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Comparison between Carbon Dioxide and Air Insufflation in Colonoscopy: A Systematic Review and Meta-Analysis Based On Randomized Control Trials

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Abstract

Objectives: The colorectal cancer is a common and lethal neoplasia. Colonoscopy detects diseases in the initial stages decreasing the mortality. Pain and abdominal discomfort are usual complaints associated mainly with the use of air insufflation. Carbon dioxide (CO2) is increasingly utilized to augment tolerance and disposition to repeat the examination. Compare which insufflation method is related to less unpleasant symptoms, safer examination and best performance are objectives of the study.

Methods: Electronic databases were accessed selecting only randomized controlled trials comparing insufflation with CO2 and ambient air in colonoscopy. The evaluated outcomes were pain, abdominal distension and flatulence, cecal intubation rate, cecal intubation and total procedure time, volume of gas, CO2 measurement, and need of sedation or analgesia, and polyp detection rate.

Results: Thirty randomized controlled trials were selected (4854 patients). Meta-analysis showed reduction in pain risk in the CO2 group immediately after the colonoscopy (Risk difference-RD 0.11[0.03, 0.19]), 1h (RD 0.29 [0.24, 0.34]), 3h (RD 0.22[0.11, 0.34]) and 6h (RD 0.21 [0.17, 0.26]) after colonoscopy. The reduction of flatulence risk 1h and 6h after the procedure was greater in CO2 group (RD 0.54 [0.43, 0.66] and RD 0.65[0.38,0.92], respectively). There were no significant differences between the two groups regarding pain during the procedure, pain and flatulence 24h after colonoscopy, abdominal bloating, request for medication, safety, gas volume, polyp detection rate, cecal intubation rate, time to cecum and total procedure time.

Conclusions: CO2 insufflation improves tolerance to colonoscopy, reducing pain and flatulence out to 6 hours following the procedure.

Keywords: Air; Carbon dioxide; Colonoscopy; Insufflations; Pain

Introduction

The colorectal cancer (CRC) is the third most common neoplasia around the world, occupying the fourth position in mortality, with an incidence of 1,360,602 new cases and 693,933 deaths in 2012 according to the World Health Organization (WHO) – Globocan database [1]. Colonoscopy is one of the methods indicated for screening of CRC with the objective of detecting the disease in the initial stages, decreasing the mortality [2,3].

However, because of the necessity of gas insufflation for the adequate visualization of the colonic mucosa, patients usually complain about pain and abdominal discomfort during and after the procedure associated mainly with the use of ambient air, which stays in the intestine for a longer period [4] due to the presence of nitrogen gas. To increase the tolerance and the disposition to repeat the examination, the insufflation of carbon dioxide (CO2) is increasingly utilized. CO2 is rapidly absorbed by the intestinal mucosa and subsequently eliminated by breath, which may lead to less pain, flatulence and distension related to the procedure [5-8]. Comparative analyses between the use of CO2 and ambient air in colonoscopy were shown in two meta-analyses published previously [9,10].

The objective of this systematic review and meta-analysis is to update this knowledge through new studies comparing which insufflation method is related to less unpleasant symptoms, faster and safer examinations, and to add outcomes that were not yet described in the literature.

Materials and Methods

Literature search

Randomized controlled trials (RCTs) that reported the use of CO2 versus ambient air in colonoscopy published until April 2016 were accessed through the following electronic databases: MEDLINE, SCOPUS, EMBASE, LILACS and CENTRAL (BVS), Cochrane Library, CAPES (Brazil) published theses, in addition to access of bibliographic references ("grey literature") to identify additional articles. Considering the MEDLINE database, the used search strategy was: "Carbon dioxide AND (endoscop* OR

colonoscop* OR enteroscop*) AND random*". For the additional databases, we employed the terms: "carbon dioxide", "CO2" and "colonoscopy".

Study Selection

For the study selection, there was no restriction of language, year of publication, patient follow-up time or publication status. After searching the titles and abstracts of the articles selected in the initial search, they were further sorted according the following criteria:

1- Study design: RCT.

2- Population: patients subjected to colonoscopy.

3- Intervention: intestinal insufflation with CO2.

4- Comparison: intestinal insufflation with ambient air.

5- Outcomes: the evaluated outcomes were pain, abdominal distension and flatulence related to colonoscopy, cecal intubation rate, cecal intubation time and total procedure time, volume of gas used, CO2 measurement at the end of the procedure, need of sedation or analgesia, and polyp detection rate.

Data Extraction

The data were extracted from the studies by two independent reviewers. In the case of opinion divergence during the process of data extraction and analysis, the doubts were taken to a discussion group in scientific methodology, obtaining a common agreement.

Risk of bias

Some data were used to generate the score of each study according to the JADAD score, which is a tool that qualifies the randomized controlled trial according to the description of randomization, blinding and existence of losses during the trial [11]. The prognostic differences between the comparison groups were also evaluated and whether the results of each study were assessed adequately and with sufficient follow-up time.

Statistical analyses

The software RevMan 5 (Review Manager Version 5.3.5 – Cochrane Collaboration, Copyright © 2014) was used to perform the meta-analysis of the outcomes [12]. The difference between results was calculated as the risk difference for dichotomous variables with the Cochran-Mantel-Haenszel (CMH) statistical method with 95% confidence interval, and as mean difference for continuous variables, using fixed effect and inverse variance as statistical method with 95% confidence interval. The heterogeneity (I2) between the studies was evaluated and modified whenever possible if >50%, conducting a sensitivity analysis when an outlier was identified through a funnel plot. When the sensitivity analysis did not bring any impact in the heterogeneity reduction, the analysis was not described and we opted for the random effect. Forest and funnel plots were used for graphical expression of the results.

Results

Through the initial search strategy, 1,830 trials were identified and we selected 150 of them to completely evaluate their titles and abstracts. Then 120 studies were excluded by the reasons (Figure 1), which resulted in the selection of 30 RCT that were in accordance with the eligibility criteria, with a total of 4,854 patients: 2,469 in the CO2 insufflation group and 2,385 in the ambient air insufflation group. The main characteristics of the selected trials and the individual risk of bias are shown in table 1.

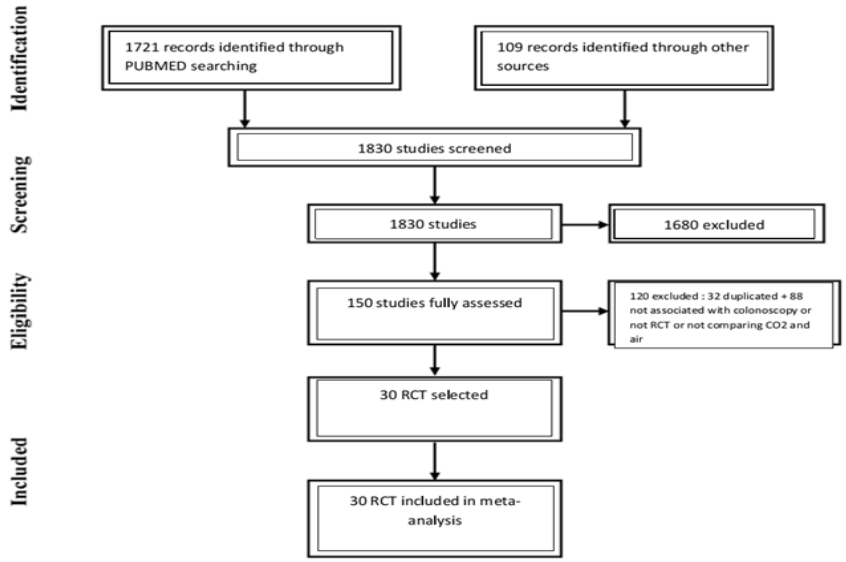

Figure 1: PRISMA flowchart: flow of information through the systematic review

Study	Population (N)	Co_2 (N)	Air (N)	Follow Up	Randomization	Blinding	Losses	Power Calculation	ITT	Prognostic	Outcomes	Jadad Score
Amato et al. 2013 [13]	228	115	113	24 hours	YES+	Only patient	NO	YES	YES	YES	YES	2
Bretthauer et al. 2002 [14]	240	121	119	24 hours	YES?	Patient and endoscopists	YES	YES	NO	YES	YES	4
Bretthauer et al. 2003 [15]	218	109	109	24 hours	YES?	Patient and endoscopists	YES	NO	NO	YES	YES	4
Bretthauer et al. 2005 [16]	103	52	51	24 hours	YES?	Patient and endoscopists	YES	NO	NO	?	YES	4
Calderon et al. 2012 [4]	214	132	82	2 hours	Yes?	Nurse	NO	NO	NO	YES	YES	1
Chao et al. 2010 [17]	104	46	58	During colonoscopy	Yes?	Patient and anesthesiologist	NO	NO	NO	YES	YES	3
Chen et al. 2013 [18]	193	96	97	24hours	YES+	Patient, endoscopist, research staff	YES	YES	YES	YES	YES	5
Chen et al. 2014 [19]	98	51	47	Until discharge	YES+	Patient and endoscopists	YES	NO	NO	YES	YES	5
Chen et al. 2016 [20]	125	63	62	24h	YES+	Patient , endoscopists, anesthesiologist, study assistant	YES	YES	YES	YES	YES	5
Church et al. 2003 [21]	247	123	124	1h	Yes -	Only patient	NO	NO	NO	YES	YES	1
Cleland et al. 2013 [22]	205	108	97	1h	Yes?	Patient, endoscopist, nurse care	NO	YES	NO	YES	YES	3
Diez-Redondo et al. 2012 [23]	270	129	141	24 hours	Yes +	Patient, endoscopist, nurse care	YES	YES	NO	YES	YES	4
Geyer et al. 2011 [24]	219	110	109	24 hours	Yes -	Patient, endoscopist	NO	YES	NO	NO	YES	3
Hsu et al. 2012 [25]	100	67	33	1 hour	Yes ?	Only patient	YES	NO	NO	YES	YES	2
Hsu et al. 2014 [26]	120	60	60	2 hours	Yes+	Patient, endoscopist, assistant nurses, nurses recovery room	NO	YES	NO	YES	YES	4
Imai et al. 2012 [27]	37	19	18	24 hours	Yes+	Patient, endoscopist	YES	YES	NO	YES	YES	5
Landaeta et al. 2014 [28]	63	30	33	24h	Yes?	Not informed	YES	NO	NO	YES	YES	2
Liu et al.2009 [29]	349	174	175	24h	Yes -	Single blinded	NO	NO	NO	YES	YES	1
Lynch et al. 2015 [30]	191	97	94	Until discharge	Yes +	Patient, endoscopist, nurse staff	YES	YES	NO	YES	YES	5
Mayr et al. 2012[31]	156	77	79	24h	Yes +	Patient, endoscopist	YES	YES	NO	YES	YES	5
Murakami et al. 2016 [32]	158	75	83	4h	Yes -	Only patient	YES	YES	NO	YES	YES	2
Riss et al. 2009 [33]	300	157	143	12h	Yes +	Only patient	YES	YES	YES	YES	YES	3
Seo et al. 2013 [34]	94	48	46	24h	Yes +	Patient, endoscopist, nurses recovery room	YES	YES	YES	YES	YES	5

Singh et al. 2012 [35]	142	70	72	Until discharge(~3)	Yes ?	Patient, endoscopist, nurse	NO	NO	NO	NO	YES	3
Stevenson et al. 1992 [36]	56	27	29	24h	Yes +	Patient, endoscopist	NO	NO	NO	?	YES	4
Sumanac et al. 2002 [37]	97	46	51	24h	Yes +	Patient, endoscopist	YES	NO	YES	YES	YES	5
Szura et al.2015[38]	200	100	100	1h	Yes +	Only patient	YES	YES	YES	YES	YES	3
Uraoka et al. 2009 [39]	114	57	57	6h	Yes +	Patient, endoscopist	YES	YES	YES	YES	YES	5
Wong et al. 2008 [40]	93	44	49	2h	Yes ?	Patient, endoscopist, assessor	YES	YES	NO	YES	YES	4
Yamano et al. 2010 [41]	120	66	54	24h	Yes ?	Patient, endoscopist	YES	NO	NO	YES	YES	4

Table 1: General characteristics of studies and individual risks of bias (Randomization: + adequated/ - inadequaded/ ? not informed; Losses: YES: losses described/ NO: losses not described ; ITT: intention to treat analysis; Prognostic: YES: similar baseline characteristics between groups/ NO: different baseline characteristics between groups/ ?: comparative analysis absent ; Outcomes: YES: adequately measured/ NO: not adequately measured)

The Jadad score was used for the critical evaluation of the methodological quality of the trials included in this systematic review with meta-analysis, obtaining 23 (77%) trials with values greater than or equal to three, which means low risk of bias. In relation to the description of losses, there was no need to exclude any trial, because all described values were lower than 20%. There was sample power calculation in 17 (57%) trials and the intention-to-treat analysis was conducted in seven (27%). The basic characteristics between the groups compared in each trial were similar in 26 (87%) studies and all used adequate tools to measure the outcomes (Table 1). The indications for colonoscopy were similar between the trials (screening, surveillance and diagnostic). There was no uniformity between the trials in relation to the type of colonic preparation used; types and dosages of sedatives/analgesics during the examination; CO2 insufflation system; patient follow-up time and number of colonoscopists involved in each trial.

Abdominal pain

Twenty-eight randomized controlled trials (RCTs) evaluated the pain related to colonoscopy [4,13,14,16,18-41]. However, the present meta-analysis included only trials with complete data and the same score of pain measurement. Whenever the continuous variable analysis (pain score mean/median) was not possible, the data were meta-analyzed using dichotomous variables (pain VS zero pain). The pain was evaluated during and immediately after the colonoscopy, as well as 1h, 3h, 6h and 24h after the procedure.

Pain during colonoscopy

During the procedure, there was statistical difference considering absence of pain favoring the CO2 insufflation group (RD 0.10 [0.03, 0.16]; I2=55%). However, if we exclude the trial by Wong et al. [40] from this analysis in order to reduce the heterogeneity related to the publication bias, the difference between groups loses statistical significance (RD 0.06 [-0.01, 0.13]; I2=0) [14,16,22,36,40] (Figure 2).

As for the pain score, there is no difference between the groups (MD -0.15[-2.56, 2.25]), but with heterogeneity of 100% [21,22,25,40].

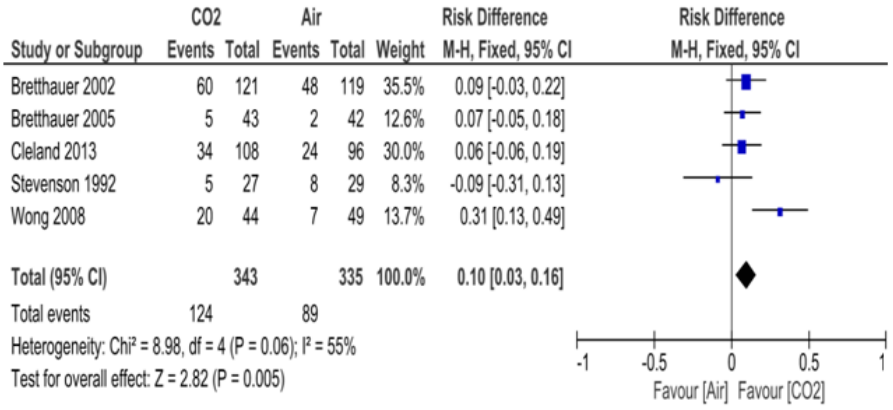

Figure 2: Pain during colonoscopy (numerical scale of pain =0). Forest plot before sensibility

Pain at the end of colonoscopy

Immediately after the colonoscopy, there was a reduction in the pain risk in the CO2 group in comparison with ambient air (RD 0.16 [0.09, 0.23]; I2=66%). The trial by Yamano et al [41] was excluded from this analysis to reduce the heterogeneity (RD 0.11 [0.03, 0.19]; I2=34%), maintaining the difference between the groups [24,26,28,37,41] (Figure 3).

Considering the calculation of the pain score, there was significant statistical difference, meaning that the CO2 group was associated with lower values of the numerical pain scale. (MD -0.71[-1.39, - 0.02]; I^2=94%) [21,24,25,26,38].

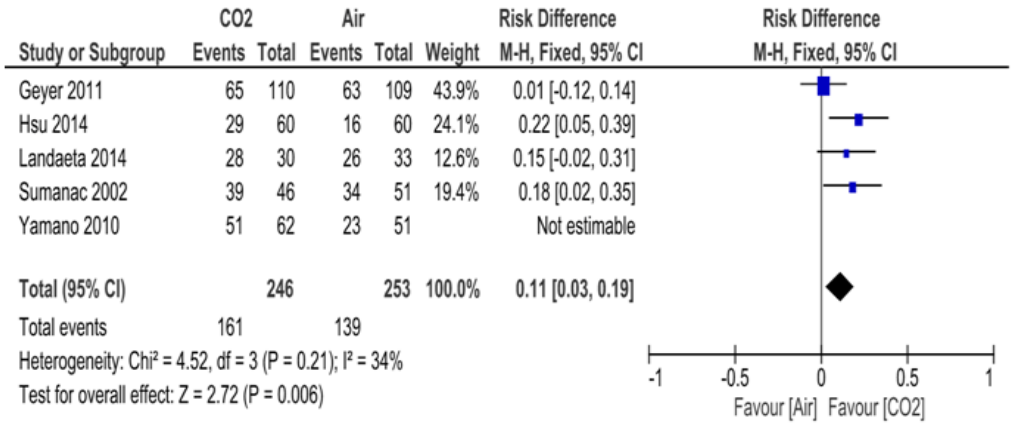

Figure 3: Pain at the end of colonoscopy (numerical scale of pain =0). Forest plot after sensibility analysis

Pain 1h, 3h, 6h and 24h post procedure

A reduction of the pain risk was observed in the CO2 group 1h after colonoscopy (RD 0.38 [0.34, 0.43]; I^2=92%); 3h (RD 0.22 [0.11, 0.34]; I^2=73%); 6h (RD 0.18 [0.14, 0.22]; I^2=72%) and 24h (RD 0.04 [0.01, 0.08]; I^2=75%). In order to reduce the heterogeneity between the trials, we excluded the trials by Liu et al [29] – pain analysis 1h after the procedure (RD 0.29 [0.24, 0.34]; I^2=42%); Geyer et al [24] ,Stevenson et al [36] and Yamano et al [41] – 6h analysis (RD 0.21 [0.17, 0.26]; I^2=31%); Bretthauer et al [14] and Stevenson et al [36] – 24h analysis (RD 0.01 [-0.03, 0.05]; I^2=28%), which was the only outcome where the difference between the analyzed groups was not maintained [14,16,20,22,24,28,29,33,34,36,37,41] (Figure 4-7).

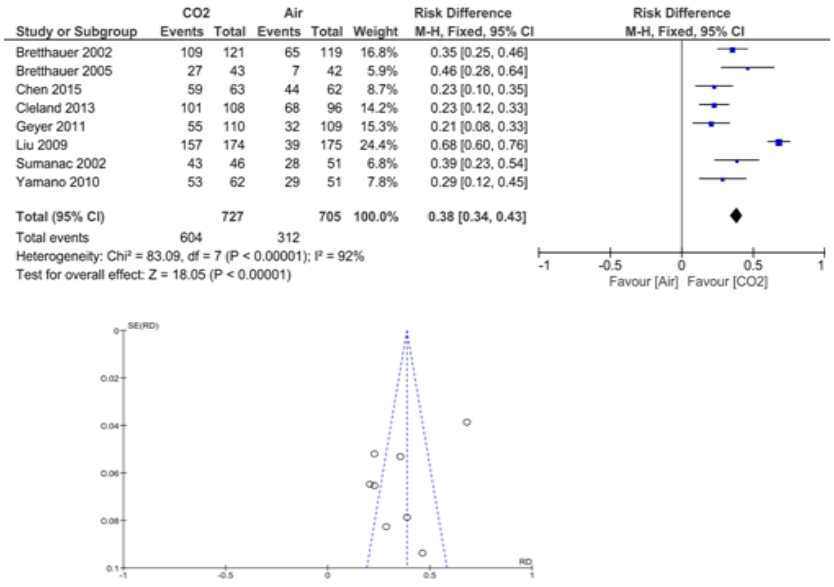

Figure 4 a): Pain at 1h post procedure (numerical scale of pain =0). Forest plot and funnel plot: a) before sensibility analysis b) after sensibility analysis

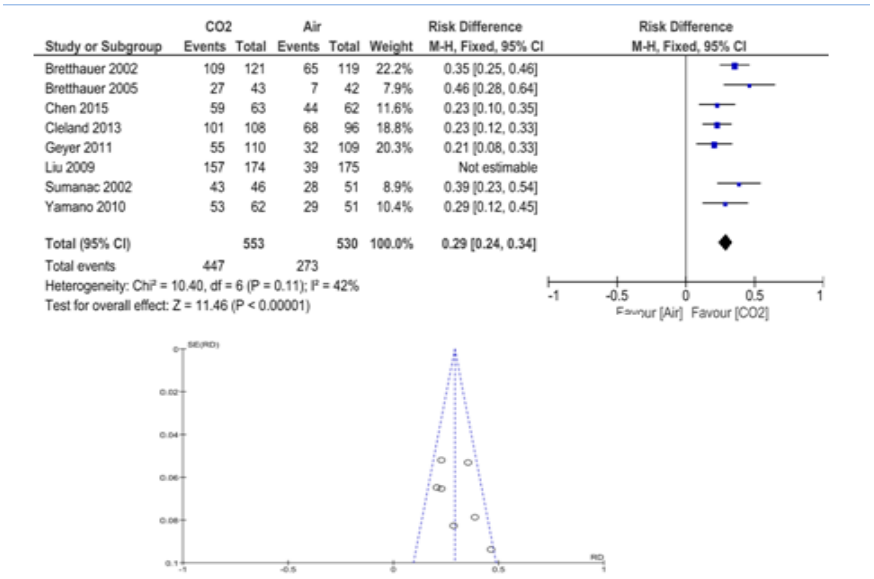

Figure 4 b):

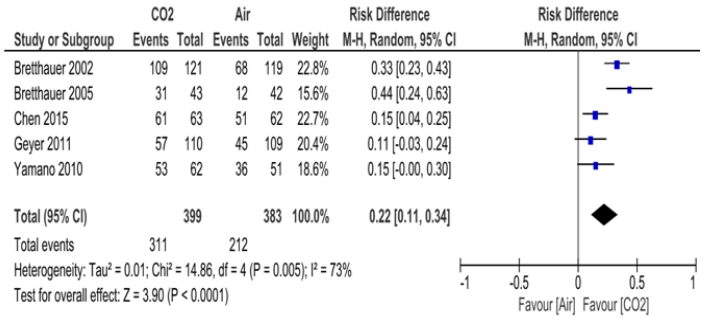

Figure 5: Forest plot for pain (numerical scale of pain =0) at 3h post procedure before sensibility analysis.

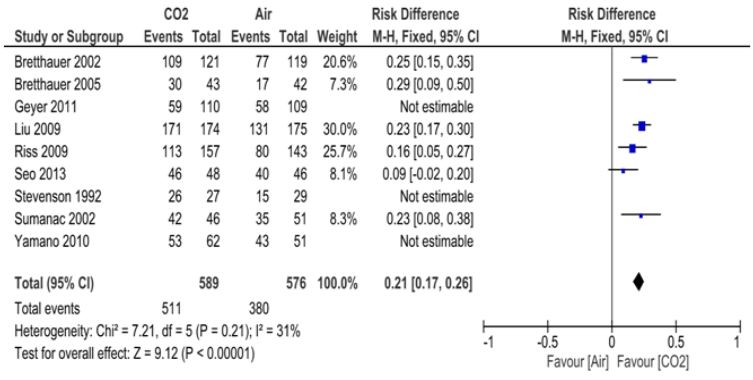

Figure 6: Pain at 6h post procedure (numerical scale of pain =0). Forest plot after sensibility analysis

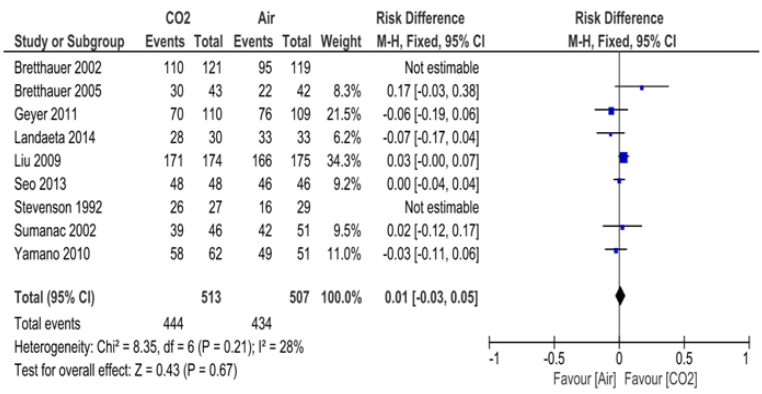

Figure 7: Pain at 24h post procedure (numerical scale of pain =0). Forest plot after sensibility analysis

Volume of gas during colonoscopy

Two trials evaluated the volume of gas used during the colonoscopy, showing that there was no significant statistical difference when the CO2 insufflation group and the ambient air insufflation group were compared (MD -0.08 [-1.03, 0,86] e I2=44%) [15,41].

Flatus 1h, 6h and 24h post procedure

Two trials evaluated the presence of flatus reported by the patients after the procedure. The reduction of flatulence risk 1h and 6h after the procedure was greater in the CO2 group (RD 0.54 [0.43, 0.66]; I2 =36%) and (RD 0.65[0.38,0.92]; I2=82%), respectively. In the analysis of 24h after colonoscopy, there was no difference between the groups (RD 0.21[-0.27,0.68]; I^2=91) [36,37].

Bloating at the end of procedure

Two trials did not show any difference related to the abdominal bloating score between the compared insufflation groups (MD -1.20 [-3.01, 0.62]; I2=93%) [24,26].

Request of medication

There was no difference in relation to the request of medication during the procedure between the CO2 and ambient air insufflation groups in the two trials included in this outcome (RD -0.06 [-0.13, 0]; I2=57%) [13,18].

Cecal intubation

Twelve trials demonstrated that there was no difference in relation to the cecal intubation rate between the CO2 insufflation group and the ambient air insufflation group (RD -0.01[-0.02, 0.01]; I2=0) [13-15,18, 20,21,24,29,35,38,40, 41] (Figure 8).

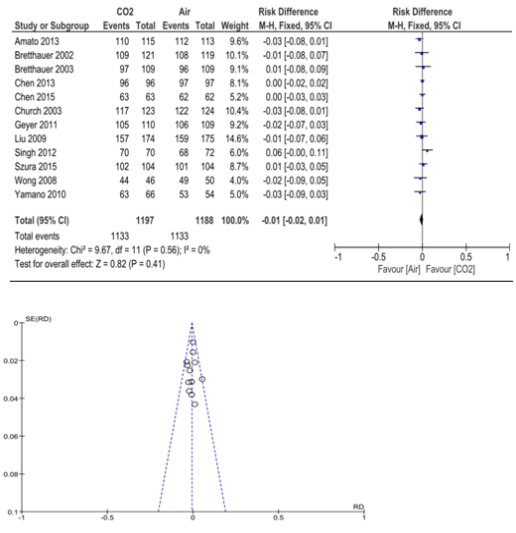

Figure 8: Cecal intubation rate. Forest plot and funnel plot

Polyp detection rate

Comparing the CO2 and ambient air groups, there was no difference in the polyp detection rate during the colonoscopy in the nine trials considered (RD -0.01 [-0.06, 0.03]; I2=0) [13,22-26,31,38,40] (Figure 9).

Time to cecum and total procedure time

There was no difference between the groups in relation to the time to reach the cecum (MD -0.17 [-0.44, 0.11]; I2=47%) and in relation to the total procedure time (MD 0.03 [-0.41, 0.47]); I2=21%) [14,15,19,20-22,24-29,31,34,38,41] (Figure 10, 11).

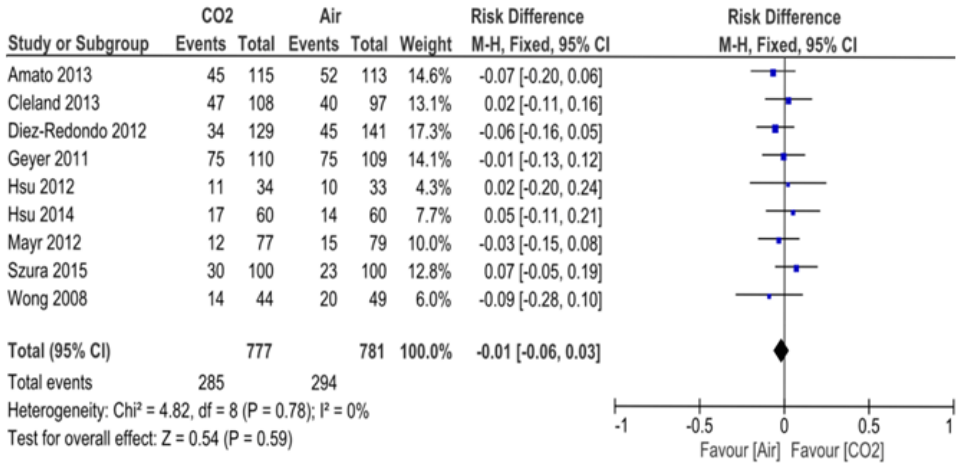

Figure 9: Polyp detection rate Forest plot.

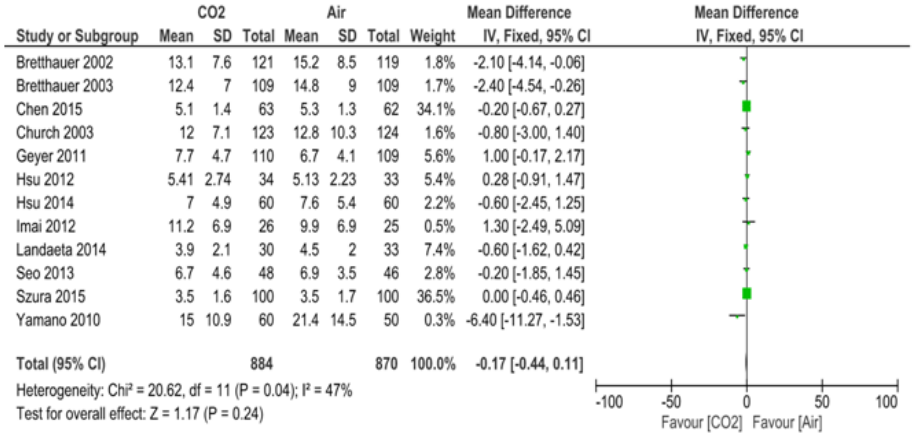

Figure 10 : Time to cecum (minutes). Forest plot

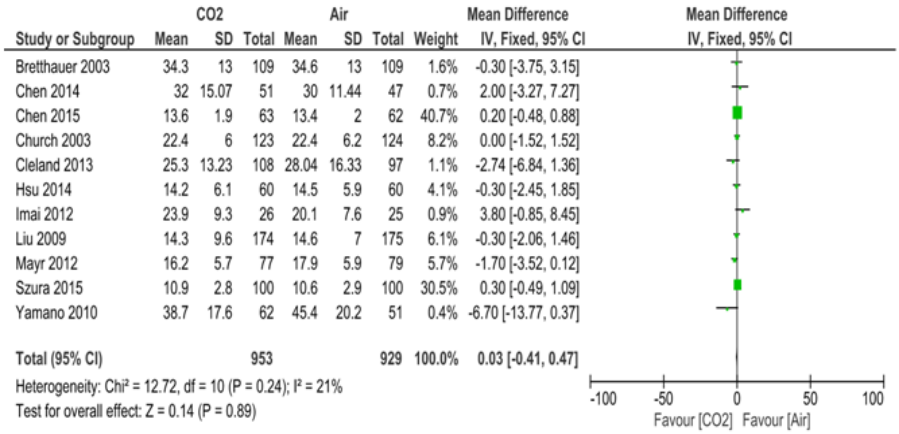

Figure 11 : Total procedure time (minutes). Forest plot

CO2 measurements after examination

The CO2 measurement (mmHg) after the examination was compared between the groups, showing no difference between the two trials included in this outcome (MD 0.23 [-2.12, 2.58]; I^2=86%) [24,34]

Discussion

The CO2 use in endoscopic examinations demonstrated that it is an efficient strategy to allow a faster absorption by the intestinal mucosa, causing less unpleasant symptoms related to the procedure [5-8].

In our systematic review, there was no difference between the CO2 insufflation group and the ambient air insufflation group in relation to pain reported during the examination. However, two meta-analysis [9,10] showed that the CO2 was associated to lower pain scores and lower pain risk during the procedure. This difference may be explained because we performed the sensibility analysis in cases of heterogeneity >50%, splitting the trials between the outcomes "pain during the colonoscopy" and "pain at the end of the colonoscopy", which was not done in the two cited meta-analyses, in addition to the inclusion of new trials.

We demonstrated that the pain risk was lower with the use of CO2 in the analysis of 1h, 3h and 6h after the examination; no clear evidence was found between the groups in the outcome of 24h. Similar results were obtained in the studies cited above, except for the 3h analysis, which was not performed.

The CO2 measurement after the procedure was compared between groups, with no significant statistical difference, which is also shown in the trials included in the systematic review by Wu et al [9]. It should be taken into account that the indirect measurements of CO2 through transcutaneous or end tidal monitoring may not be reliable. Arterial blood gases are more adequate, but not acceptable by the patients [42]. There was also no difference in relation to cecal intubation. Sajid et al [10] demonstrated that the cecum was reached faster using CO2, but our meta-analysis did not arrive at the same conclusion.

Among the strong points of our systematic review and meta-analysis, we can cite the addition of trials of high methodological quality (77% with Jadad>3), the number of involved patients and the outcomes that were not evaluated in the previous meta-analysis, such as abdominal distention, polyp detection rate, total procedure time, request for analgesia/sedation during the examination.

Among the limitations of this study, we should punctuate that the high heterogeneity of some outcomes led to the execution of sensibility analysis, modifying some results, which is not possible especially in the outcomes that involve only two studies. Examinations performed in different periods (1992-2015) with particulate clinical practices, different employed methodologies and various forms of outcome measurements are some of the reasons. The presence of analgesia/sedation, type of preparation performed, exam time related to the endoscopist experience and the volume of gas used may relate more with pain, abdominal distention and flatulence than with the type of gas used during the examination.

The cost of a CO2 insufflator varies between 7,000 and 7,400 Euros. The cost of the CO2 gas per colonoscopy is less than 1 euro [43]. Yamano et al. state that the total cost of one endoscopy increases about 2.5% with the use of CO2 [41]. Thus, the cost-benefit relationship between these two insufflation methods must be analyzed in other studies, considering the financial reality of dozens of developing countries.

Trials that evaluate the complications related to the

colonoscopy and the evolution of those patients depending on the type of gas used are very important to consolidate the CO2 in the clinical practice.

Conclusion

CO2 insufflation improves tolerance to colonoscopy, reducing pain immediately, and 1, 3 and 6 hours after the procedure. CO2 is also associated with lower pain scores and reduction of flatulence. However, there was no difference in polyp detection rate, cecal intubation and procedure time between groups.

Acknowledgments

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Declarations

Clinical Trial Registration:

N/A as this is e systematic review.

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