Is the type of insufflation a key issue in gastro-intestinal endoscopy?

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Abstract

Endoscopic procedures continue to play an emerging role in diagnosing and treating upper and lower gastrointestinal (GI) disorders. In particular, the introduction of colonoscopy in bowel cancer screening has underlined its promising role in decreasing the incidence of colorectal cancer and reducing tumour related mortality. To achieve these goals patients need to contemplate endoscopic examinations as painless and fearless procedures. The use of carbon dioxide (CO₂) as an alternative insufflation gas in comparison to air has been considered as an essential key to improving patients’ acceptance in undergoing endoscopic procedures. CO₂ is absorbed quickly through the bowel mucosa causing less luminal distension and potentially less abdominal pain. However, its exact role has not been defined completely. In particular, the beneficial use of CO₂ in upper GI endoscopy and in sedated patients is still conflicting. In the present review, we aimed to assess the current evidence for using CO₂ in endoscopy and to evaluate its potential role in the future.

INTRODUCTION

In the last decade, endoscopy has become an essential diagnostic and therapeutic instrument in daily clinical practice. As a consequence, the number of endoscopic examinations has increased continuously, in particular, as a result of constant efforts to improve patient’s acceptance and compliance to participate in bowel cancer screening programs. However, some patients still have a fear of undergoing colonoscopy, as they associate it with
considerable pain and discomfort.

A number of studies aimed to investigate how to ease abdominal symptoms in lower and upper gastrointestinal (GI) endoscopy[1]. The introduction of moderate or deep sedation has certainly been an essential step to increase its attractiveness and to reduce the anxiety and concerns of the patients[2]. Recent evidence demonstrates that sedation can be safely administered in colonoscopy without increasing the risk of respiratory or abdominal complications[3].

Another technique that has emerged in the last few years is the use of carbon dioxide (CO$_2$) as an alternative insufflation gas. CO$_2$ is rapidly absorbed by the intestinal mucosa and easily expired through the respiratory tract, with the potential advantage of reducing the duration of large bowel distension. However, there have also been concerns as whether CO$_2$ results in a raise in arterial pressure of CO$_2$ (pCO$_2$) leading to cardiac or respiratory compromise[4].

Notably, several studies revealed promising results with significantly less abdominal pain during and after endoscopic procedures by using CO$_2$ compared to air insufflation, which is still considered the standard gas to insufflate the bowel[5-7]. In addition, in upper GI endoscopy the use of CO$_2$ gas remains conflicting in the current literature and convincing evidence is still missing to warrants its routine use[8]. It is also debatable whether the use of CO$_2$ is still beneficial in patients, who are deeply sedated during the procedure.

In the present review, we aimed to assess the current evidence for the use of CO$_2$ insufflation during diagnostic and therapeutic endoscopic procedures and to define its role in the future.

**LOWER GI ENDOCOSPY**

A high number randomised controlled trials comparing endoscopic insufflation with either CO$_2$ or air were conducted in the last decade (Table 1). Interestingly, no studies to date have noted any technical disadvantages when using CO$_2$ insufflation; insertion and withdrawal times, caecal intubation rates and complication rates are comparable or even superior in favour of CO$_2$[5]. The volume of gas used has also been compared in several studies and no difference has been found when using CO$_2$ compared to air[10].

The primary outcome measure in the majority of studies was pain, as measured using a visual analogue scale (VAS). Findings have consistently shown lower pain scores when CO$_2$ insufflation was used in contrast to air, although some studies have shown a peak difference in pain score during the procedure or shortly after whereas others have shown evidence of a more delayed effect several hours after the procedure[5,11,12]. There is considerable heterogeneity between studies in the time intervals at which pain was measured.

Several studies have attempted to assess the degree of abdominal bloating objectively post procedure by assessing either the degree of colonic distension present on abdominal radiograph or the changes in waist circumference post procedure[7,11,13,14]. Findings have consistently demonstrated less distension in the group undergoing CO$_2$ insufflation. The differences were marked with very little overlap between groups. For example Sunanac found that 71% of patients had large bowel dilatation of > 6 cm 1 h after colonoscopy with air insufflation compared with only 4% in the CO$_2$ group[7].

Iida et al[15] investigated patients having CO$_2$ compared to air insufflation colonoscopies and measured their levels of salivary alpha-amylase (SAA) as an objective maker of stress[16]. SAA levels increased as a result of colonoscopy in both groups as expected but the rise was significantly higher in the air group than the CO$_2$ group. VAS scores were also measured however and there was no significant difference between the groups.

**Sedation**

Available studies used a wide range of sedation methods from no sedation to deep sedation with agents such as propofol. There has been some question as to whether the potential benefits of reduced pain with CO$_2$ insufflation may be lost when deep sedation is used. The evidence would point to the contrary however with the majority of studies showing benefits lasting beyond the time that the sedation would have worn off[5,11,16,17]. Riss et al[13] used deep sedation and observed the greatest improvement in pain scores between 15 min and 6 h post-procedure showing that there is still a potential benefit.

**Effects on screening**

Making colonoscopy more comfortable is an issue of particular concern when considering bowel cancer screening programmes where asymptomatic patients are voluntarily undergoing the procedure with no guaranteed benefit. Several studies have addressed patients’ feelings about undergoing further colonoscopies when comparing air and CO$_2$ insufflation to determine whether a more comfortable procedure would increase compliance with ongoing screening. The results showed a high level of satisfaction with the procedure, with the vast majority of patients reporting that they would be happy to go ahead with a repeat colonoscopy if necessary and would recommend it to others[5,16]. Geyer et al[17] found that overall satisfaction was slightly higher in the CO$_2$ group (9.6 vs 9.3 on a VAS) however other studies have found no significant difference between the air and CO$_2$ groups[5,13,15]. This does not strongly support the hypothesis that the use of CO$_2$ could improve compliance with screening programmes.

**CO$_2$ insufflation only during scope withdrawal**

There has been recent interest in whether using CO$_2$ insufflation only for the withdrawal phase of colonoscopy retains the same benefits of reduced pain and distension as when CO$_2$ is used for the entire procedure. Chen et al[18] and Hsu et al[19] both found that there was no difference in
Table 1  Studies comparing carbon dioxide and air insufflation in colonoscopy

| Ref. | Patients (n) | Exclusion criteria | Sedation | Findings |
|------|--------------|--------------------|----------|----------|
| Stevenson et al[6], 1992 | 56 | Previous colonic resections, children | Moderate | No difference in pain during procedure but better in CO₂ group at 6 and 24 h post AXR | 1 h - 94% trace/v little gas in CO₂ group, air 18% > 10 cm, 57% > 6 cm |
| Sumanac et al[6], 2002 | 100 | GI bleed, IBD, colectomy | Moderate | AXR at 1 h - 71% > 6 cm in air vs 4% in CO₂ group Reduced pain score at 1 and 6 h in CO₂ group |
| Breithauer et al[1], 2002 | 240 | Previous resection, malignancy, severe cardiac or respiratory disease | None | Lower pain score at all time points in CO₂ group No difference in ETCO₂ |
| Church et al[1], 2003 | 247 | None | Moderate | Lower pain score 10 min post procedure in CO₂ group but no difference during |
| Breithauer et al[1], 2005 | 103 | Severe COPD, children | Moderate /none | Lower pain in CO₂ group at 1, 3, and 6 h Higher ETCO₂ in both groups when sedated |
| Wong et al[2], 2008 | 96 | COPD, colectomy, bleeding, obstruction | Moderate | Lower pain score in CO₂ group during procedure and in first 30 min then no difference 93% CO₂ vs 98% air would have procedure again 89% CO₂ vs 96% air would recommend to others |
| Liu et al[3], 2009 | 349 | None | None | Lower pain score in CO₂ group No difference in ETCO₂ |
| Riss et al[4], 2009 | 300 | Severe COPD, children | Deep | Lower pain score in CO₂ group at 15 m, 30 m and 6 h but not during procedure 98% overall would have procedure again, no difference between groups |
| Geyer et al[5], 2011 | 109 | None | Moderate/ deep | Less pain and bloating (peak at 1 h) in CO₂ group No change in TCCO₂ |
| Yamano et al[6], 2010 | 120 | Previous resection, malignancy, severe cardiac or respiratory disease, active bleeding, obstruction | None | Lower pain score in CO₂ group |
| Mayr et al[7], 2012 | 156 | None | Moderate | No rise in TCCO₂ |
| Singh et al[8], 2012 | 142 | Previous resection | Deep | No pain in 84% of CO₂ group vs 65% of air group Higher caecal intubation rate and faster in CO₂ group |
| Diez-Redondo et al[9], 2012 | 282 | None | Moderate/ deep | Reduced pain scores in CO₂ group for first 6 h |
| Chen et al[10], 2013 | 193 | None | None | No difference in VAS Reduced salivary stress hormones in CO₂ group No difference in VAS score |
| Iida et al[11], 2013 | 100 | None | Moderate | No difference in VAS score |
| Uraoka et al[12], 2009 | 114 | Easy colonoscopies | None | Overall lower pain in CO₂ group, particularly when done by less experienced endoscopists |
| Fernández-Calderón et al[13], 2012 | 214 | None | Deep | Lower pain in CO₂ group Greater increase in waist circumference in air group |
| Lee et al[14], 2013 | 94 | None | Moderate | Greater increase in waist circumference in air group |

CO₂: Carbon dioxide; AXR: Abdominal radiograph; GI: Gastrointestinal; IBD: Inflammatory bowel disease; ETCO₂: End-tidal carbon dioxide; COPD: Chronic obstructive pulmonary disease; TCCO₂: Transcutaneous carbon dioxide; VAS: Visual analogue score.

Given that there seem to be no proven disadvantages in using CO₂ for the entire procedure it is unclear what advantage would be offered by using air for insertion then changing to CO₂ mid-procedure. One would assume that using two insufflation systems for each patient would have negative implications in terms of both time and cost.

**Upper GI Endoscopy, Endoscopic Retrograde Cholangiopancreatography and Endoscopic Resection Procedures**

There is increasing interest in the use of CO₂ insufflation in gastric and oesophageal endoscopic submucosal resection procedures as well as endoscopic retrograde cholangiopancreatography (ERCP) where lengthy procedures may be necessary and abdominal pain from small bowel distension may be significant. There have been no studies looking at CO₂ insufflation solely for gastroscopy without endoscopic surgery, ERCP or consecutive colonoscopy, presumably because post procedural pain is less of a problem than with colonoscopy.

A meta-analysis of 7 high quality RCTs (including a total of 756 patients) comparing CO₂ to air insufflation in ERCP was carried out by Shi et al[15]. The authors found that there was a significant reduction in abdominal pain at 1, 3 and 6 h post procedure when CO₂ was used although at 24 h there was no significant difference. There was no difference in the procedure time but a
borderline reduction in complications was found in the CO₂ group (pooled OR = 0.51; 95%CI: 0.27-0.97, \( P = 0.04 \)). Further similar meta-analyses have been carried out by Cheng et al[30] and Wu et al[31] (Table 2) with similar findings[21,22]. There may be particular advantages for less experienced endoscopists when using CO₂ insufflation as small bowel distension can make the procedure technically more difficult: Muraki et al[23] used physiological parameters and complications as outcome measures when ERCP was being carried out by non-expert endoscopists and found that although pCO₂ rose to a median peak of 39 mmHg, this was acceptable and easily controllable and there was little correlation with procedure time. In patients undergoing sedated colonoscopy, particularly in deep sedation, an increase in CO₂ has been found during the procedure but this was equally true for both air and CO₂ groups and was likely to be due to respiratory depression due to sedation rather than the reabsorption of CO₂ from the colon[24]. One potential limitation of many of these studies is the unreliability of indirect CO₂ measurement with transcutaneous or end tidal CO₂ measurement. Serial arterial blood gases may be more accurate but it was felt that this would be unacceptable to patients and therefore has not been widely used in studies so far.

### SAFETY CONCERNS

There have been established concerns that the use of CO₂ insufflation may increase the systemic partial pCO₂ and put strain on the respiratory system in trying to eliminate this. Hypercapnia can have a range of physiological effects in addition to respiratory stimulation including direct and indirect effects (via stimulation of the sympathetic nervous system). Predominantly the effects are cardiovascular, including peripheral vasoconstriction and tachycardia, and neurological, including confusion and reduced consciousness. For this reason the majority of RCTs have excluded large groups of patients such as those with cardiac or respiratory disease, those taking opiate analgesia and those known to have high baseline pCO₂ levels. Several studies have attempted to quantify the effects on blood CO₂ by measuring this either transcutaneously, with end-tidal CO₂ or blood sampling[16,27].

Brethauer found no difference in ETCO₂ in unsedated patient undergoing colonoscopy, in fact CO₂ levels fell during the procedure in both groups[25]. In patients undergoing sedated colonoscopy, particularly in deep sedation, an increase in CO₂ has been found during the procedure but this was equally true for both air and CO₂ groups and was likely to be due to respiratory depression due to sedation rather than the reabsorption of CO₂ from the colon[26]. One potential limitation of many of these studies is the unreliability of indirect CO₂ measurement with transcutaneous or end tidal CO₂ measurement. Serial arterial blood gases may be more accurate but it was felt that this would be unacceptable to patients and therefore has not been widely used in studies so far.

For ERCP, safety data was analyzed in three of the RCTs. In two studies using sedation there was no difference in pCO₂ between the two groups but in a single study which carried out ERCP under general anaesthetic with endotracheal intubation there were significantly higher pCO₂ levels in the CO₂ insufflation group, although this was easily compensated for by hyperventilation[29,31]. All RCTs excluded patients with COPD although some only excluded patients with severe COPD evidenced by known CO₂ retention or use of home oxygen. The rise in CO₂ in patients having ERCP under general anaesthetic may be of concern as it implies that patients probably hyperventilate to some degree to remove the extra CO₂. When they were anaesthetized this didn’t happen and CO₂ rose. In patients with significant respiratory disease it may be that they are not able to cope with this compensation but only small numbers of patients have been studied so far.

Suzuki et al[28] monitored the arterial pCO₂ in 100 patients undergoing prolonged CO₂ insufflation for endoscopic submucosal dissection under general anaesthesia and found that although pCO₂ rose to a median peak of 39 mmHg, this was acceptable and easily controllable and there was little correlation with procedure time. There was no air group for comparison. Takano et al[25]...
carried out a crossover trial and found no difference in pCO₂ when air or CO₂ insufflation was being used.

So far the majority of studies have found no significant increase in pCO₂ in patients undergoing endoscopy with CO₂ insufflation compared to air insufflation. Although CO₂ insufflation has been shown to be safe in all studies to date, the exclusion of patients with respiratory disease in many studies means that these results cannot be applied to all patient groups and the participants are not representative of a screening population. Later studies have addressed this by removing any exclusion criteria. Geyer found that there was no significant rise above normal CO₂ levels in an unselected population[3]. Changing over to use CO₂ as standard for endoscopy would mean using this in high risk groups where less safety data is available but there is no evidence so far to suggest that exclusion of particular patient groups is necessary.

Current sedation and monitoring guidelines are summarized by Lichtenstein et al.[1]. They advocate the use of opioids and benzodiazepine for moderate sedation and monitoring with clinical observation, pulse oximetry and non-invasive blood pressure measurement. The use of capnography or other advanced monitoring was not advocated for patients undergoing moderate sedation. In “low risk” patients as included in most studies there were not significant problems with hypcapnia therefore this level of monitoring is likely to be adequate. In “high risk” patients more at risk of hypcapnia or respiratory complications further monitoring could be considered due to the current paucity of evidence in this population.

COST ANALYSIS

Yamano et al.[2] estimated that the use of CO₂ in their unit increased the cost of each colonoscopy by 2.5%. This cost estimation was related to the gas used and the initial cost of a CO₂ insufflation system also needs to be taken into account by units considering changing to CO₂ rather than air insufflation. This may be offset in the longer term by less use of sedation, potentially shorter stays following the procedure and a lower readmission rate.

A cost analysis was carried out as part of the meta-analysis by Cheng et al.[3] comparing air and CO₂ insufflation in ERCP. They analysed equipment, hospital, radiology and physician costs and found no significant cost difference between the two methods.

CONCLUSION

In the light of available RCT’s and subsequent meta-analyses, several conclusions can be drawn with potential clinical relevance. The use of CO₂ in colonoscopy has significant advantages compared to air insufflation. Especially, abdominal pain and bloating during and after the procedure were reduced in the CO₂ insufflation group in the vast majority of published studies. Notably, this positive effect was also detectable in patients, who were deeply sedated during endoscopy. The question of whether CO₂ insufflation results in improved patient satisfaction was found to be controversial, however, it is assumable that patients with less pain also tend to repeat or recommend colonoscopy more likely. The concern that CO₂ increases the risk of complications due to elevated systemic partial pressure of CO₂ has not been studied intensively, but recent data support its widespread use in an unselected population.

In contrast, the use of CO₂ in upper GI endoscopy is not clearly defined and further well designed studies are mandatory to assess it exact role in this field.

REFERENCES

1. Leung FW. Methods of reducing discomfort during colonoscopy. Dig Dis Sci 2008; 53: 1462-1467 [PMID: 17999189 DOI: 10.1007/s10620-007-0225-9]
2. Rex DK. Review article: moderate sedation for endoscopy: sedation regimens for non-anesthesiologists. Aliment Pharmacol Ther 2006; 24: 163-171 [PMID: 16842446 DOI: 10.1111/j.1365-2036.2006.02986.x]
3. Rex DK, Overley C, Kinser K, Coates M, Lee A, Goodwine BW, Strahl E, Lemler S, Sipe B, Rahmani E, Helper D. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. Am J Gastroenterol 2002; 97: 1159-1163 [PMID: 12014721 DOI: 10.1111/j.1572-0241.2002.05683.x]
4. Price HL. Effects of carbon dioxide on the cardiovascular system. Anesthesiology 1960; 21: 652-663 [PMID: 13737968]
5. Riss S, Akan B, Mikola B, Rieder E, Karner-Hanusch J, Dirle 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: 464-468 [PMID: 19657610 DOI: 10.1007/s00508-009-1202-y]
6. Singh R, Neo EN, Nordeen N, Shammuganathan 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: 3250-3253 [PMID: 22783048 DOI: 10.3748/wjg.v18.i25.3250]
7. Sumanac K, Zealley J, 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: 190-194 [PMID: 12145595]
8. Wang WL, Wu ZH, Sun Q, Wei JF, Chen XF, Zhou DK, Zhou L, Xie HY, Zheng SS. Meta-analysis: the use of carbon dioxide insufflation vs. room air insufflation for gastrointestinal endoscopy. Aliment Pharmacol Ther 2012; 35: 1145-1154 [PMID: 22452652 DOI: 10.1111/j.1365-2036.2012.05078.x]
9. Wu J, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. Endoscopy 2012; 44: 128-136 [PMID: 22271023 DOI: 10.1055/s-0031-1291487]
10. Breflhauser M, Hoff GS, Thiis-Evensen E, Huppertz-Hauss G, Skovlund E. Air and carbon dioxide volumes insufflated during colonoscopy. Gastrointest Endosc 2003; 58: 203-206 [PMID: 12672966 DOI: 10.1016/S0016-5107(03)01431-4]
11. Stevenson GW, Wilson JA, Wilkinson J, Norman G, Goodacre RL. Pain following colonoscopy: elimination with carbon dioxide. Gastrointest Endosc 1992; 38: 564-567 [PMID: 1397911]
12. Wong JC, Yau KK, Cheung HY, Wong DC, Chung CC, Li MK. Towards painless colonoscopy: a randomized controlled trial on carbon dioxide-insufflating colonoscopy.
Intracolonic pressure results during colonoscopy were analyzed by salivary stress markers. Reducing the discomfort due to colonoscopy as objectively analyzed by salivary stress markers suggests that gas insufflation reduces the discomfort due to colonoscopy as objectively analyzed by salivary stress markers.
Edmundowicz SA. Carbon dioxide insufflation during ERCP for reduction of postprocedure pain: a randomized, double-blind, controlled trial. *Gastrointest Endosc* 2009; 70: 278-283 [PMID: 1952621 DOI: 10.1016/j.gie.2008.12.050]

Kuwatani M, Kawakami H, Hayashi T, Ishiwatari H, Kudo T, Yamato H, Ehira N, Haba S, Eto K, Kato M, Asaka M. Carbon dioxide insufflation during endoscopic retrograde cholangiopancreatography reduces bowel gas volume but does not affect visual analogue scale scores of suffering: a prospective, double-blind, randomized, controlled trial. *Surg Endosc* 2011; 25: 3784-3790 [PMID: 21656688 DOI: 10.1007/s00464-011-1789-8]

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