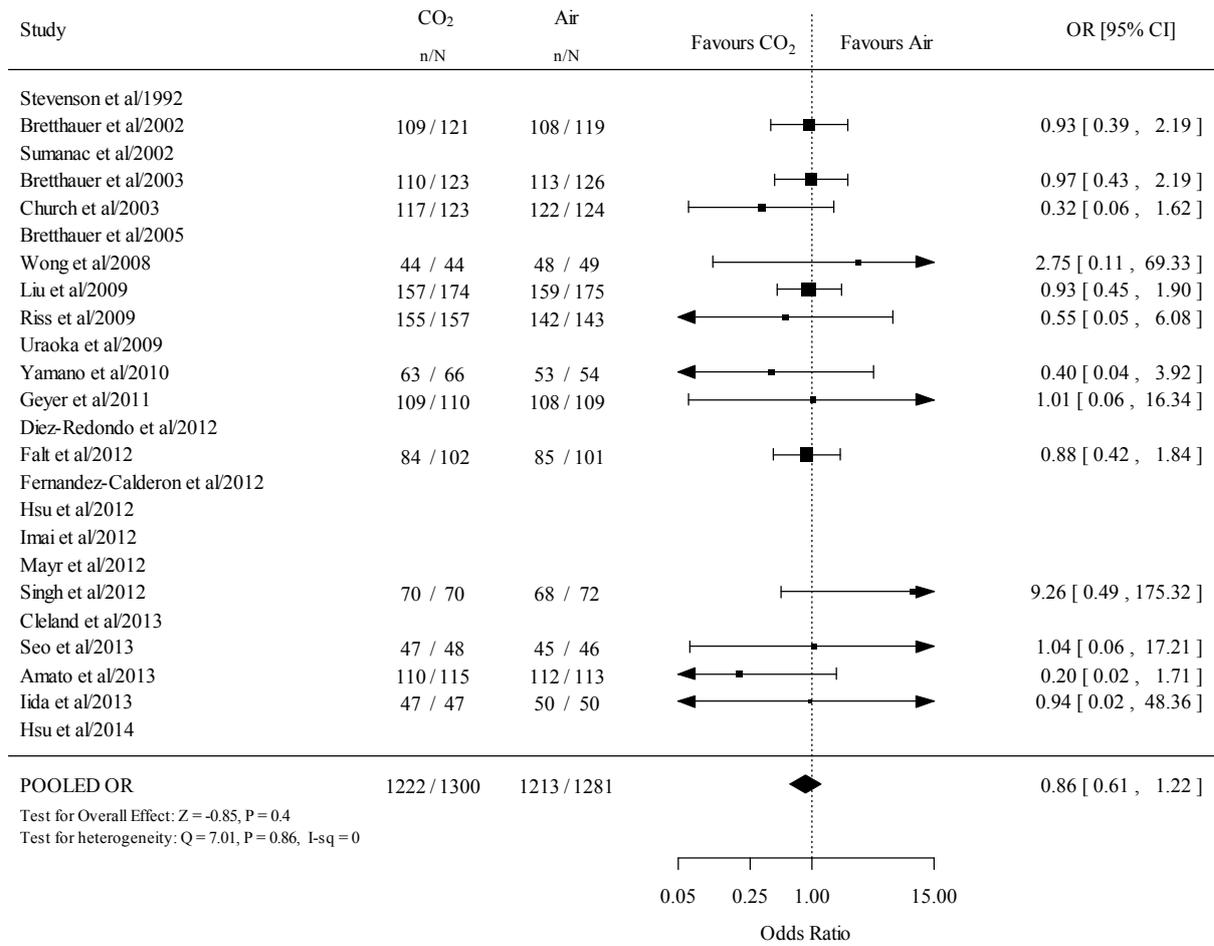


Figure 8. Cecal/ileal intubation time

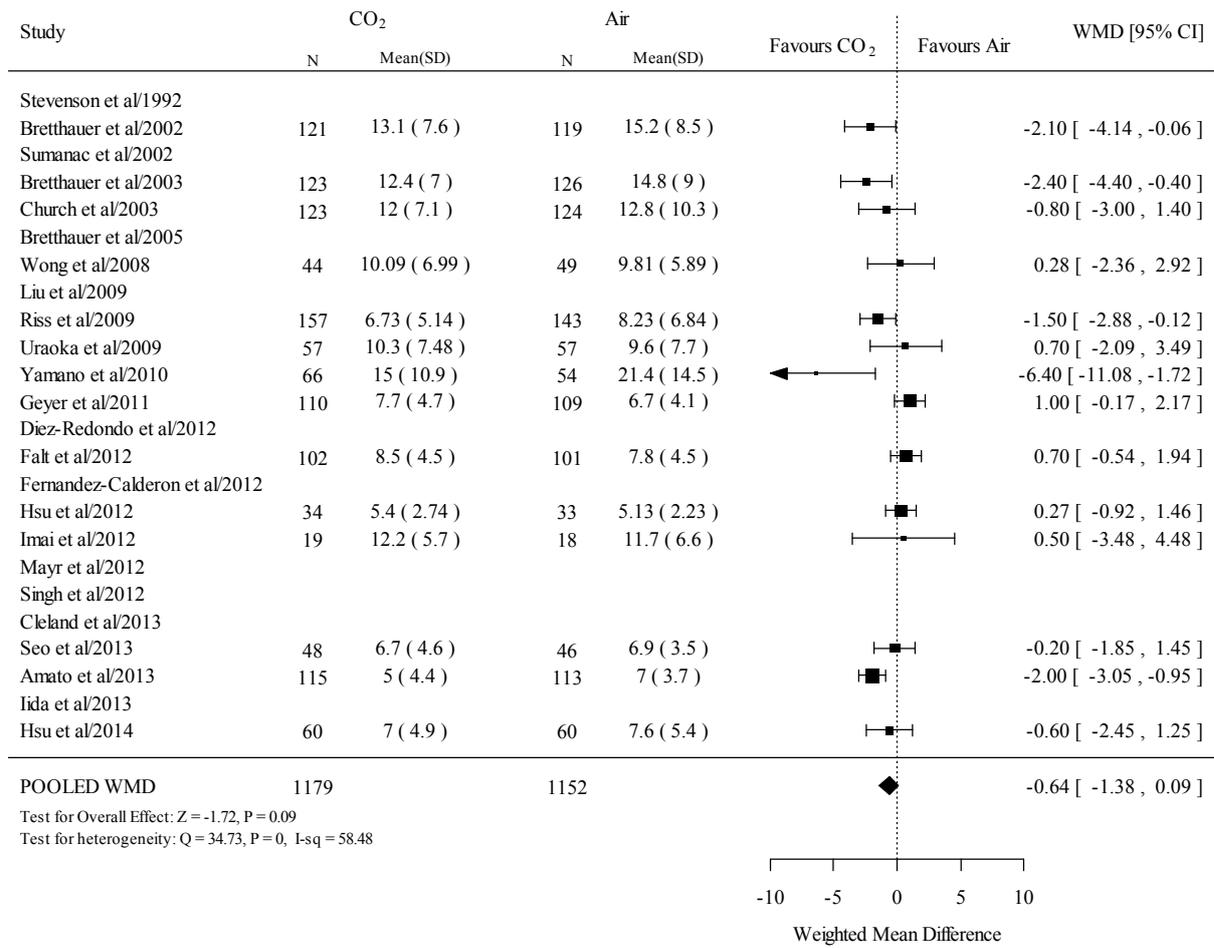


Figure 9: Total examination time

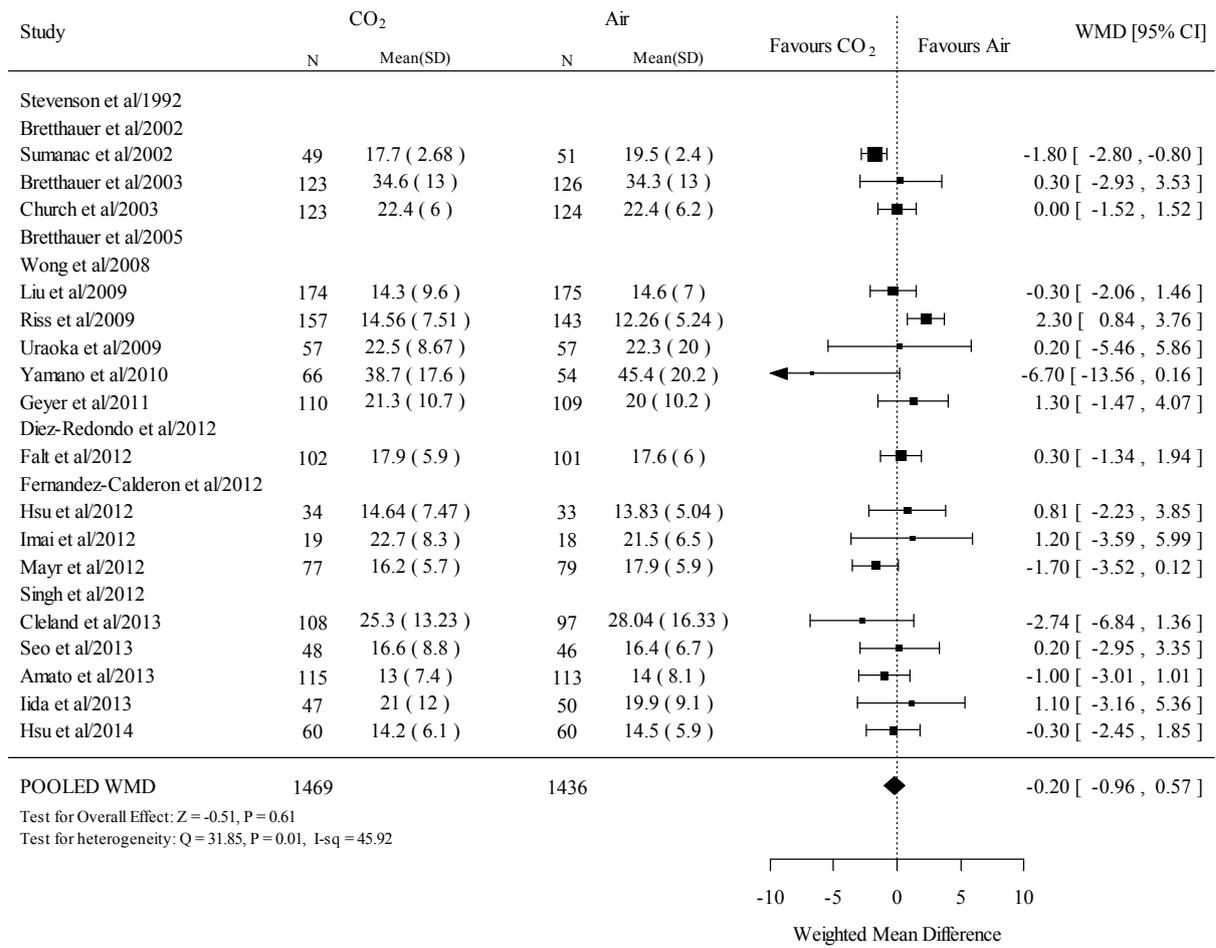


Table 1: Jadad Score

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) df	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	RC T	Patients		Male		Female		Age		Routine Sedation	FU	Indications
			CO ₂ n	Air n	CO ₂ n	Air n	CO ₂ n	Air n	CO ₂ Mean or median	Air Mean or median			
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 et 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: CO₂ measure during and after colonoscopy

Author/Year	Routine Sedation	CO ₂ measurement during procedure and post-procedural				CO ₂ measurement
		During Procedure		Post-procedural		
		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	CO ₂ 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	

ETCO₂= End Tidal CO₂, N= No, N/A= Not available, PtCO₂= Transcutaneous partial pressure of CO₂, PtcCO₂= Processed Transcutaneous CO₂, T= Total, tcpCO₂= Transcutaneous pCO₂, Y= Yes