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Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation

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Abstract
Background It is well known that carbon dioxide (CO_2) is absorbed faster in the body than air and also that it is rapidly excreted through respiration. This study aimed to investigate the safety of CO_2 insufflation used for esophageal and gastric endoscopic submucosal dissection (ESD) in patients under deep sedation.
Methods Patients with either early gastric or esophageal cancers that could be resected by ESD were enrolled in this study from March 2007 to July 2008 and randomly assigned to undergo ESD procedures with CO_2 insufflation (CO_2 group) or air insufflation (air group). A TOSCA measurement system and TOSCA 500 monitor were used to measure and monitor both transcutaneous partial pressure of CO_2 ($PtcCO_2$) and oxygen saturation (SpO_2).
Results The study enrolled 89 patients and randomly assigned them to a CO_2 group (45 patients) or an air group (44 patients). The mean CO_2 group versus air group measurements were as follows: $PtcCO_2$ (49.1 ± 5.0 vs. 50.1 ± 5.3 mmHg; nonsignificant difference [NS]), maximum $PtcCO_2$ (55.1 ± 6.5 vs. 56.8 ± 7.0 mmHg; NS), $PtcCO_2$ elevation (9.1 ± 5.4 vs. 11.4 ± 5.6 mmHg; $p = 0.054$), SpO_2 (99.0 ± 0.7% vs. 99.0 ± 1.0%; NS), minimum SpO_2 (96.5 ± 2.4% vs. 95.4 ± 3.3%; $p = 0.085$), and SpO_2 depression (2.4 ± 2.3% vs. 3.3 ± 2.9%; NS). The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in $PtcCO_2$ elevation and minimum SpO_2.
Conclusions The findings demonstrated CO_2 insufflation to be as safe as air insufflation for upper gastrointestinal tract ESDs performed for patients under deep sedation without evidencing any adverse effects.

Keywords Carbon dioxide insufflation · Deep sedation · Endoscopic submucosal dissection · Transcutaneous partial pressure of carbon dioxide · Upper gastrointestinal tract

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Several recent studies investigating colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) have reported that carbon dioxide (CO_2) insufflation reduces abdominal pain and discomfort caused by bowel hyperextension and can be used as safely as air insufflation [1–6]. It is well known that CO_2 is absorbed faster in the body than air and that it also is rapidly excreted through respiration unless some type of pulmonary dysfunction exists [1, 2]. To date, almost all endoscopic procedures have been performed using air insufflation, although it has led to some problems of abdominal pain and discomfort in routine examinations and perforation-related subcutaneous or mediastinal emphysema and pneumoperitoneum in endoscopic treatments [7, 8].

With the relatively recent development and increasingly widespread use of endoscopic submucosal dissection (ESD) as a minimally invasive treatment, performance of ESD for early gastrointestinal (GI) neoplasm in the esophagus, stomach, and colorectum has increased dramatically [9–16]. Quite naturally, the number of complications also has increased as a direct result, including perforations that occur during the technically difficult ESD procedure itself and the delayed bleeding experienced afterward [7, 8, 14, 17, 18]. In fact, the reported ESD perforation rate is 7% for cases involving the esophagus, 4% for cases involving the stomach, and 5% for cases involving the colorectum [10, 14, 15]. Perforation can cause peritonitis and mediastinitis, and possibly also thromboembolism due to blood flow congestion (compartment syndrome) when significant pneumatic leakage results in excess internal pressure [19–24]. It is anticipated that such associated problems will be minimized by further use of CO_2 insufflation.

Colonoscopy with conscious sedation and the use of CO_2 insufflation has become more generally accepted since the demonstration of the safety and effectiveness of CO_2 insufflation in a previously published reported [5]. We previously conducted a case–control study that showed CO_2 insufflation to be both safe and effective for colorectal ESD with conscious sedation [25]. However, the safety of CO_2 insufflation has not been established for upper GI tract endoscopic treatment such as ESD with deep sedation in which CO_2 retention and decreased oxygenation are more important factors than in colonoscopy performed with conscious sedation.

This study aimed to investigate the safety of CO_2 insufflation for esophageal and gastric ESDs with deep sedation. Both operations are lengthy procedures.

Materials and methods

Patients

We prospectively assessed the safety of CO_2 insufflation for upper GI tract ESDs performed with the patient under deep sedation compared with air insufflation from March 2007 to July 2008 at the National Cancer Center Hospital (NCCH) in Tokyo, Japan. The study enrolled 89 patients with either early gastric or esophageal cancer that could be resected by ESD and randomly assigned them to undergo ESD procedures with CO_2 insufflation (CO_2 group) or air insufflation (air group).

The study excluded patients with severe pulmonary disease including either chronic obstructive pulmonary disease (COPD) or disease resulting in less than 80% of vital capacity (%VC) or less than 70% of the forced expiratory volume in 1 s as a percentage of the forced vital capacity (FEV1%), patients with severe cardiovascular disease including NYHA III or IV heart failure or arrhythmia with any treatment history, patients with hepatic or renal dysfunction, and patients with a change in insufflation methods from CO_2 to air or from air to CO_2 for any reason during their ESDs.

Endoscopic procedures

All ESD procedures were performed with Olympus video endoscopes and a standard videoendoscope system (EVIS LUCERA; Olympus Optical Co., Ltd., Tokyo, Japan). For ESD procedures, an insulation-tipped diathermic knife (IT-knife; Olympus) was used from March to October 2007 and an improved IT-knife (IT-knife 2; Olympus) from November 2007 to July 2008 [11, 26, 27].

First, marking dots were made around the lesion using a needleknife (Olympus). This was followed by injection of diluted epinephrine with normal saline (1:200,000) to lift the submucosal layer and allow the tip of the IT-knife or IT-knife 2 to be inserted into the submucosal layer. A small initial incision then was made by a needleknife, and a complete circumferential mucosal incision around the periphery of the marking dots was performed with the IT-knife or IT-knife 2. After an additional submucosal injection, the submucosal layer beneath the lesion was directly dissected using the same IT-knife or IT-knife 2.

Although all ESDs were generally performed in this manner, we sometimes used not only other devices such as an argon plasma coagulation probe for the marking dots and a bipolar needleknife (B-knife; XEMEX Co., Tokyo, Japan) for the initial incision and submucosal dissection [15, 28], but also another injection solution, sodium hyaluronate (MucoUp; Johnson & Johnson Co., Ltd., Tokyo, Japan) diluted with normal saline (1:1), especially for esophageal ESDs [12, 29–31]. The final objective was to achieve successful en bloc resections for precise pathologic evaluations.

Patients received midazolam, propofol, or both for deep sedation, and oxygen (O_2) was administered nasally (2 l/min) during ESD. Initially, 3–5 mg of midazolam was used for induction of venous anesthesia, with an additional 1–3 mg given repeatedly as necessary based on the judgment of the individual endoscopist. Propofol was administered initially at a dosage of 20 mg for induction, with another 0.1–0.5 mg/kg/h given continuously for maintenance depending on the condition of the patient.

CO_2 insufflation and transcutaneous measurements

A CO_2 regulator prototype (Olympus) connected to a CO_2 bottle was used for CO_2 insufflation until the Olympus UCR (Fig. 1) became commercially available in Japan in May 2008 [25]. During the procedure, CO_2 insufflation was set at a constant rate of 1.2 l/min, which is a moderate level. In upper GI endoscopy, the UCR has three insufflation levels, which can be controlled by the use of three types of connecting tubes. These insufflation amounts are almost equivalent to the original three regulation levels of the EVIS LUCERA (Olympus).

Measurement of the arterial partial pressure of CO_2 (partial pressure of carbon dioxide [PCO_2] and arterial partial pressure of carbon dioxide [$PaCO_2$]) is an invasive, intermittent, and unpleasant process widely used for

Fig. 1 UCR (CO_2 regulator). The UCR in upper gastrointestinal endoscopy has three levels of insufflation which can be controlled by using three types of connecting tubes. These amounts of insufflation are almost equivalent to the original three regulation levels of the EVIS LUCERA

Fig. 2 The TOSCA measurement system and TOSCA 500 monitor, a noninvasive and continuous monitoring device for transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) that takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe

various patients as the gold standard, but determining the variation of $PaCO_2$ during ESD using CO_2 insufflation has proved to be quite difficult.

In this study, a TOSCA measurement system and TOSCA 500 monitor (Linde Medical Sensors, Basel, Switzerland) (Fig. 2) was used to measure and monitor both transcutaneous partial pressure of CO_2 ($PtcCO_2$) and oxygen saturation (SpO_2). This system, which takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe, is a noninvasive, continuous, trend-monitoring device for $PtcCO_2$ reported in several studies to provide general agreement between $PtcCO_2$ and $PaCO_2$ measurements [32–37]. We used a default temperature setting of 42°C for the earlobe sensor and recalibrated the TOSCA system to minimize the possibility of measurement error before each ESD. Procedure time was measured from endoscope insertion to its completed withdrawal after ESD, with $PtcCO_2$ and SpO_2 recorded every 3 s for both groups using the TOSCA system.

Statistical analysis

All variables in this study were described in terms of mean ± standard deviation as well as median and range. We used chi-square and *t*-tests to compare baseline characteristics and measurements between the two groups. All statistical analyses were performed using the SAS Statistical Package (SAS Institute, Tokyo, Japan), and a p value less than 0.05 was considered statistically significant.

Ethics

The ethics committee at NCCH approved the study protocol, and written informed consent was obtained from all patients before they were enrolled in the study.

Results

No significant differences in patient characteristics between the two groups were observed (Table 1). The CO_2 group study consisted of 45 patients (39 men and 6 women) with 52 lesions. These 45 patients (involving 15 esophageal and 30 gastric ESD cases) had a mean age of 68.5 ± 8.8 years (range, 50–84 years). The air group consisted of 44 patients (38 men and 6 women) with 51 lesions. These 44 patients (involving 12 esophageal and 32 gastric ESD cases) had a mean age of 67.6 ± 8.0 years (range, 43–84 years).

The macroscopic types of tumors included 13 elevated lesions, 32 flat and depressed lesions, 6 combined lesions, and 1 residual lesion in the CO_2 group and 11 elevated lesions, 34 flat and depressed lesions, 5 combined lesions, and 1 residual lesion in the air group (nonsignificant difference [NS]). In the CO_2 group, the median size of the tumors, determined histopathologically, was 13 mm (range, 5–60 mm), and the 35 adenocarcinomas included 2 Barrett's carcinomas, 15 squamous cell carcinomas (SCCs), and 2 adenomas. The median size of the tumors in the air group was 19 mm (range, 5–55 mm), and the 37 adenocarcinomas included 2 Barrett's carcinomas, 13 SCCs, and 1 adenoma. The difference between the two groups was not significant. The median specimen size was 35 mm (range, 20–75 mm) in the CO_2 group and 35 mm (range, 20–68 mm) in the air group (NS). The median procedure time was 115 min (range, 30–575 min) in the CO_2 group and 96 min (range, 38–309) in the air group (NS). Midazolam was received by 30 patients at a median

Table 1 Patient characteristics

	CO_2 (*n*)	Air (*n*)	*p* Value
Patients/lesions	45/52	44/51	
Mean age (years)	68.5 ± 8.8	67.6 ± 8.0	NS
Male/female	39/6	38/6	NS
Esophagus/stomach	15/30	12/32	NS
Macroscopic type			
Elevated	13	11	
Flat and depressed	32	34	
Combined	6	5	
Residual	1	1	NS
Histopathologic type			
SCC	15	13	
Adenocarcinoma	35	37	
Adenoma	2	1	NS
Median tumor size: mm (range)	13 (5–60)	19 (5–55)	NS
Median specimen size: mm (range)	35 (20–75)	35 (20–68)	NS
Median procedure time: min (range)	115 (30–575)	90 (38–309)	NS
Perforations	3	0	NS
Patients receiving midazolam	30	31	NS
Patients receiving propofol	15	13	NS
Dosage of midazolam: mg (range)	12 (5–20)	12 (4–23)	NS
Dosage of propofol: mg (range)	640 (130–2460)	370 (180–1116)	NS

CO_2 carbon dioxide, *NS* not significant, *SCC* squamous cell carcinoma

dosage of 12 mg (range, 5–20 mg) in the CO_2 group and by 31 patients at a median dosage of 12 mg (range, 4–23 mg) in the air group (NS), and propofol was received by 15 patients at a median dosage of 640 mg (range, 130–2,460 mg) in the CO_2 group and by 13 patients at a median dosage of 370 mg (range, 180–1,116) in the air group (NS).

All the tumors were resected en bloc by ESD except in one esophageal case in the air group, In this case, the patient's main lesion was resected en bloc by ESD, whereas another smaller synchronous lesion was treated by using endoscopic mucosal resection (EMR) with a cap-fitted panendoscope, resulting in a piecemeal resection [38].

Measurements of $PtcCO_2$ and SpO_2

The mean CO_2 group versus air group measurements were as follows: $PtcCO_2$ (49.1 ± 5.0 vs. 50.1 ± 5.3 mmHg; NS), maximum $PtcCO_2$ (55.1 ± 6.5 vs. 56.8 ± 7.0 mmHg; NS), $PtcCO_2$ elevation (9.1 ± 5.4 vs. 11.4 ± 5.6 mmHg; $p = 0.054$), SpO_2 (99.0 ± 0.7% vs. 99.0 ± 1.0%; NS), minimum SpO_2 (96.5 ± 2.4% vs. 95.4 ± 3.3%; $p = 0.085$), and SpO_2 depression (2.4 ± 2.3% vs. 3.3 ± 2.9%; NS) (Table 2; Fig. 3A–F). The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but in $PtcCO_2$ elevation and minimum SpO_2, the CO_2 group was better than the air group.

The patient characteristics did not differ significantly between the two groups when esophageal and gastric ESD cases were considered separately, nor did the $PtcCO_2$ and SpO_2 measurements differ significantly between the two groups when only esophageal ESD cases were considered. The CO_2 group versus air group measurements in gastric ESD cases were as follows: $PtcCO_2$ elevation (8.0 ± 5.2 vs. 10.8 ± 5.7 mmHg; $p = 0.049$) and SpO_2 depression (1.9 ± 1.8% vs. 2.8 ± 2.5%; $p = 0.087$). Although the $PtcCO_2$ and SpO_2 measurements again were similar for the two groups, when only gastric ESD cases were considered, the CO_2 group was better than the air group in $PtcCO_2$ elevation and SpO_2 depression.

Table 2 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and oxygen saturation (SpO_2) measurements

	CO_2	Air	*p* Value
Mean $PtcCO_2$ (mmHg)	49.1 ± 5.0	50.1 ± 5.3	NS
Maximum $PtcCO_2$ (mmHg)	55.1 ± 6.5	56.8 ± 7.0	NS
$PtcCO_2$ elevation (mmHg)	9.1 ± 5.4	11.4 ± 5.6	0.054
Mean SpO_2 (%)	99.0 ± 0.7	99.0 ± 1.0	NS
Minimum SpO_2 (%)	96.5 ± 2.4	95.4 ± 3.3	0.085
SpO_2 depression (%)	2.4 ± 2.3	3.3 ± 2.9	NS

NS not significant

Five CO_2 group patients and five air group patients experienced a maximum $PtcCO_2$ exceeding 60 mmHg that continued for more than 5 min (NS). The median duration time was 12 min (range, 6–166 min) for the CO_2 group and 35 min (range, 10–148 min) for the air group (NS). The

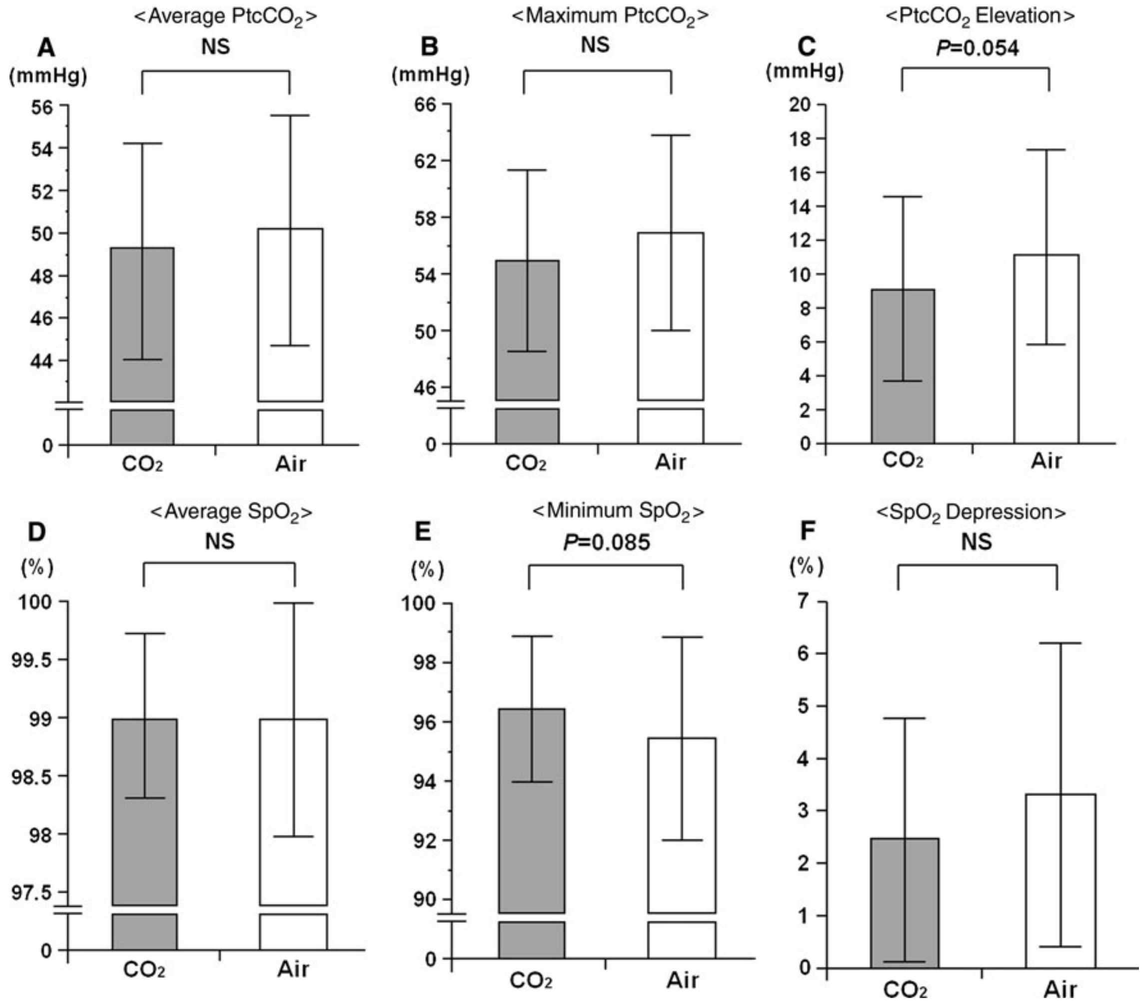

Fig. 3 Transcutaneous partial pressure of carbon dioxide (PtcCO_2) and oxygen saturation (SpO_2) measurements. The PtcCO_2 and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in PtcCO_2 elevation and minimum SpO_2

maximum PtcCO_2 was 72 mmHg in the CO_2 group and 74 mmHg in the air group (NS) (Table 3). None of the cases in either group involved an SpO_2 level lower than 90% that continued for more than 1 min, and no harmful oxygenation effects occurred. Temporary SpO_2 depression lower than 90% for less than 1 min resulted from the aspiration of two patients in the air group, but the condition subsequently improved and did not impair treatment (Table 3).

Table 3 Maximum transcutaneous partial pressure of carbon dioxide (PtcCO_2) and minimum oxygen saturation (SpO_2)

	CO_2 ($n = 45$)	Air ($n = 44$)	p Value
Maximum PtcCO_2 >60 mmHg[a]	5	5	NS
Median duration: min (range)	12 (6–166)	35 (10–148)	NS
Maximum PtcCO_2 (mmHg)	72	74	–
Minimum SpO_2 <90%[b]	0	0	NS
Median duration: min (range)	–	–	–
Minimum SpO_2 (%)	91	88	–

[a] >5-min duration

[b] >1-min duration

No adverse effects were caused by CO_2 insufflation in the CO_2 group. Perforations involving CO_2 insufflation occurred in three cases including two esophageal ESD cases and one gastric ESD case, but x-rays did not show any subcutaneous or mediastinal emphysema or pneumoperitoneum. As for the three patients in the CO_2 group with perforations, histopathologic examinations of the one gastric ESD patient showed a well-differentiated intramucosal adenocarcinoma located in the cardia, and the two esophageal ESD patients had SCCs within the lamina propria mucosae located in either the middle or lower thoracic esophagus. Antibiotics were administrated for all three patients over 3 to 5 days. Oral diet intake was started on either postoperative day 2 or 4, and each patient was discharged on postoperative day 6 without any invasive intervention, as is the usual course for gastric and esophageal ESD patients at our hospital. All the CO_2 group procedures were completed without delays, and none of the 45 CO_2 insufflation patients required extended hospitalization.

Discussion

To the best of our knowledge, this is the first study to investigate the safety of CO_2 insufflation in lengthy upper GI tract ESD procedures for patients under deep sedation. The results of our study indicate that CO_2 insufflation can be used as safely as air insufflation without any adverse effects by continuous monitoring of $PtcCO_2$ and SpO_2 during both esophageal and gastric ESDs.

Bretthauer et al. [4, 6] reported no significant observed difference in $PtcCO_2$ elevation between air and CO_2 insufflation groups during ERCP with deep sedation, and no significant increase in end-tidal CO_2 levels was demonstrated between the two groups in colonoscopy examinations without sedation, although patient abdominal discomfort was significantly less in the CO_2 group. In our study, midazolam and propofol were used, so it was difficult to measure patient discomfort levels using a visual analog scale after ESD because of considerable differences in the rate of recovery between those two sedatives.

The PCO_2 level basically depends on ventilation, so PCO_2 elevation can be regarded generally as caused by depression of both the ventilation rate and the tidal volume. Nelson et al. [39] reported $PtcCO_2$ elevation exceeding 40 mmHg and a maximum $PtcCO_2$ greater than 100 mmHg in ERCP using air insufflation, although there were no evident adverse effects.

In our results, the maximum $PtcCO_2$ per duration time, with $PtcCO_2$ exceeding 60 mmHg, was 72 mmHg for 166 min in the CO_2 group and 74 mmHg for 148 min in the air group, but with no adverse events in either group. No harmful oxygenation effects resulted from using CO_2 insufflation during ESDs because all the patients received O_2 nasally. These results suggest that $PtcCO_2$ elevation, which registered a maximum value of 74 mmHg without SpO_2 depression, did not represent a clinical problem, and no actual correlation was found between the two measurements in any of the cases. We believe that $PtcCO_2$ elevation was not caused solely by CO_2 insufflation but that other important factors were involved, including sedation levels and respiratory status, because the air group showed even higher $PtcCO_2$ values than the CO_2 group (Table 2; Fig. 3A–C) [5, 40].

Concerning the observation of differences between the two groups in $PtcCO_2$ elevation and minimum SpO_2 in all cases as well as $PtcCO_2$ elevation and SpO_2 depression in only the gastric ESD cases, we considered that ventilation rate and tidal volume were difficult to decrease because abdominal distension and diaphragm elevation were reduced to relieve bowel hyperextension. Accordingly, it also can be speculated that CO_2 insufflation may stimulate the respiratory center, leading theoretically to hyperventilation. Except for patients with COPD, who were excluded from this study, $PtcCO_2$ elevation may have been caused by hypoactivity of the respiratory center resulting from deep sedation rather than CO_2 insufflation or oxygen administration.

In the upper GI tract, especially the esophagus, the most serious complications are arrhythmia, cardiac collapse, thromboembolism produced by blood flow congestion resulting from a perforation (compartment syndrome), and pneumothorax [19–24]. We also considered why no subcutaneous or mediastinal emphysema or pneumoperitoneum appeared, and we suspected that leaked CO_2 in the three patients who experienced perforations probably was absorbed rapidly into the surrounding tissue [1, 2]. It can be expected that CO_2 insufflation will reduce all such complications. Because CO_2 insufflation was demonstrated to be safe in this study, it is recommended that to avoid any unexpected developments during treatment in the upper GI tract, particularly in the esophagus, ESD should be performed from the start using CO_2 insufflation. In addition, CO_2 insufflation is recommended for endoscopists with limited ESD experience, who likely will need more time to complete the procedure and may have a greater possibility of a perforation occurring because of their relative inexperience.

It generally is considered that a severe acidosis condition leads to arrhythmia, cardiac collapse, or hyperkalemia. If CO_2 retention does occur, the CO_2 can serve as a factor in decreasing the pH balance, although no clinical problem is involved if the pH balance is preserved within normal limits by other factors. Based on our findings, it appears that no adverse events may result if normal oxygenation is maintained even when a $PtcCO_2$ exceeding 60 mmHg persists for some time. Although CO_2 insufflation is not recommended for patients with severe pulmonary or cardiovascular disease, it is associated with no clinical disadvantage compared with air insufflation. We currently recommend, however, that $PtcCO_2$ be measured for enhanced safety during upper GI ESDs.

Several studies have shown a close correlation between $PtcCO_2$ and $PaCO_2$, so $PtcCO_2$ currently is regarded as a reliable and accurate measurement, although it is known that a discrepancy can exist between the two under certain body temperature and skin conditions [41]. No blood gas samples were taken in this study, so we have no data on actual patient pH levels and $PaCO_2$ values during the ESD procedures.

We were able to perform continuous measurement of the $PtcCO_2$ level and monitoring of its elevation during upper

GI tract endoscopic treatments, neither of which had previously been completely certain. Although more than 2,000 upper GI tract ESDs have been performed for patients at NCCH [42], very few major respiratory-related problems with the use of air insufflation have occurred despite the lack of certainty about previous $PtcCO_2$ levels. The advantage of having precise $PtcCO_2$ data is avoidance of additional sedatives resulting in excessively deep sedation that may cause respiratory dysfunction because PCO_2 elevation suggests depression of the ventilation rate and tidal volume. This also prevents tracheal intubation due to pulmonary arrest.

Use of a bispectral index (BIS) monitor that indicates a patient's sedation level by monitoring brain waves has been reported recently, so it is conceivable that the combined use of CO_2 insufflation with continuous $PtcCO_2$ measurement and the BIS monitor could result in safer upper GI tract endoscopic treatment procedures in the future [43, 44].

Conclusions

This study demonstrated CO_2 insufflation to be as safe as air insufflation for upper GI tract ESDs performed for patients under deep sedation without evidencing any adverse effects. We believe that CO_2 insufflation may be particularly effective for esophageal cases in which severe subcutaneous or mediastinal emphysema can be caused by perforations that may occur during the ESD procedure.

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Disclosures Satoru Nonaka, Yutaka Saito, Hajime Takisawa, Yongmin Kim, Tsuyoshi Kikuchi, and Ichiro Oda have no conflict of interests or financial ties to disclose.

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