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TOPIC HIGHLIGHT

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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 (CO_2) as an alternative insufflation gas in comparison to air has been considered as an essential key to improving patients' acceptance in undergoing endoscopic procedures. CO_2 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 CO_2 in upper GI endoscopy and in sedated patients is still conflicting. In the present review, we aimed to assess the current evidence for using CO_2 in endoscopy and to evaluate its potential role in the future.

Key words: Gastrointestinal endoscopy; Colonoscopy; Endoscopic retrograde cholangiopancreatography; Insufflation gas; Carbon dioxide

Core tip: With the increasing use of gastrointestinal endoscopy, especially for screening in an asymptomatic population, increasing the tolerability of the procedure is of paramount importance. Our review summarizes evidence that carbon dioxide (CO_2) insufflation can reduce both pain and bloating in colonoscopy and endoscopic retrograde cholangiopancreatography although the evidence in gastroscopy is still lacking. Despite established safety concerns about hypercapnia, significant harm has never been demonstrated in the literature. Patients thought to be at higher risk of hypercapnia need to be included in more studies to demonstrate that CO_2 insufflation is safe in an unselected screening population but early evidence is encouraging.

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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 ENDOSCOPY

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[9]. 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[7,11,12]. 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 Sumanac 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[15]. 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[5,7,11,16,17]. Riss *et al*[5] 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[5,12]. 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[5,12,17]. 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*[11], 1992	56	Previous colonic resections, children	Moderate	No difference in pain during procedure but better in CO_2 group at 6 and 24 h post AXR at 1 h - 94% trace/v little gas in CO_2 group, air 18% > 10 cm, 57% > 6 cm
Sumanac *et al*[7], 2002	100	GI bleed, IBD, colectomy	Moderate	AXR at 1 h - 71% > 6 cm in air *vs* 4% in CO_2 group Reduced pain score at 1 and 6 h in CO_2 group
Bretthauer *et al*[16], 2002	240	Previous resection, malignancy, severe cardiac or respiratory disease	None	Lower pain score at all time points in CO_2 group No difference in $ETCO_2$
Church *et al*[33], 2003	247	None	Moderate	Lower pain score 10 min post procedure in CO_2 group but no difference during
Bretthauer *et al*[34], 2005	103	Severe COPD, children	Moderate /none	Lower pain in CO_2 group at 1, 3, and 6 h Higher $ETCO_2$ in both groups when sedated
Wong *et al*[12], 2008	96	COPD, colectomy, bleeding, obstruction	Moderate	Lower pain score in CO_2 group during procedure and in first 30 min then no difference 93% CO_2 *vs* 98% air would have procedure again 89% CO_2 *vs* 96% air would recommend to others
Liu *et al*[35], 2009	349	None	None	Lower pain score in CO_2 group No difference in $ETCO_2$
Riss *et al*[5], 2009	300	Severe COPD, children	Deep	Lower pain score in CO_2 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*[17], 2011	109	None	Moderate/ deep	Less pain and bloating (peak at 1 h) in CO_2 group No change in $TCCO_2$
Yamano *et al*[27], 2010	120	Previous resection, malignancy, severe cardiac or respiratory disease, active bleeding, obstuction	None	Lower pain score in CO_2 group
Mayr *et al*[36], 2012	156	None	Moderate	No rise in $TCCO_2$ No pain in 84% of CO_2 group *vs* 65% of air group
Singh *et al*[6], 2012	142	Previous resection	Deep	Higher caecal intubation rate and faster in CO_2 group Less discomfort in CO_2 group
Díez-Redondo *et al*[37], 2012	282	None	Moderate/ deep	Reduced pain scores in CO_2 group for first 6 h
Chen *et al*[18], 2013	193	None	None	No difference in VAS
Iida *et al*[15], 2013	100	None	Moderate	Reduced salivary stress hormones in CO_2 group No difference in VAS score
Uraoka *et al*[38], 2009	114	Easy colonoscopies	None	Overall lower pain in CO_2 group, particularly when done by less experienced endoscopists
Fernández-Calderón *et al*[13], 2012	214	None	Deep	Lower pain in CO_2 group Greater increase in waist circumference in air group
Seo *et al*[14], 2013	94	None	Moderate	Less pain in CO_2 group Greater increase in waist circumference in air group

CO_2: Carbon dioxide; AXR: Abdominal radiograph; GI: Gastrointestinal; IBD: Inflammatory bowel disease; $ETCO_2$: End-tidal carbon dioxide; COPD: Chronic obstructive pulmonary disease; $TCCO_2$: Transcutaneous carbon dioxide; VAS: Visual analogue score.

pain score when CO_2 was used only for withdrawal[18,19].

Given that there seem to be no proven disadvantages in using CO_2 for the entire procedure it is unclear what advantage would be offered by using air for insertion then changing to CO_2 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 CO_2 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 CO_2 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 CO_2 to air insufflation in ERCP was carried out by Shi *et al*[20]. The authors found that there was a significant reduction in abdominal pain at 1, 3 and 6 h post procedure when CO_2 was used although at 24 h there was no significant difference. There was no difference in the procedure time but a

Table 2 Summary of studies comparing the type of insufflation in endoscopic retrograde cholangiopancreatography

Ref.	Patients (*n*)	Exclusion criteria	Sedation	Findings
Bretthauer *et al*[29], 2007	118	COPD with known CO_2 retention	Moderate	Less pain up to 24 h in CO_2 group Increased $TCCO_2$ equally in both groups while under sedation
Maple *et al*[39], 2009	105	COPD, pre-procedure abdominal pain	Deep	Less pain at 1 h CO_2 group, no difference at 24 h
Dellon *et al*[30], 2010	78	COPD on home O_2, known CO_2 retention or opiate use	Moderate	Fewer adverse events in CO_2 group No difference in pain scores Increased $TCCO_2$ equally in both groups while under sedation
Kuwatani *et al*[40], 2011	80	COPD, pre-procedure abdominal pain	Deep	No difference in pain scores
Luigiano *et al*[31], 2011	110	COPD, pre-procedure abdominal pain	General anaesthesia	Less pain at 1, 3 and 6 h in CO_2 group, no difference at 24 h Higher $TCCO_2$ in CO_2 group but easily compensated for with hyperventilation
Muraki *et al*[23], 2012	208	COPD	Deep	Less evidence of physiological stress in CO_2 group Borderline lower complications in CO_2 group

COPD: Chronic obstructive pulmonary disease; CO_2: Carbon dioxide; $TCCO_2$: Transcutaneous carbon dioxide.

borderline reduction in complications was found in the CO_2 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*[21] and Wu *et al*[22] (Table 2) with similar findings[21,22]. There may be particular advantages for less experienced endoscopists when using CO_2 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 CO_2 insufflation resulted in less physiological stress and borderline lower complications when compared to air.

Only a small number of studies have investigated the use of CO_2 insufflation for endoscopic resection procedures so far. The majority have concentrated on safety rather than pain scores[24,25]. Maeda *et al*[26] found that there was less gas present in the GI tract (assessed on CT scan) after CO_2 insufflation but no difference in VAS scores or complication rates.

SAFETY CONCERNS

There have been established concerns that the use of CO_2 insufflation may increase the systemic partial pCO_2 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 pCO_2 levels. Several studies have attempted to quantify the effects on blood CO_2 by measuring this either transcutaneously, with end-tidal CO_2 or blood sampling[16,27].

Bretthauer found no difference in $ETCO_2$ in unsedated patient undergoing colonoscopy, in fact CO_2 levels fell during the procedure in both groups[16]. In patients undergoing sedated colonoscopy, particularly in deep sedation, an increase in CO_2 has been found during the procedure but this was equally true for both air and CO_2 groups and was likely to be due to respiratory depression due to sedation rather than the reabsorption of CO_2 from the colon[28]. One potential limitation of many of these studies is the unreliability of indirect CO_2 measurement with transcutaneous or end tidal CO_2 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 pCO_2 between the two groups but in a single study which carried out ERCP under general anaesthetic with endotracheal intubation there were significantly higher pCO_2 levels in the CO_2 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 CO_2 retention or use of home oxygen. The rise in CO_2 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 CO_2. When they were anaesthetized this didn't happen and CO_2 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*[24] monitored the arterial pCO_2 in 100 patients undergoing prolonged CO_2 insufflation for endoscopic submucosal dissection under general anaesthesia and found that although pCO_2 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 pCO_2 when air or CO_2 insufflation was being used.

So far the majority of studies have found no significant increase in pCO_2 in patients undergoing endoscopy with CO_2 insufflation compared to air insufflation. Although CO_2 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 CO_2 levels in an unselected population[17]. Changing over to use CO_2 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*[32]. They advocate the use of opiates 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 hypercapnia therefore this level of monitoring is likely to be adequate. In "high risk" patients more at risk of hypercapnia or respiratory complications further monitoring could be considered due to the current paucity of evidence in this population.

COST ANALYSIS

Yamano *et al*[27] estimated that the use of CO_2 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 CO_2 insufflation system also needs to be taken into account by units considering changing to CO_2 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*[21] comparing air and CO_2 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 CO_2 in colonoscopy has significant advantages compared to air insufflation. Especially, abdominal pain and bloating during and after the procedure were reduced in the CO_2 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 CO_2 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 CO_2 increases the risk of complications due to elevated systemic partial pressure of CO_2 has not been studied intensively, but recent data support its widespread use in an unselected population.

In contrast, the use of CO_2 in upper GI endoscopy is not clearly defined and further well designed studies are mandatory to assess it exact role in this field.

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