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***Randomized Controlled Trial***

**Safety and efficacy of carbon dioxide insufflation during gastric endoscopic submucosal dissection**

Takada J *et al*. CO2 insufflation for gastric ESD

Jun Takada, Hiroshi Araki, Fumito Onogi, Takayuki Nakanishi, Masaya Kubota, Takashi Ibuka, Masahito Shimizu, Hisataka Moriwaki

**Jun Takada, Hiroshi Araki, Fumito Onogi, Takayuki Nakanishi, Masaya Kubota, Takashi Ibuka, Masahito Shimizu, Hisataka Moriwaki,** Departments of Gastroenterology, Internal Medicine, Gifu University Graduate School of Medicine, Gifu 5011194, Japan

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**Correspondence to:** **Hiroshi Araki, MD, PhD, Assistant Professor,** Departments of Gastroenterology, Internal Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 5011194, Japan. araara@gifu-u.ac.jp

**Telephone:** +81-58-2306308

**Fax:** +81-58-2306310

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**Abstract**

**AIM:** To compare the safety and efficacy of carbon dioxide (CO2) *vs* air insufflation during gastric endoscopic submucosal dissection (ESD).

**METHODS:** Our study involved the 116 patients who underwent gastric ESD during the study period. After eliminating 29 patients who fit the exclusion criteria, 87 patients, without known pulmonary dysfunction, were randomized into the CO2 insufflation (*n =* 36) or air insufflation (*n =* 51) group. Standard ESD was performed, with a CO2 regulation unit (constant rate of 1.4 L/min) used for patients undergoing CO2 insufflation. Patients received diazepam for conscious sedation and pentazocine for analgesia. Transcutaneous CO2 tension (PtcCO2) was recorded 15 min before, during, and after ESD with insufflation. PtcCO2, the correlation between PtcCO2 and procedure time, and ESD-related complications were compared between the 2 groups. Arterial blood gases were analyzed after ESD in the first 30 patients (12 with CO2 and 18 with air insufflation) to assess the correlation between arterial blood CO2 partial pressure (PaCO2) and PtcCO2.

**RESULTS:** There were no differences in respiratory functions, median sedative doses, or median procedure times between the groups. Similarly, there was no significant difference in post-ESD blood gas parameters, including PaCO2, between the CO2 and air groups (44.6 mmHg *vs* 45 mmHg, respectively). Both groups demonstrated median pH values of 7.36, and none of the patients exhibited acidemia. No significant differences were observed between the CO2 and air groups with respect to baseline (39 mmHg *vs* 40 mmHg), peak PtcCO2 (52 mmHg *vs* 51 mmHg) during ESD, or median PtcCO2 (50 mmHg *vs* 50 mmHg) after ESD. There was a strong correlation between PaCO2 and PtcCO2 (*r =* 0.66, *P* < 0.001). The incidence of Mallory-Weiss tears was significantly lower (*P* = 0.013) with CO2 insufflation (0%) than with air insufflation (15.6%). CO2 insufflation did not cause any adverse events, such as CO2 narcosis or gas embolisms.

**CONCLUSION:** CO2 insufflation, during gastric ESD, results in similar blood gas levels as air insufflation, and also reduces the incidence of Mallory-Weiss tears.

**Key words:** Carbon dioxide; Insufflation; Gastric endoscopic submucosal dissection; Randomized controlled trial; Mallory-Weiss tear

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**Core tip:** We compared the safety and efficacy of carbon dioxide (CO2) and air insufflation during gastric endoscopic submucosal dissection (ESD) in a randomized controlled trial (RCT). We measured both the transcutaneous CO2 tension (PtcCO2) and the partial pressure of CO2 in the arterial blood (PaCO2) to directly evaluate CO2 retention or acidemia. Our findings strongly suggest that CO2 insufflation is as safe as air insufflation with regard to blood gas levels. The present study is the first RCT to demonstrate the benefit of CO2 insufflation in reducing the risk of Mallory-Weiss tears during ESD.

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**INTRODUCTION**

Endoscopic submucosal dissection (ESD) for gastric neoplasms enables *en bloc* resection of even an extensive superficial lesion[[1-8](#_ENREF_1)]. However, gastric ESD is technically difficult and time consuming, and therefore, extensive gas insufflation is required to maintain adequate visualization during the procedure. Although air is commonly used for insufflation, it results in the retention of a large amount of residual gas after ESD. Residual gas in the gastrointestinal tract can induce post-ESD pain or discomfort, and in rare cases can give rise to life-threatening complications such as air embolism and tension pneumothorax[[9-17](#_ENREF_9)].

It is well known that carbon dioxide (CO2) is absorbed faster in the body than air and is also rapidly excreted through the lungs, except in cases of pulmonary dysfunction. Therefore, CO2 insufflation is expected to reduce the pain and abdominal discomfort associated with endoscopic examination and therapy[[18-25](#_ENREF_18)].

Perforation and major bleeding are severe complications of ESD. The reported incidence of perforation in ESD ranges from 1% to 6.1%[[1-5](#_ENREF_1)] and subsequent peritonitis or mediastinitis could be fatal. CO2 insufflation reportedly minimizes these ESD-related complications[[26](#_ENREF_26)]. The safety and efficacy of CO2 insufflation during ESD for lesions of the esophagus, stomach, and colorectum have been demonstrated in randomized, controlled trials (RCTs)[[27](#_ENREF_27),[28](#_ENREF_28)] and prospective studies[[29-31](#_ENREF_29)]. However, these RCTs measured only transcutaneous CO2 tension (PtcCO2) or end-tidal CO2 pressure, not partial pressure of CO2 in the arterial blood (PaCO2).

In the present prospective RCT, we aimed to assess the safety and efficacy of CO2 insufflation during ESD for gastric neoplasms in patients under conscious sedation. We measured both PtcCO2 and PaCO2 in order to directly evaluate CO2 retention or acidemia. We also attempted to validate a continuous PtcCO2 measuring system to monitor patient safety during CO2 insufflation.

**MATERIALS AND METHODS**

***Study design and participants***

This study was designed as a single-center RCT. Between January 2009 and December 2009, all consecutive patients undergoing ESD for gastric neoplasms at Gifu University Hospital in Japan were screened for this study. Gastric ESD was indicated for differentiated adenocarcinoma that was confined to the mucosa with no risk of lymph node metastasis, and for adenoma, regardless of its size or the presence of ulceration.

Patients were excluded if (1) they had chronic pulmonary dysfunction defined as a forced expiratory volume in 1.0 second/forced vital capacity (FEV1.0%) of < 70% or a vital capacity (%VC) of < 80%; or (2) they were unable to understand the consent information required for participation; or (3) they declined participation. The study design was approved by the ethics committee for clinical research at Gifu University Hospital. All eligible individuals provided written informed consent prior to study enrollment. Randomization was conducted using sealed envelopes and patients were divided into 2 groups: the CO2 insufflation group (CO2 group) and air insufflation group (Air group).

***Examination schedule for study events before and after ESD***

ESD was conducted during the first afternoon after hospital admission. On the second day in the hospital, blood tests, esophagogastroduodenoscopy, and computed tomography (CT) of the chest and abdomen were performed. Blood tests for leukocyte count and C-reactive protein (CRP) levels were repeated on the third hospital day. Axillary temperature was assessed 1 h after ESD and daily thereafter, at 06:00, 14:00, and 20:00 hours.

***ESD procedure and conscious sedation method***

The standard ESD procedure was performed using a gastroscope with a single working channel and water jet function (GIF-Q260J; Olympus Optical Co., Tokyo, Japan) and a cap attachment (D-201-11804; Olympus). The gastric lesion was resected using either the Dual-KnifeTM (KD-630L; Olympus) or the IT2 KnifeTM (KD-611L; Olympus), depending on its location. A 0.4% high-molecular-weight hyaluronic acid solution containing epinephrine was injected into the submucosal layer to raise the lesion. Incision of the mucosal layer around the circumferential markings and subsequent direct dissection of the submucosal layer were performed with the Dual-Knife and IT2-Knife.

Patients received diazepam for conscious sedation and pentazocine for analgesia. At the start of the ESD procedure, 5–10 mg of diazepam and 7.5–15 mg of pentazocine were injected intravenously for induction of anesthesia and analgesia, with an additional 5 mg of diazepam or 7.5 mg of pentazocine administered repeatedly as necessary. When the combination of diazepam and pentazocine could not achieve conscious sedation, intravenous midazolam was administered. Oxygen was administered nasally at 2.0 L/min during ESD, and the flow volume was adjusted by monitoring transcutaneous oxygen saturation (SpO2). Arterial blood samples were immediately analyzed using a blood gas analyzer (ABL700, Radiometer Medical, Copenhagen, Denmark) after the ESD procedure, for the first 30 consecutive patients.

***CO2 insufflation and transcutaneous gas analysis***

CO2 was delivered using a CO2 regulation unit (OLYMPUS UCR; Olympus). The TOSCA measurement system and TOSCA 500 monitor (Linde Medical Sensors, Basel, Switzerland) were used to measure the PtcCO2 noninvasively and continuously. The low-flow gas tube (MAJ-1742; Olympus) of the Olympus UCR was set at a constant rate of 1.4 L/min for CO2 insufflation in all patients. PtcCO2 was recorded using the TOSCA measurement system and the TOSCA 500 monitor with an earlobe sensor attached by a low pressure clip. We used a default temperature setting of 42 °C for the sensor and recalibrated the system before each ESD.

***Definitions of outcome parameters and complications***

Operation time was measured from the start of circumferential marking to the completion of resection. A diagnosis of perforation was made by direct endoscopic observation of visceral organs during ESD or by the presence of free air on follow-up plain chest radiography. Evidence of aspiration pneumonia was determined by the appearance of an obvious pneumonia shadow on a plain chest CT 1 day after ESD. Bleeding was defined as clinical evidence of bleeding after ESD, such as hematemesis or melena that required endoscopic treatment. A Mallory-Weiss tear (MWT) was defined as a mucosal tear or laceration adjacent to the esophagogastric junction with active bleeding, either spurting or oozing, during ESD.

***Statistical analysis***

Values are expressed as the number of patients (%) or median (range). Differences in distribution of categorical variables between the two groups were analyzed by the chi-squared test or by Fisher exact test when required. The non-parametric Mann-Whitney *U* test was used for comparing continuous variables. A *P* value of < 0.05 was considered significant. All statistical analyses were conducted with JMP version 10 (SAS Institute, Cary, NC, United States).

**RESULTS**

***Patient enrolment and allocation into groups***

Of the 116 candidate patients for gastric ESD, 87 were enrolled in the trial and randomized. Among them, 36 received CO2 insufflation and 51 received air insufflation. Twenty-nine patients were excluded due to impaired respiratory function (*n =* 24), severe chronic obstructive pulmonary disease requiring oxygen (*n =* 3), and inability to understand the consent information required for participation (*n =* 2). The first 30 participants (12 from the CO2 group and 18 from the Air group) underwent arterial blood gas analysis (Figure 1).

***Baseline characteristics***

Baseline characteristics for each treatment group are shown in Table 1. The location (*P =* 0.012) and histopathology (*P* = 0.020) of the gastric lesions were significantly different between the groups. The median procedure time was 46 min in the CO2 group and 48 min in the Air group (not significant). There were no differences in respiratory function (FEV1.0% and %VC) between the groups. No significant differences were observed in the median dose of sedative drugs administered to the patients in each group.

***Arterial blood gas analysis***

No significant differences were observed between the 2 groups that received blood gas analysis after ESD with respect to the median procedure time and the median dose of sedative drugs (Table 2). There was no significant difference in any blood gas parameters including PaCO2 between the CO2 group and the Air group (44.6 mmHg *vs* 45 mmHg). The median pH values were 7.36 in both groups, and there were no patients with acidemia. As shown in Figure 2, PtcCO2 was significantly correlated with PaCO2 (*r =* 0.66, *P* < 0.001). The median difference between PaCO2 and PtcCO2 was 4.8 mmHg.

***PtcCO2 and SpO2 before and after ESD***

The median (range) PtcCO2 before (baseline) and after ESD was 39 mmHg (28–52 mmHg) and 50 mmHg (41–68 mmHg), respectively, in the CO2 group, and 40 mmHg (22–51 mmHg) and 50 mmHg (40–64 mmHg), respectively, in the Air group. The PtcCO2 increased significantly (*P* < 0.001) after the procedure in both groups, although there was no significant difference between the groups. The median (range) peak PtcCO2 during the procedure was 52 mmHg (43–68 mmHg) in the CO2 group and 51 mmHg (40–64 mmHg) in the Air group (not significant, Table 3). There was no correlation between the procedure time and PtcCO2 elevation in either the CO2 group (Figure 3a) or the Air group (Figure 3b). The median minimum SpO2 level and oxygen flow rate were similar between the groups (98% and 2.0 L/min, respectively)(Table 3).

***Incidence of complications and durations of hospital stay***

ESD-related complications and the duration of the hospital stay are listed in Table 4. CO2 insufflation did not cause any adverse events such as CO2 narcosis or gas embolism. No significant difference was observed between the 2 groups with respect to the incidence of fever (body temperature > 37.5 °C), pneumonia, perforation, or post-ESD hemorrhage. The incidence of MWTs was significantly lower in the CO2 group than in the Air group (*P* = 0.013). Serum CRP levels and white blood cell counts on days 1 and 3 after ESD were not significantly different between the groups, and the median hospital stay was equivalent at 7 days for each group.

**DISCUSSION**

The safety and efficacy of insufflation using CO2 as an alternative to air has been demonstrated in several RCTs for various kinds of endoscopic procedures[[18-20](#_ENREF_18),[22-24](#_ENREF_22),[27](#_ENREF_27),[28](#_ENREF_28)]. In gastric ESD, Maeda *et al*[[28](#_ENREF_28)] reported that CO2 insufflation significantly reduced the volume of residual gas in the digestive tract compared with air insufflation. In the present study, under similar ESD conditions with regard to procedure time, respiratory function, sedative drug doses, and minimum SpO2, neither the post-procedure PaCO2 nor the median PtcCO2 differed between the CO2 group and the Air group. The peak PtcCO2 during ESD also did not differ between the 2 groups. Furthermore, we confirmed a strong correlation between PaCO2 and PtcCO2 (*r =* 0.66, P < 0.001). Therefore, the PtcCO2 value can be used as a surrogate marker of CO2 retention in patients who received CO2 insufflation during ESD.

In this study, the maximum PtcCO2 and PaCO2 reached 68 mmHg and 53 mmHg in the CO2 group, and 64 mmHg and 50 mmHg in the Air group, respectively. However, no adverse events such as acidemia, CO2 narcosis, or SpO2 depression were reported in either group. We speculate that the elevated PtcCO2 in both groups after the procedures is likely due to respiratory depression associated with conscious sedation. Several studies have demonstrated that such respiratory depression is involved in the elevation of PaCO2 or PtcCO2 in patients undergoing endoscopic treatment[[27](#_ENREF_27),[29-31](#_ENREF_29)]. There was no correlation between procedure time and PtcCO2 elevation in the present study. These results indicate that CO2 insufflation is as safe as air insufflation for gastric ESD when the CO2 insufflation rate is 1.4 L/min and the median procedure time is 48 min.

With regard to complications, the incidence of MWTs was significantly lower in the CO2 group than in the Air group. We believe that this may be due to the rapid absorption of CO2 by the body compared to air. Indeed, CO2 insufflation in esophagogastroduodenoscopy efficiently reduces MWTs by lowering the tension of the gastric mucosa caused by residual gas in the stomach[[32](#_ENREF_32)]. To our knowledge, the present study is the first RCT to demonstrate the benefit of CO2 insufflation in reducing the risk of MWTs during ESD.

Because respiratory depression due to conscious sedation may lead to CO2 retention, arterial CO2 monitoring during lengthy endoscopic procedures is important, even if the patient’s respiratory function is normal. However, arterial blood sampling is invasive and it is not practical to measure PaCO2 serially in all ESD patients. Instead, PtcCO2, which correlates well with PaCO2, can be measured noninvasively and continuously. PtcCO2 is usually greater than PaCO2 by 5–6 mmHg[[33](#_ENREF_33),[34](#_ENREF_34)]. Indeed, in the present study, the median difference between these values was 4.8 mmHg. Because of the strong correlation between PtcCO2 and PaCO2, a PtcCO2 monitoring system is considered a reliable and efficient alternative to PaCO2 measuring. Thus, we finished arterial blood analysis after the first 30 patients.

Our study has some limitations. First, we excluded 27 patients (23.3%) who had chronic pulmonary dysfunction, since the safety of CO2 insufflation during gastric ESD has not been established for these patients. We have recently reported the safety of CO2 insufflation during gastric ESD in patients with pulmonary dysfunction (FEV1.0% < 70% or %VC < 80%) under conscious sedation[[35](#_ENREF_35)]. However, in patients with severe obstructive pulmonary disease, a longer procedure time may increase the risk of CO2 retention because there was a significant correlation between PtcCO2 elevation and ESD procedure time in patients with pulmonary dysfunction[[35](#_ENREF_35)]. Therefore, PtcCO2 should be carefully monitored in these patients to avoid severe complications such as CO2 narcosis and acidemia. Second, the number of patients who underwent arterial blood gas analysis in the present study may be too small. The present study was also a single-center trial. Therefore, further larger prospective multicenter studies are required to confirm the safety and efficacy of CO2 insufflation for gastric ESD by evaluating both PtcCO2 and PaCO2 values.

In conclusion, this study strongly suggests that CO2 insufflation is safe and effective during gastric ESD under conscious sedation in patients without pulmonary dysfunction. Furthermore, CO2 insufflation reduces the incidence of MWTs compared to air insufflation. However, conscious sedation might increase the risk of CO2 retention and the PtcCO2 should be monitored carefully in these cases.

**COMMENTS**

***Background***

The safety and efficacy of insufflation using carbon dioxide (CO2) as an alternative to air has been demonstrated in several randomized controlled trials (RCTs) for various kinds of endoscopic procedure. However, there has been no report on the safety and efficacy of CO2 insufflation for gastric endoscopic submucosal dissection (ESD) based on the measurement of both the partial pressure of CO2 in the arterial blood (PaCO2) and transcutaneous CO2 tension (PtcCO2).

***Research frontiers***

Based on the observation that CO2 is rapidly absorbed from the bowel, we investigated the effect of CO2 insufflation on patients undergoing gastric ESD.

***Innovations and breakthroughs***

CO2 insufflation remarkably reduced the incidence of Mallory-Weiss tears without any adverse events.

***Applications***

The safety and efficacy of CO2 insufflation during gastric ESD in patients under conscious sedation were demonstrated in this study. Further investigation in patients with pulmonary dysfunction is necessary.

***Peer-review***

The present study is the first RCT to demonstrate that CO2 insufflation can reduce the risk of Mallory-Weiss tears during ESD, and represents a major contribution to this field.

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**Table 1 Patients and examination characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CO2 group** | **Air group** | ***P-*value** |
| Patients | 36 | 51 |  |
| Age, yr | 74 (52–87) | 70 (45–93) | NS |
| Sex, Male/Female | 22/14 | 36/15 | NS |
| FEV1.0% | 72 (70–89) | 73 (70–93) | NS |
| %VC | 103 (80–102) | 109 (80–152) | NS |
| Location of lesion:  upper/middle/lower | 5/22/9 | 12/15/24 | 0.012 |
| *En bloc* resection | 36 (100) | 51 (100) | NS |
| Histopathologic type:  tub1/tub2/por/sig/adenoma | 18/3/0/0/15 | 36/6/2/1/6 | 0.020 |
| Histological depth: M/SM1/SM2 | 32/2/2 | 42/1/8 | NS |
| Histopathologically curative resection | 31 (86.1) | 43 (84.3) | NS |
| Tumor size, mm | 18 (4–75) | 17 (3–47) | NS |
| Resection size, mm | 35 (22–110) | 37 (23–95) | NS |
| Procedure time, min | 46 (18–194) | 48 (15–145) | NS |
| Dose of diazepam, mg | 20 (5–30) | 20 (5–30) | NS |
| Dose of pentazocine, mg | 18.8 (7.5–45) | 22.5 (7.5–45) | NS |
| Patients receiving midazolam | 3 (8.3) | 5 (9.8) | NS |
| Dose of midazolam, mg | 10 (2.5–20) | 7.5 (2.5–10) | NS |

Data are presented as *n*, *n* (%), or median (range). FEV1.0%: Forced expiratory volume 1.0 second/forced vital capacity; %VC: Vital capacity; tub1: Well differentiated tubular adenocarcinoma; tub2: Moderately differentiated tubular adenocarcinoma; por: Poorly differentiated adenocarcinoma; sig: Signet ring cell carcinoma; M: Tumor confined to the mucosa; SM1: Tumor confined to the submucosa and tumor invasion within 0.5 mm of the muscularis mucosae; SM2: Tumor confined to the submucosa and tumor invasion of 0.5 mm or more into the muscularis mucosae; NS: not significant.

**Table 2 Patient characteristics and parameters of arterial blood analysis**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CO2 group** | **Air group** | ***P* value** |
| Patients | 12 | 18 |  |
| Age (range), yr | 73 (63–82) | 70 (45–87) | NS |
| Procedure time, min | 66 (26–156) | 56 (23–107) | NS |
| Dose of diazepam, mg | 17.5 (10–22.5) | 20 (5–30) | NS |
| Dose of pentazocine, mg | 15 (15–30) | 22.5 (15–37.5) | NS |
| Patients receiving midazolam | 1 (8.3) | 1 (5.6) | NS |
| Dose of midazolam, mg | 2.5 | 5 |  |
| pH value | 7.36 (7.34–7.39) | 7.36 (7.33–7.4) | NS |
| PaCO2, mmHg | 44.6 (39–53) | 45 (40–50) | NS |
| PaO2, mmHg | 168 (68–203) | 143 (78–259) | NS |
| HCO3- , mEq/L | 25.1 (23–30) | 25.5 (22–27) | NS |
| Base excess, mEq/L | -0.05 (-2±4) | 0.3 (-3.1±2.6) | NS |

Values are expressed as the number of patients (%) or median (range). PaO2: Partial pressure of oxygen in arterial blood; PaCO2: Partial pressure of carbon dioxide in arterial blood; NS: Not significant.

**Table 3 Transcutaneous carbon dioxide tension values, transcutaneous oxygen saturation values, and oxygen flow rate**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CO2 group**  **(*n =* 36)** | **Air group**  **(*n =* 51)** | ***P-*value** |
| Baseline PtcCO2, mmHg | 39 (28–52) | 40 (22–51) | < 0.001 |
| PtcCO2 after ESD, mmHg | 50 (41–68) | 50 (40–64) |
| Peak PtcCO2, mmHg | 52 (43–68) | 51 (40–64) | NS |
| PtcCO2 > 60 mmHg during ESD | 3 (8.3) | 2 (3.9) | NS |
| Minimum SpO2 | 98% (90%–100%) | 98% (89%–100%) | NS |
| Oxygen flow rate, L/min | 2 (1–5) | 2 (2–4) | NS |

Data are presented as *n* (%) or median (range). ESD: Endoscopic submucosal dissection; PtcCO2: Transcutaneous carbon dioxide tension; SpO2: Transcutaneous oxygen saturation.

**Table 4 Complications from endoscopic submucosal dissection, blood parameters, and duration of hospital stay**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CO2 group**  **(*n =* 36)** | **Air group**  **(*n =* 51)** | ***P*-value** |
| Fever (body temperature, > 37.5 °C) | 9 (25.0) | 9 (17.6) | NS |
| Pneumonia | 3 (8.3) | 5 (9.8) | NS |
| Perforation | 1 (2.7) | 1 (1.9) | NS |
| Post-procedure hemorrhage | 0 | 4 (7.8) | NS |
| Mallory-Weiss tears | 0 | 8 (9.8) | 0.013 |
| CRP on day 1 after ESD, mg/dL | 0.3 (0.09–6.19) | 0.4 (0.04–3.62) | NS |
| CRP on day 3 after ESD, mg/dL | 2.0 (0.18–7.83) | 2.0 (0.08–14.2) | NS |
| WBC on day 1 after ESD, n/μL | 9020 (3730–15680) | 8090 (4510–13450) | NS |
| WBC on day 3 after ESD, n/μL | 6310 (2560–11200) | 6260 (3100–10660) | NS |
| Hospital stay, d | 7 (7–16) | 7 (7–20) | NS |

Data are presented as *n*, *n* (%), or median (range). ESD: Endoscopic submucosal dissection; CRP: C-reactive protein; WBC: White blood cell.

Assessed for eligibility (*n* = 116)

Excluded (*n* = 29)

Exclusion criteria (*n* = 29)

Randomized (*n* = 87)

Received air insufflation (*n* = 51)

Arterial blood sample taken (*n* = 18)

Received CO2 insufflation (*n* = 36)

Arterial blood sample taken (*n* = 12)

**Figure 1 Flow chart of patient enrollment in the study and allocation into groups.**

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**Figure 2 Correlation between partial pressure of carbon dioxide in arterial blood (PaCO2) and transcutaneous carbon dioxide tension (PtcCO2) after endoscopic submucosal dissection.**

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**Figure 3 Elevation of transcutaneous carbon dioxide tension in the carbon dioxide insufflation group (a) and in the air insufflation group (b).** There was no significant correlation between the procedure time and transcutaneous carbon dioxide tension (PtcCO2) elevation in either group.