performed in 210 cases, a proximal gastrectomy was performed in 31 cases, a total gastrectomy was performed in 17 cases, and a pylorus-preserving gastrectomy was performed in 127 cases. Ten patients were treated by laparoscopy-assisted surgery. Lymph node dissection was performed for D1+α, D1+β or D2, where α refers to lymph nodes 7 and 8a in cases of lower third cancer, and β refers to lymph nodes 7, 8a, and 9. Cases with local and segmental resection and lymph node dissection less than D1 were excluded. Staging and classification were determined according to the general rules for surgical and pathological gastric cancer studies in Japan.[17] The control group was 285 patients treated by a conventional gastrectomy for early gastric cancer based on their clinical stages between 1991 and 1998 (non-ANP group), because we began performing an autonomic nerve-preserving gastrectomy in 1994 and have performed this procedure for almost all patients with a clinical T1 N0 M0 stage after 1999.

Operative Procedure

The preserved autonomic nerves included the hepatic branch originating from the anterior trunk of the vagus nerve and the celiac branch, the plexus surrounding the common hepatic artery and the splenic artery, and the pancreatic branch and the hepatic branch originating from the posterior trunk of the vagus nerve. The celiac branch was followed upward from the root of the left gastric artery or downward from the posterior trunk of the vagus nerve, taped, and preserved. The left gastric artery was divided at the peripheral side of the confluence of the celiac branch (Fig. 1).

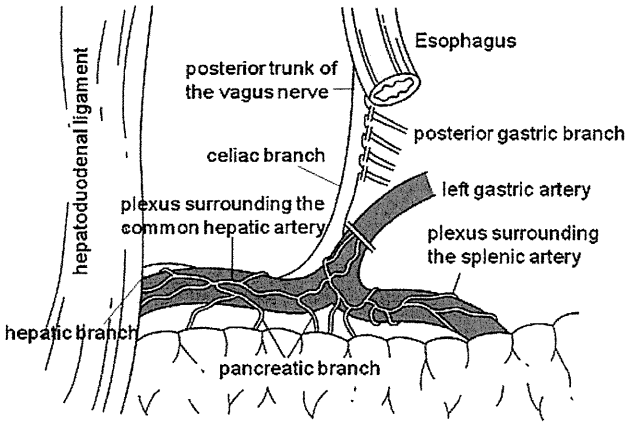

Fig. 1. Preserved autonomic nerves and cutting lines (*double lines*) for the left gastric artery and the posterior gastric branches

Statistical Analysis

The clinicopathological features and survival rates of the ANP group were compared with those of the non-ANP group. The median follow-up time was 5.7 years. Statistical analyses were conducted using the Statcel version 2.0 software program (OMS, Tokyo, Japan). Statistically significant differences were determined using the χ^2 test or Student's *t*-test. The survival rates were calculated using the Kaplan–Meier method and the log-rank test. The level of significance was set at $P < 0.05$.

Results

Clinicopathological Features

Table 1 shows the clinicopathological data for both groups. Fewer patients in the ANP group were treated by a total gastrectomy in comparison to the non-ANP group. In the histological analyses, the numbers of patients with tumor invasion to the mucosa, submucosa, muscularis propria, and subserosa were 210, 166, 9, and 0 in the ANP group and 166, 98, 15, and 6 in the non-ANP group, respectively. Although the non-ANP group contained significantly more patients with tumors exhibiting deeper invasion than the ANP group, the extent of lymph node metastasis and tumor staging were similar in the two groups. The number of dissected lymph nodes was greater in the ANP group than in the non-ANP group. In the ANP group, the number of patients with lymph node metastasis was 25 (6.5%) and the number of patients over stage T1 N0 M0 was 32 (8.3%).

Survival

The overall 5-year survival rates were 94.7% in the ANP group and 90.4% in the non-ANP group ($P = 0.003$) (Fig. 2). The 5-year survival rates of patients at stages IA, IB, and II were 94.8%, 96.2%, and 83.3% in the ANP group, and 89.5%, 96.2%, and 83.3% in the non-ANP group, respectively (Fig. 3). The survival rate in the ANP group was superior to that in the non-ANP group for stage IA ($P = 0.003$). Because there was no significant difference in the disease-specific survival rates for stage IA (99.7% vs 98.5%, $P = 0.571$, Fig. 4), the difference in the survival rates of the stage IA patients between the ANP and non-ANP groups may have been caused by death from other diseases. In contrast, the 5-year survival rates of the patients in the ANP group were 94.9% in those without lymph node metastasis and 91.8% in those with metastasis, respectively, with no significant difference (Fig. 5).

Table 1. Clinicopathological findings of patients who underwent a gastrectomy with or without the preservation of the autonomic nerves

	ANP ($n = 385$)	Non-ANP ($n = 285$)	P value
Age, years (range)	62.6 (25–88)	62.0 (28–85)	0.451
Sex			0.436
Male	251	194	
Female	134	91	
Tumor location			0.053
U	44	31	
M	244	158	
L	97	96	
Tumor size (mm)	27.5	28.3	0.579
Lymph node dissection			0.391
D1	85	71	
D2	300	214	
Operation method			<0.001
DG	210	222	
PG	31	7	
TG	17	32	
PPG	127	24	
Depth of tumor invasion			0.001
pM	210	166	
pSM	166	98	
pMP	9	15	
pSS	0	6	
Lymph node metastasis			0.894
pN0	360	268	
pN1	21	15	
pN2	4	2	
fStage			0.297
IA	353	251	
IB	26	28	
II	6	6	
Histologic type			0.124
Differentiated	246	202	
Undifferentiated	138	83	
Unknown	1	0	
Number of dissected lymph nodes (range)			
All	37.8 (5–110)	32.4 (2–127)	<0.001
Group2[a]	13.9 (0–52)	10.9 (0–72)	<0.001

U, upper third; M, middle third; L, lower third; DG, distal gastrectomy; PG, proximal gastrectomy; TG, total gastrectomy; PPG, pylorus-preserving gastrectomy; M, mucosa and/or muscularis mucosa; SM, submucosa; MP, muscularis propria; SS, subserosa

[a] Group 2 lymph nodes refer to Nos. 7, 8a, 9, and 11

Although 26 patients died in the ANP group and 50 patients died in the non-ANP group, only 3 and 5 deaths, respectively, were disease-specific. Among these patients, only one in each group had lymph node metastasis (Table 2). The mortality was only one patient in each group.

Discussion

In gastric cancer patients, there are two types of postgastrectomy syndrome that are classified based on their etiology, namely, postgastrectomy syndrome from resection of the stomach and injury to the vagus nerve from lymph node dissection.[18] Many limited gastrectomy techniques have been developed to reduce the incidence of postgastrectomy syndrome, including pylorus-preserving gastrectomy, proximal gastrectomy, segmental gastrectomy, and local resection. The hepatic and celiac branches of the vagus nerve innervate the region from the pylorus to the large intestine as far as the distal portion of the transverse colon, the biliary tract, and the other upper abdominal organs. Preservation of the vagus nerve minimizes the loss of digestive and absorptive functions, thereby improving recovery of postoperative bodyweight and reducing diarrhea.[5,10,13–15] Furthermore, vagus nerve preservation decreases the incidence of cholelithiasis[3,13,14] and pre-

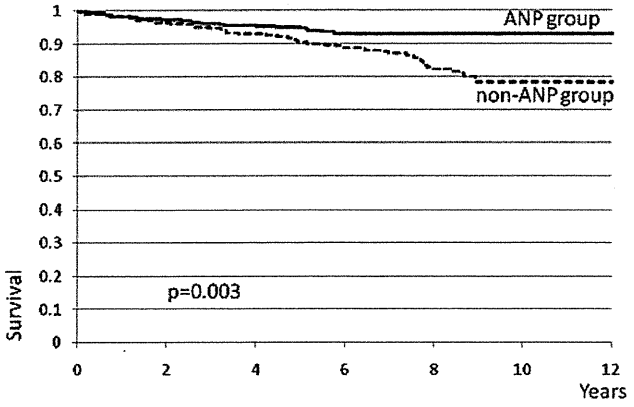

Fig. 2. Survival curves of the patients who underwent a gastrectomy with (*ANP*) and without (*non-ANP*) the preservation of the autonomic nerves. The overall 5-year survival rates are 94.7% in the ANP group and 90.4% in the non-ANP group ($P = 0.003$, log-rank test)

serves pancreatic insulin release.[9,11] We previously reported the superiority of this procedure.[10,13]

We designated our nerve-preserving procedure an "autonomic nerve-preserving gastrectomy," although it has also been referred to as a vagus nerve-preserving gastrectomy in previous reports. The reason for this designation is that the procedure preserves the plexus surrounding the common hepatic artery and the splenic artery, the pancreatic branch, and the hepatic branch originating from the posterior trunk of the vagus nerve as well as the sympathetic nervous system from the celiac ganglia.[19] It seems reasonable that the preservation of both the sympathetic and parasympathetic nervous systems is important for maintaining the function of the upper gut after a gastrectomy.[20,21]

A gastrectomy with extensive nodal dissection appears to prevent recurrence and improve cancer-specific survival in early gastric cancer patients with

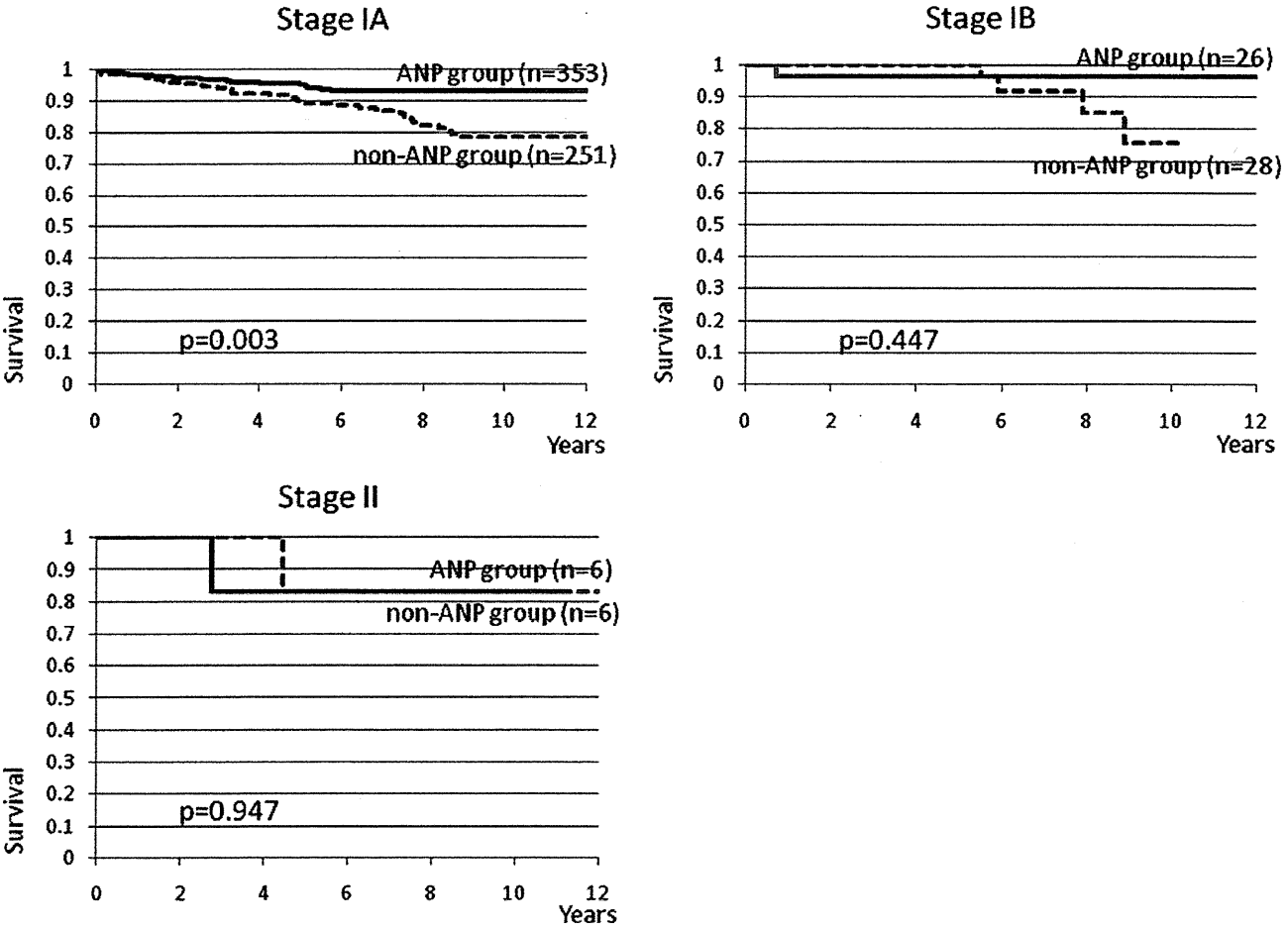

Fig. 3. Survival curves for stage IA, IB, and II patients who underwent a gastrectomy with (*ANP*) and without (*non-ANP*) the preservation of the autonomic nerves. The survival rate in the ANP group is superior to that in the non-ANP group for stage IA ($P = 0.003$, log-rank test). The survival rates between the ANP and non-ANP groups do not differ significantly for stages IB ($P = 0.433$, log-rank test) and II ($P = 0.947$, log-rank test)

Table 2. Patient mortality due to gastric cancer

pT	pN	fStage	Lesion of nodal metastasis	No. of nodal metastases	Organ of recurrence
ANP group					
M	N0	IA	—	0	Remnant stomach, liver, LN
SM	N0	IA	—	0	Liver
SM	N2	II	Nos. 1, 3, 4d, 6, 7, 8a, 9, 11	25	Peritoneum, LN
Non-ANP group					
M	N0	IA	—	0	Brain
M	N0	IA	—	0	Mediastinum, LN, bone
M	N0	IA	—	0	Unknown
M	N0	IA	—	0	Unknown
M	N1	IB	No.4d	1	Peritoneum

M, mucosa and/or muscularis mucosa; SM, submucosa; LN, lymph node

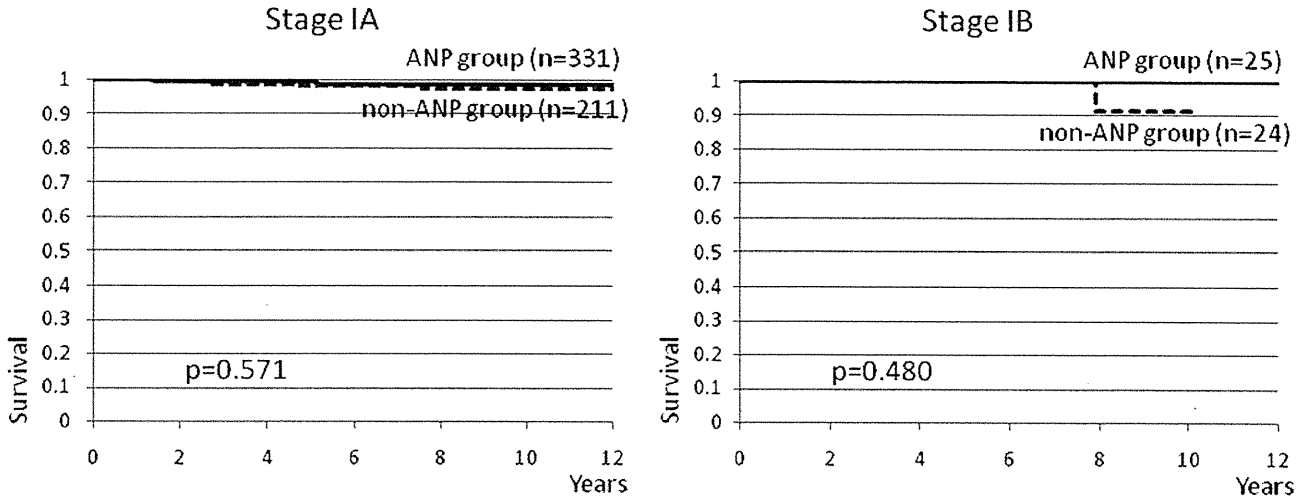

Fig. 4. Disease-specific survival curves for stage IA and IB patients who underwent a gastrectomy with (*ANP*) and without (*non-ANP*) the preservation of the autonomic nerves. The survival rates between the ANP and non-ANP groups do not differ significantly for stages IA ($P = 0.571$, log-rank test) and IB ($P = 0.480$, log-rank test)

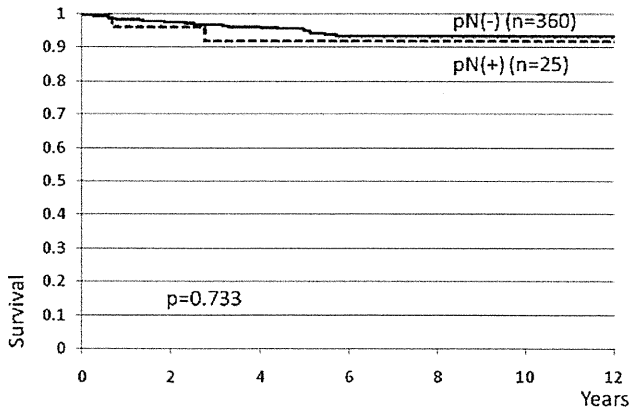

Fig. 5. Five-year survival rates of the patients in the ANP group are 94.9% in those without lymph node metastasis and 91.8% in those with metastasis ($P = 0.733$, log-rank test)

nodal metastasis in comparison to a gastrectomy with a limited lymph node dissection.[22] However, a recent study reported no significant difference in the survival rates between the standardized D2 lymphadenectomy and the D2 plus para-aortic lymphadenectomy in gastric cancer surgery.[23,24] The purpose of a nerve-preserving gastrectomy is to maintain both the postoperative quality of life and the curability of the patient. The left gastric artery and the common hepatic artery are enveloped in connective tissue, and the lymphatics along the arteries encircle this connective tissue. The nerves are dispersed within the connective tissue surrounding the arteries.[15,16] Therefore, an autonomic nerve-preserving gastrectomy may provide a curative operation even for patients with intracapsular microscopic metastases.[15,16] The number of dissected lymph nodes was actually greater in the ANP group than in the non-ANP group

although the dissection levels of both groups were equal. We achieved technical improvement of the dissection by confirming the location of the autonomic nerves. Although macroscopic diagnosis of lymph node metastases is possible, a previous study found that 15 of 158 gastric cancer patients with macroscopically negative nodes had lymph node metastases, and the false-negative rate was 3.8%.[25] In the present study the false-negative rate was 6.5%, and the survival of such patients was same in both groups. In addition, only one patient experienced recurrence in comparison to the four patients who had metastasis to lymph nodes near the celiac branch, such as No. 1 or No. 7. Therefore, our retrospective study indicates that an autonomic nerve-preserving gastrectomy did not reduce the patient survival rate, even in patients with microscopic lymph node metastases, thus suggesting that this procedure can eliminate lymphatic invasion (including microscopic metastases) as effectively as a conventional gastrectomy.

This study was a retrospective analysis and therefore had some degree of bias. Given that significantly more patients in the non-ANP group had tumors with histologically greater invasion, the surgeons may have selected a conventional gastrectomy when advanced cases were suspected based on intraoperative findings. In the present study, although the most important factor was lymph node metastasis, no significant differences with regard to the extent of the lymph node metastasis and staging were observed between the two groups. A prospective randomized trial is therefore necessary in the future to solve and elucidate the problems identified in our study.

In conclusion, an autonomic nerve-preserving gastrectomy did not reduce the survival of patients with early gastric cancer as compared with a conventional gastrectomy. Therefore, an autonomic nerve-preserving gastrectomy appears to be a useful function-preserving procedure for the treatment of clinical early gastric cancer. In addition, we recently started to perform a laparoscopy-assisted autonomic nerve-preserving gastrectomy,[26] and this method is expected to be both a function-preserving and minimally invasive treatment modality.

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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

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,

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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

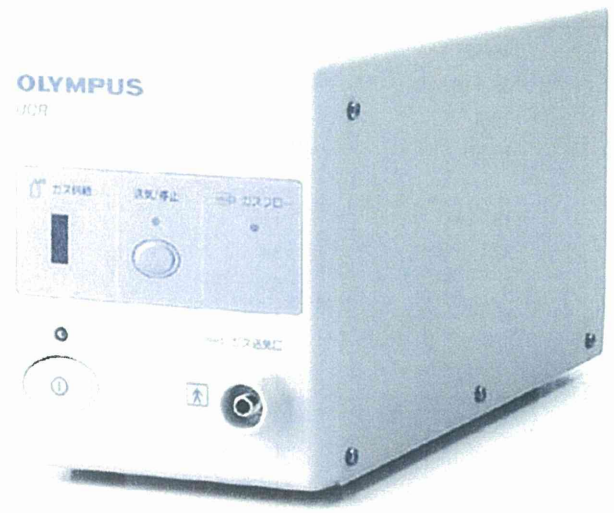

Fig. 1 UCR (CO_2 regulator). The UCR in upper gastrointestinal endoscopy has three levels of insufflation which can be controlled by using three types of connecting tubes. These amounts of insufflation are almost equivalent to the original three regulation levels of the EVIS LUCERA

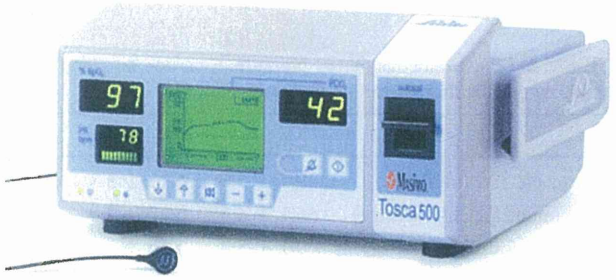

Fig. 2 The TOSCA measurement system and TOSCA 500 monitor, a noninvasive and continuous monitoring device for transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) that takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe

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

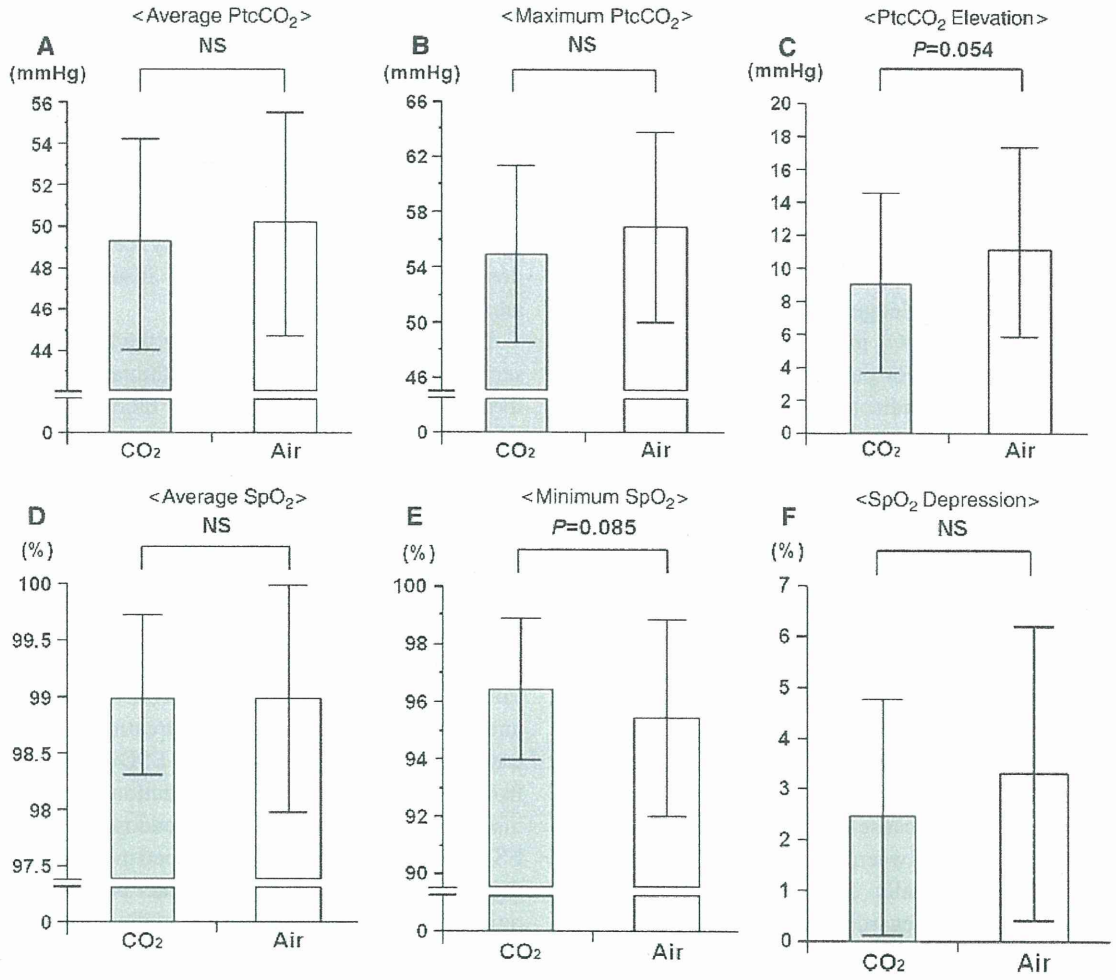

Fig. 3 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and oxygen saturation (SpO_2) measurements. The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in $PtcCO_2$ elevation and minimum SpO_2

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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ORIGINAL ARTICLE

Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: A prospective, randomized, controlled, blinded trial

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Abstract

Objective. To assess whether endoscopic flushes of the bubble-bursting agent Gascon and the mucolytic agent Pronase are as effective in terms of improving endoscopic mucosal visibility as a pre-endoscopic drink of the same agents. ***Material and methods.*** A total of 112 patients attending a Japanese tertiary referral centre for upper gastrointestinal endoscopy were randomized to receive either the standard Japanese procedure of a pre-endoscopic drink of water containing Gascon and Pronase with endoscopic flushes of 20-ml aliquots of water, or no pre-endoscopic therapy but endoscopic flushes of 20-ml aliquots of water containing Gascon, with or without Pronase as necessary. ***Results.*** Visibility scores were significantly better in the pre-endoscopic drink group than in either of the endoscopic flush groups. The group receiving a pre-endoscopic drink required fewer flushes during the procedure and there was no difference in the endoscopic time between the three groups. ***Conclusions.*** Our results suggest that endoscopic spraying of these bubble-bursting and mucolytic agents is not able to offer equivalent improvements in endoscopic mucosal visibility when compared with the standard Japanese therapy of a pre-endoscopic drink of these agents. The addition of Pronase to the spray solution had no measurable benefit over Gascon alone. We therefore cannot recommend endoscopic spraying of mucous clearing agents over their use as a pre-endoscopic drink.

Key Words: *Endoscopy, gascon, mucolytic, pronase, simethicone, visibility*

Introduction

Since the advent of gastrointestinal endoscopy, practitioners have been frustrated by foam and mucous obscuring the field of view. Mucosal toileting techniques with bubble-bursting agents such as Gascon (simethicone) have been used since the 1950s [1–3] and more recent studies have shown that the addition of a mucolytic such as Pronase further improves mucosal visualization [4,5]. These mucosal toileting techniques have become standard practice in Japan [6,7], where cancers tend to be detected earlier than in the West. Patients there are routinely asked to drink 100 ml of water containing 2 ml of Gascon and 20,000 units of Pronase 10 min prior to the endoscopy. These medications are freely available in Europe but it is not usual practice for them to be used. One explanation for this is concern amongst Western endoscopists of an increased risk of aspiration during the procedure if a drink is taken beforehand.

Minimally invasive techniques such as photodynamic therapy and endoscopic mucosal resection (EMR) are now able to offer excellent results for cancers detected at early stages. EMR often offers complete cure but can only be considered for tumours that are well characterized at endoscopy. Detection and characterization of early changes can be achieved through a variety of diagnostic techniques, including chromoendoscopy, high-magnification endoscopy, confocal endoscopy and narrow-band imaging, but all depend upon optimized mucosal views. In addition, chromoendoscopy requires a clear field in order

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that the dye binds to the intended cells rather than the overlying mucous [8,9]. Effective and acceptable mucosal toileting techniques are therefore increasingly vital as advanced endoscopic techniques become used more frequently.

In an attempt to provide the proven benefits of Gascon and Pronase [9–12] without the theoretical increased risk of pulmonary aspiration associated with a pre-endoscopic drink, this study was designed to compare the effectiveness and practicality of spraying Gascon, with or without Pronase, directly onto the mucosa as intermittent flushes through the biopsy channel of the endoscope during the procedure, compared with identical treatment given as a drink prior to endoscopy (conventional Japanese mucosal toileting).

Material and methods

Patients

The Japanese national screening programme for gastric cancer involves the majority of people over the age of 40 years undergoing an annual barium swallow. The tertiary referral centre in which this trial was set accepts patients for gastroscopy either directly (patients with abnormal results on these tests or with appropriate symptoms), or as referrals from other hospitals where early cancers have been detected that are thought to be suitable for EMR. This study was restricted to the screening population because there are differences in the endoscopy technique for those requiring a therapeutic procedure (e.g. the use of zoom scopes and special dyes requiring additional time). A total of 148 of these patients were recruited into this study over a 2-week period. Patients were excluded from the study if they had previously undergone oesophagectomy or gastrectomy, if the endoscopy revealed a lesion requiring a therapeutic procedure such as EMR or if there was active gastrointestinal bleeding or strictures in the upper gastrointestinal tract. The results from 112 patients were therefore available for analysis (Figure 1).

Pre-medication and endoscopic procedure

The study gained ethical approval and informed consent was obtained from all participants. Sealed envelopes were used to randomly allocate patients to one of three groups, as follows. Group S: standard Japanese procedure comprising a pre-endoscopic drink of 100 ml of water, 2 ml of Gascon and 20,000 units of Pronase. During the endoscopy, flushes of 20-ml

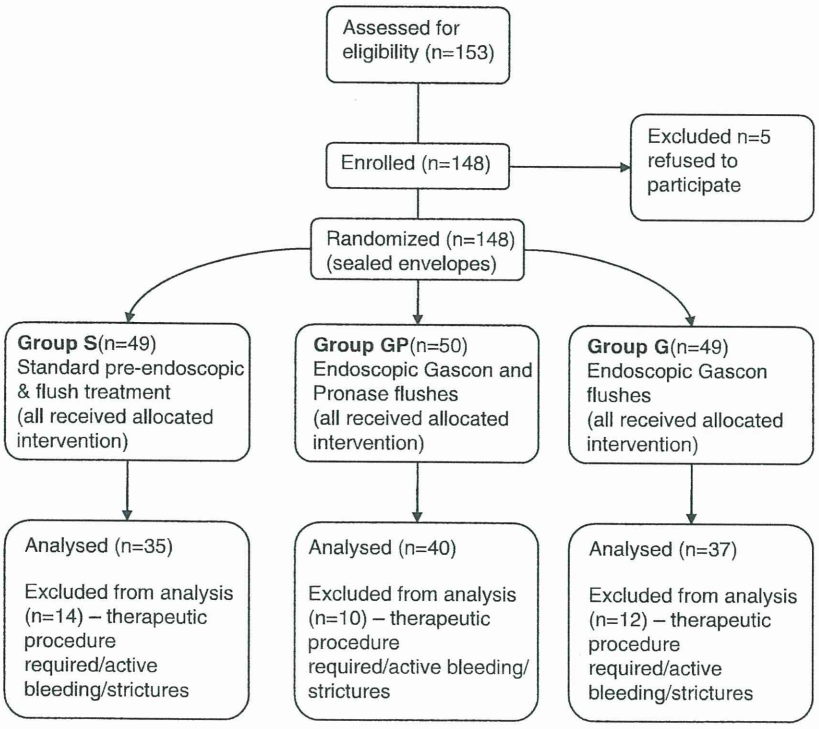

Figure 1. Flowchart showing the disposition of the study patients.

aliquots of water were used as required. Group G: no pre-endoscopic preparation. During the endoscopy, flushes of 20-ml aliquots of pre-mixed solution containing 100 ml of water and 2 ml of Gascon were used as required. Group GP: no pre-endoscopic preparation was given. During the endoscopy, flushes of 20-ml aliquots of pre-mixed solution containing 100 ml of water, 2 ml of Gascon and 20,000 units of Pronase were used as required.

All patients underwent routine gastroscopy, including chromoendoscopy, by one of 14 experienced unblinded endoscopists. The endoscopist was free to use as many flushes as deemed necessary to produce a satisfactory view. Once all flushes had been given, one extra photograph was taken from each of four predefined areas: the oesophagogastric junction, the antrum, the lower body and the upper body of the stomach. A record was kept of the total time taken to perform the procedure (from intubation to extubation) and the number of flushes required.

A single, blinded investigator who was experienced in endoscopy but had played no part in the endoscopic procedure then reviewed all of the pictures and assigned each of them a score between one and three for mucosal visibility: 1 = no adherent mucus and clear view of the mucosa; 2 = a thin coating of mucus but not obscuring vision; and 3 = adherent mucus obscuring vision.

The individual scores for each of the four photographs taken were then totalled for each patient to give an overall visibility score ranging from four to 12.

A second blinded investigator separately reviewed and scored the pictures from 20 patients and the results were compared with the original assigned scores.

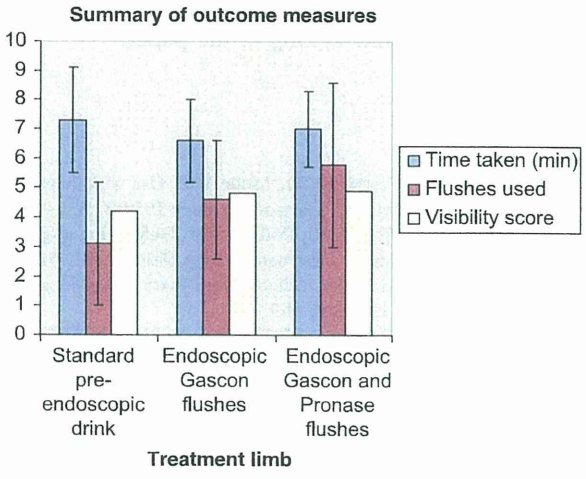

Figure 2. Outcomes.

Statistical analysis

The sample-size calculations showed that 35 participants were required in each treatment group (105 patients overall) to detect a 20% improvement in visibility scores, from 7 to 5.6, assuming a standard deviation of 2 for each group and a power of 90%. Allowing for a 30% attrition rate, we aimed to recruit 150 participants.

Differences between the number of flushes and the time taken were analysed using ANOVA and Fisher's least significant difference. As visibility scores were non-normally distributed, the Kruskal–Wallis and Dwass–Steel–Chritchlow–Fligner tests were used for these results. All analyses used SPSS software (SPSS Inc, Chicago, IL). A *P*-value of 0.05 was taken to be significant throughout.

Results

A total of 112 patients were evaluable in the study, with a mean age of 61 years. The study population comprised 51 males (46%) and 61 females (54%). There were no significant differences between treatment groups (Table I) for a summary of outcome measures please see Figure 2.

Visibility

Visibility scores allocated by the two independent visibility score assessors correlated well (Cohen's weighted kappa 0.604, standard error 0.187, 95% CI 0.237–0.971).

There were significant differences in the visibility scores assigned between groups (H = 17.8, P = 0.0001). The photographs taken from the premedicated Group S scored significantly better for visibility than either of the endoscopic therapy groups GP and G (P = 0.0002 and P = 0.0008, respectively). There was no significant difference in visibility scores between Groups GP and G (P = 0.999).

Table I. Patient characteristics.

	Group		
Characteristic	S (n = 35)	G (n = 37)	GP (n = 40)
Gender; n (%)			
Male	18 (51)	14 (38)	19 (48)
Female	17 (49)	23 (62)	21 (52)
Age (years); mean (SD)	63 (1.9)	61 (1.6)	61 (2.1)

Number of flushes needed

There were significant differences in the mean number of flushes used between groups ($F = 12$, $P = 0.0001$). Significantly fewer flushes were used during the procedure in those patients receiving conventional Japanese pre-medication (Group S) than either of the other groups (Group GP, $P = 0.008$; Group G, $P < 0.001$). In the groups receiving endoscopic flush therapy only, significantly fewer flushes were used in the group with Pronase added to the Gascon mixture ($P = 0.023$).

Time taken for procedure

There was no significant difference in the time taken to complete the procedure between any of the three groups ($F = 2.23$, $P = 0.112$).

Safety

There were no complications in any of the groups. In particular, there were no clinically detectable cases of pulmonary aspiration.

Discussion

Optimal mucosal visualization is vital for thorough endoscopic inspection, particularly when using newer methods such as chromoendoscopy [13–16]. The use of bubble-bursting agents and mucolytics has been shown to improve mucosal visibility in previous trials [17–20], but safety concerns have discouraged generalized use in the West.

We assessed a potentially more acceptable technique of spraying these agents endoscopically. Gascon (simethicone or dimethicone) is silicone-based and non-absorbable, with an excellent safety record. It causes gas bubbles to burst by reducing their surface tension and is marketed for the relief of abdominal bloating. Pronase is a mixture of proteases isolated from *Streptomyces griseus*. These agents were chosen for the study as they both have proven efficacy and have been adopted as standard treatment at the trial centre.

Our results showed that spraying the anti-foam and mucolytic agents endoscopically was not as effective in terms of improved mucosal visibility as pre-endoscopic treatment with the same combination, despite the endoscopist using a greater number of flushes to attempt to clear the mucous. We would ideally have compared the endoscopic flushes with Western standard practice, which in the UK would be to give no pre-endoscopic preparation and to use water endoscopic flushes, but were unable to do this in Japan as using mucous-clearing medication has become so accepted that it was considered unethical not to do so. Adding Pronase to the basic endoscopic flush mixture did not add any advantage in terms of mucosal visibility. The apparent superiority of a pre-endoscopic drink of mucous-clearing solution as compared to endoscopic flush therapy may reflect the more diffuse application of the solution or the 10-min delay between the drink and endoscopy.

No technique resulted in clinically detectable pulmonary aspiration but rates of aspiration during a standard gastroscopy are less than one in a thousand [21] and a larger trial would therefore be needed to properly evaluate this risk.

We conclude that the standard Japanese practice of administering a pre-endoscopic drink containing a mucolytic and anti-bubble agent is superior in terms of endoscopic mucosal visibility to endoscopic application of either both agents or an anti-bubble agent alone. We cannot recommend applying these agents as an endoscopic spray.

Whether improved mucosal visibility results in a higher detection rate of early cancers or improved clinical outcomes remains unknown and well-designed large clinical trials will be needed in the future to evaluate this.

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Remarkable progress in endoscopic resection of early gastric cancer

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Endoscopic resection is accepted in many countries as a less invasive local resection of early gastric cancer with a negligible risk of lymph-node metastasis.[1,2] Endoscopic resection preserves the stomach and therefore improves patient quality of life compared with surgery. Remarkable progress has been made during the past decade because of technical improvements and an expansion of the indications for endoscopic resection. The methods vary from polypectomy to conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD).[1,2] EMR procedures include inject and cut, strip biopsy, EMR with a cap-fitted endoscope (EMRC), endoscopic aspiration mucosectomy (EAM) and EMR with a ligating device (EMRL), whereas ESD is a relatively new endoscopic resection method that facilitates one-piece resection.

In the past, the accepted indications for endoscopic resection of early gastric cancer were a small intramucosal cancer less than 2 cm in size, having a differentiated histopathological type and without an ulcer finding.[2] Recently, the indications for endoscopic resection of early gastric cancer have been expanded, as shown in Table 1, to cover other lesions with a negligible risk of lymph-node metastasis.[2,3] These expanded indications include larger lesions and lesions with ulceration. Such lesions were previously resected by surgery because of the difficulty in effectively using EMR techniques. As a result, ESD was developed to achieve one-piece resections even for larger and ulcerative lesions.[1,2]

In volume 24 issue 6 of the *Journal of Gastroenterology and Hepatology*, Hoteya *et al.* report on the advantages of ESD for treating early gastric cancer compared to EMR.[4] The local complete resection (one-piece resection with a negative tumor margin) rate (EMR, 64%; ESD, 95%) and the curative resection rate (EMR, 60%; ESD, 83%) were significantly higher for ESD than for EMR in their study. In addition, 13 local recurrences (4.0%) were detected in the EMR group during follow up in comparison to no local recurrences in the ESD group.

One-piece resection with a negative tumor margin is optimal for endoscopic resection because it substantially reduces the risk of local recurrence. One-piece resection with a positive tumor margin and piecemeal resection both have an increased risk of local recurrence, although the thermal effect from endoscopic resection may help to prevent this. Hoteya and his colleagues demonstrated in their article that the rate of one-piece resection with a negative tumor margin was higher regardless of location in ESD compared to EMR, thus reducing the overall risk of local recurrence. Their results were similar to previously published reports.[5–8]

Table 1 Histopathological criteria for curative endoscopic resection

Early gastric cancer with negligible risk of lymph-node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumor size without ulcer finding or intramucosal cancer ≤ 30 mm in size with ulcer finding or minute submucosal cancer (sm1) ≤ 30 mm in size
Resection margin
Tumor-free lateral margin
Tumor-free vertical margin

One-piece resection is also optimal because endoscopic resection is a local resection procedure without lymph-node dissection. It is therefore indicated for early gastric cancer with a negligible risk of lymph-node metastasis. The early gastric cancer criteria for a negligible risk of lymph-node metastasis are shown in Table 1. Tumor depth is one of the most important factors, but endoscopic prediction of early gastric cancer in terms of tumor depth is not always accurate, even when endoscopic ultrasonography is used.[9–11] The curability of endoscopic resection therefore must be determined histopathologically based on criteria for early gastric cancer with a negligible risk of lymph-node metastasis, as well as the resection margin (Table 1).

Endoscopic resection is considered to be non-curative if a tumor is diagnosed as having either a possible risk of lymph-node metastasis or a positive lateral margin. In fact, lymph-node metastasis has been reported among 6.3% of patients who had surgery following non-curative endoscopic resection with a possible risk of lymph-node metastasis.[12] Piecemeal resections can make it difficult to histopathologically evaluate curability, thus resulting in some findings that suggest a possible risk of lymph-node metastasis being overlooked. Without surgical treatment in such cases, there could be a risk of distant metastasis developing. It follows that histopathological staging using specimens obtained by one-piece resection is crucial with endoscopic resection so as to decide on the need for any subsequent treatment.

Hoteya *et al.* also demonstrated that there were no significant differences in complication (postoperative bleeding and perforation) rates between EMR and ESD. Endoscopic resection techniques should be safe, but endoscopic resection has been associated with an increased risk of complications such as bleeding and perforation. Although there was no reported significant difference in the perforation rate between the EMR and ESD groups, several earlier articles indicated that the risk of perforation was higher for ESD than for EMR.[2,5] It has also been reported previously that the risk of perforation is related to tumor location, size and an ulcer finding,[13,14] as has the usefulness of endoscopic closure with endoclips for gastric perforations.[14]

Whereas the rate of postoperative bleeding was similar between EMR and ESD, intraoperative bleeding occurs infrequently with EMR, but is quite common with ESD.[15] Management of intraoperative bleeding plays a critical role in achieving complete resection during ESD. Cautery is used for hemostasis during endoscopic resection because endoclips interfere with the subsequent resection.

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