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

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

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).

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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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
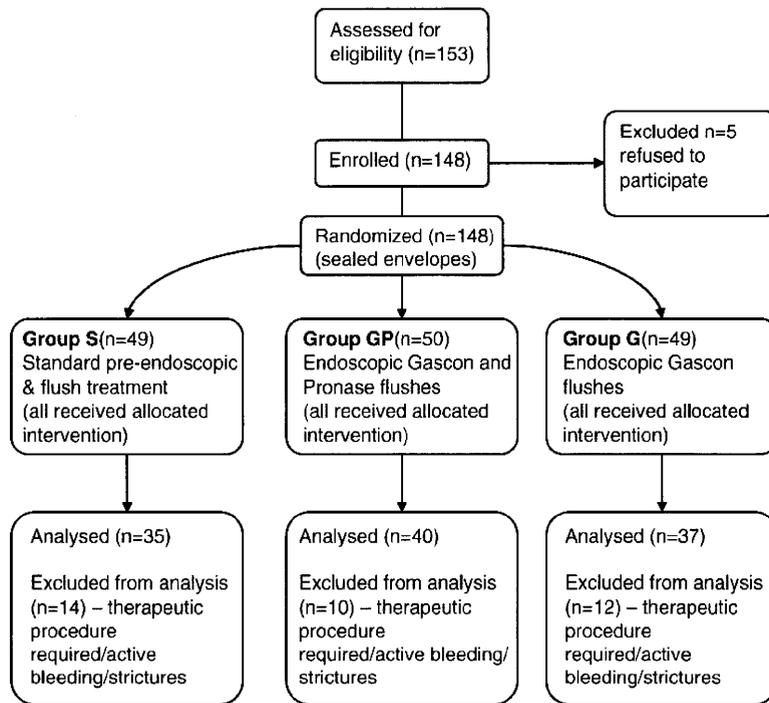

Figure 1. Flowchart showing the disposition of the study patients.

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.
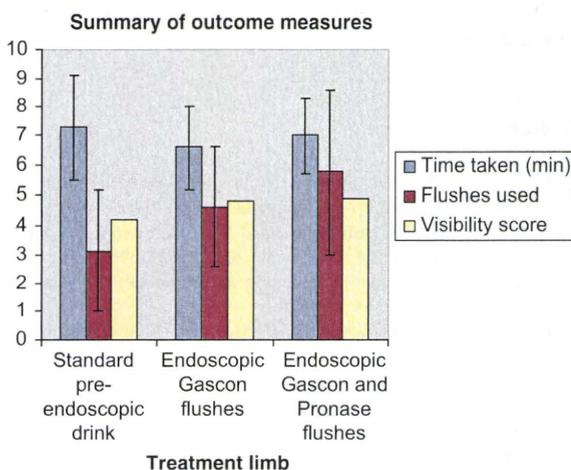

Figure 2. Outcomes.

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.

Characteristic	Group		
	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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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

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]

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.

Minor oozing can be controlled by cautery using cutting devices such as the needle knife, IT knife, Hook knife or Flex knife. Cautery using hemostatic forceps is suitable for arterial bleeding.[15]

The number of early gastric cancer patients undergoing endoscopic resection is increasing in Japan because of the expanded indications and technical improvements mentioned above. Consequently, the actual number of complications associated with endoscopic resection has also increased. Thus, endoscopists must now be aware of both the risk factors and the rate of complications as well as how to effectively treat such complications.

Early detection is essential for carrying out endoscopic resection. Japan has had a well-organized mass-screening program for gastric cancer as part of its public health services since the mid-1960s.[16] This program has, however, most often used gastrophotofluorography which has comparatively poor resolution so that sensitivity for early-stage cancer was low (39%), albeit sensitivity for advanced cancer was high (92%).[17] Recently, the development of video endoscopy has had a substantial impact on improving early diagnosis, and early gastric cancer now accounts for nearly 50% of all gastric cancers treated at major medical facilities in Japan.[18,19] In fact, most cases (78%) of early gastric cancer at our hospital between 2001 and 2003 were detected by endoscopy.[20]

The use of endoscopy for mass screening nationwide would be impractical and difficult, because of its low cost-effectiveness and the lack of a sufficient number of endoscopists. An alternative mass-screening approach has been proposed using endoscopy after the identification of high-risk subjects.[21] An initial screening test would be carried out using combination assays of serum *Helicobacter pylori* antibody and pepsinogen, followed by endoscopic examination of those individuals determined to be high-risk subjects. Such a strategy might also prove useful for the detection of early gastric cancer in other countries where the ratio of early gastric cancer to all gastric cancer cases is still low.

Finally, Hoteya and his colleagues also reported that the rate of one-piece resection with a negative tumor margin did not differ significantly between EMR and ESD for lesions ≤ 5 mm in diameter. Such lesions can therefore be treated by either EMR or ESD. The precise method of resection is less important because the primary aim of endoscopic resection as a local resection procedure is to achieve one-piece resection with a negative tumor margin. In other words, alternative resection methods that may be developed in the future, such as a full-thickness resection procedure, could eventually replace ESD for the local resection of early gastric cancer.

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原 著

胃癌に対する深達度診断の現状

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要旨：胃癌の治療方針決定には正確な深達度診断が要求される．深達度診断の今後の検討課題を明らかにするために，2001 年から 2003 年に当院で外科切除あるいは内視鏡切除された単発胃癌 1846 例を対象に，通常内視鏡による深達度診断正診率および肉眼型，UL の有無，部位，腫瘍径，組織型別の早期癌誤診例の検討を行った．早期癌，進行癌の正診率は 95%，86%，早期癌 1258 例の M，SM の正診率は 85%，46% であった．早期癌誤診例はⅡa＋Ⅱc 型，UL＋，21mm 以上，未分化型でそれぞれ他の因子に比し有意に高率であった．胃癌の深達度診断は，特に SM の正診率が低く，今後さらなる診断精度の向上が望まれる．

索引用語：胃癌，深達度診断，内視鏡診断

緒 言

胃癌に対する治療方針の決定に際しては，正確な深達度診断が必要である．たとえば，外科手術における定型手術あるいは縮小手術の選択にはT1とT2の鑑別，内視鏡切除の適応決定には，MとSMとの鑑別が重要となる[1]．内視鏡による胃癌の深達度診断は，これまで多くの検討が行われてきたが[2]~[5]，いまだ十分とはいい難い．また，超音波内視鏡[6]に加えて，近年では拡大内視鏡[7]，狭帯域フィルター内視鏡（Narrow Band Imaging；NBI）など特殊光観察[8]も用いられ，その診断精度の向上が期待されている．そこで今回われわれは，今後さらに発展すると思われる拡大内視鏡，特殊光観察時代に向けての検討課題を明らかにするために，当院において拡大内視鏡，特殊光観察導入以前の症例を対象に，通常内視鏡による胃癌の深達度診断の現状を検討した．

Ⅰ 対象と方法

2001 年から 2003 年までの 3 年間に国立がんセンター中央病院で外科的に胃切除あるいは内視鏡切除が施行された単発胃癌 1846 症例を対象に以下の検討を行った．対象の年齢中央値は 64 歳（26～93），性別は男/女；1301/545 であった．検討 1 として，内視鏡による臨床診断（c）と切除後病理診断（p）より深達度診断正診率の検討を行った．内視鏡による臨床診断（c），特に M と SM との診断は，2001 年の小野らの報告[4]に基づき，胃癌取扱い規約による肉眼型[9]ごとに診断した．具体的には，Ⅰ型は 2cm 以下では M，2cm を超えかつ広基性や表面にくずれ・陥凹をともなう場合に SM と診断した（Figure 1a，b）．Ⅱa型は基本的に M であるが，大小不同の結節が目立つ，中心陥凹がある，表面にびらん・発赤をともなう場合は SM とした（Figure 1c，d）．陥凹型では，著明な発赤，ひだ先端の融合，壁の厚み，陥凹内隆起，粘膜表面の無構造化，辺縁粘膜下腫瘍様隆起は SM（もしくは SM 以深）を示唆する所見とした（Figure 1e，f）．また，陥凹型では

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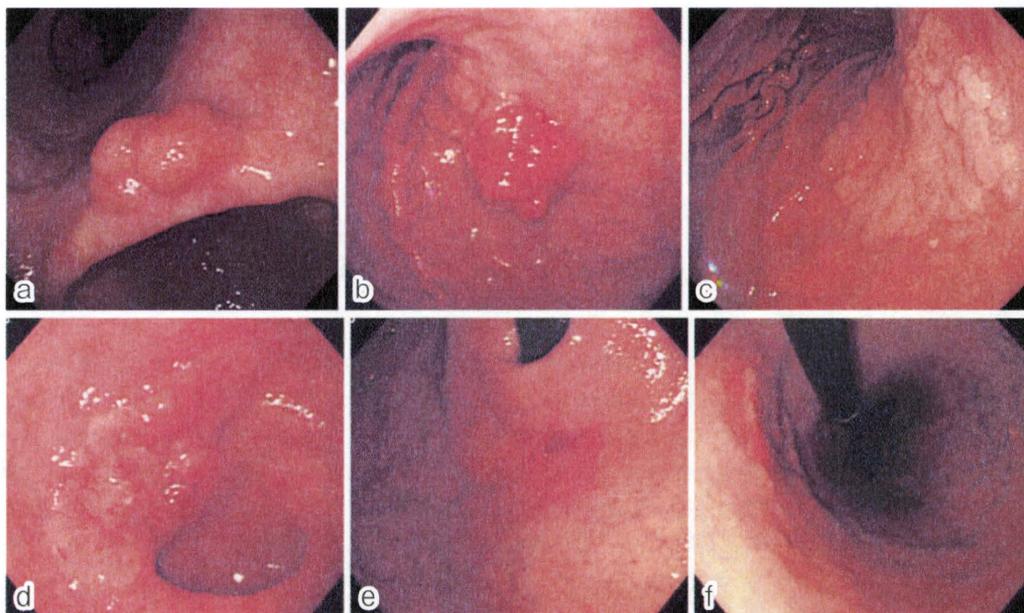
Figure 1. 通常内視鏡による深達度臨床診断　**a**：1.5cm 大のⅠ型病変で表面にくずれ・陥凹などを認めず，Mと診断する．**b**：2.5cm 大，広基性のⅠ型病変で，SMと診断する．**c**：5cm 大のⅡa型病変で表面に陥凹などを認めず，Mと診断する．**d**：2.5cm 大の中心陥凹をともなう隆起性病変（Ⅱa＋Ⅱc型）でSMと診断する．**e**：2cm 大の浅い陥凹性病変（Ⅱc型）で，粘膜模様は保たれ，壁の厚みなどを認めず，Mと診断する．**f**：2.5cm 大の陥凹性病変（Ⅱc型）で，壁の厚みをともないSMと診断する．

大きさも深達度と相関している（2cm 以上では約半数でSM）ことを考慮した．また，実際の内視鏡検査は内視鏡経験3年以上の複数の内視鏡医によって行い，全対象症例の内視鏡による臨床診断（c）は，内視鏡部，放射線診断部，外科，病理部の合同によって術前に毎週開催される症例検討会により最終決定した．切除後病理診断（p）は，内視鏡切除の病理報告書，外科的胃切除の病理報告書よりデータを採取し，内視鏡切除後に追加外科的胃切除を施行した場合は最深の深達度とした．検討2として，早期胃癌における誤診例を肉眼型，UL有無，部位，腫瘍径，組織型別に検討した．検討に際して，肉眼型はⅠ・Ⅱa型，Ⅱa＋Ⅱc型，Ⅱc・Ⅱb型に，UL有無はUL＋とUL－に，部位はU領域，M領域，L領域に，腫瘍径は10mm 以下，11～20mm，21mm 以上に，組織型は優勢な組織像に従い分化型，未分化型に大別し[9]，それぞれの因子における誤診率および浅読みあるいは深読みに関する内訳を検討した．

各因子別の誤診率は，χ^2検定を用い，$p<0.05$を有意差ありと判定した．

Ⅱ　結　果

【検討1】深達度診断の正診率

対象期間中の日常臨床において，内視鏡による臨床診断は，概ねcM，cSM，cMP-SS，cSEと診断されていた．SMの臨床診断（cSM）はcSM1とcSM2に亜分類されていなかった．早期癌と進行癌の鑑別ではp早期癌，p進行癌の正診率はそれぞれ95％，86％であった（Table 1）．

早期癌1258症例のうちpMは836症例，pSMは422症例であった．pM 836症例の正診率は85％で，14％がcSMに，1％がcMP以上に深読みされていた．pSMの正診率は46％で，42％はcMと浅読み，12％はcMP以上に深読みされていた（Table 2）．

pSM 422症例のうち，pSM1は155症例，pSM2は267症例であった．Table 3に示すようにpSM1のうちcSMと臨床診断された症例は30％で，

Table 1. 早期癌と進行癌の診断

		臨床診断	
		c 早期癌	c 進行癌
病理診断	p 早期癌	95% (1199/1258)	5% (59/1258)
	p 進行癌	14% (84/588)	86% (504/588)

Table 2. M と SM の診断

		臨床診断		
		cM	cSM	cMP
病理診断	pM	85% (714/836)	14% (112/836)	1% (10/836)
	pSM	42% (177/422)	46% (196/422)	12% (49/422)

Table 3. SM1 と SM2 の診断

		臨床診断		
		cM	cSM	cMP
病理診断	pSM1	65% (100/155)	30% (47/155)	5% (8/155)
	pSM2	29% (77/267)	56% (149/267)	15% (41/267)

65% は cM と診断されていた. pSM2 では, 56% が cSM に臨床診断され, 29% が cM と浅読み, 15% が cMP 以上に深読みされていた.

【検討 2】早期胃癌における誤診例の検討

Table 4 に肉眼型, UL 有無, 部位, 腫瘍径, 組織型別の早期胃癌誤診例を示している. 肉眼型別の誤診率は II a + II c 型で 36% と他の I・II a 型, II c・II b 型に比し有意に高率であった ($p <$ 0.05). I・II a 型では pSM を cM と浅読みした例が多く, II a + II c 型と II c・II b 型では浅読みと深読みともに分布していた.

UL の有無別には UL + で UL − に比し誤診率が 37% と有意に高率であった ($p < 0.01$). UL − では浅読みした例が多く, UL + では浅読みと深読みともに分布していた.

部位別には, U 領域で他の M 領域, L 領域より誤診率が高率であったが, 有意差は認めなかった. また, U 領域, M 領域では浅読みした例が多く, L 領域では深読みした例が多かった.

腫瘍径別には, 誤診率は 21mm 以上で 37% と他の 10mm 以下, 11〜20mm に比し有意に高率であった ($p < 0.01$). また, 10mm 以下, 11〜20 mm では浅読みした例が多く, 21mm 以上では深読みした例が多かった.

組織型別には, 分化型 22% に比し未分化型で 42% と誤診率が有意に高率であった ($p < 0.01$). 誤診例の内訳をみると分化型では浅読みした例が多く, 未分化型では深読みした例が多かった. また, 分化型のうち, 中分化型管状腺癌 (34%：37/ 110, $p < 0.01$) と乳頭腺癌 (42%：5/12, $p < 0.05$) の誤診率は, 高分化型管状腺癌 (20%：160/789) の誤診率に比し有意に高率であった.

III 考 察

近年, 治療技術の向上にともなって, 早期胃癌に対する縮小手術, 内視鏡切除は広く普及してきているが, その治療方針決定には正確な深達度診断が要求される. 誤診例のうち, 深読みは, 縮小手術や内視鏡切除で根治可能な病変を過剰に治療する原因となる. 一方, 術前に浅読みされ縮小手術や内視鏡切除が行われた場合, 根治的治療とし

Table 4. 肉眼型，UL 有無，部位，腫瘍径，組織型と誤診例

	誤診率			
	pSM を cM と浅読み	pSM を cMP 以上と 深読み	pM を cSM 以上と 深読み	計
肉眼型				
I・IIa（n = 236）	15%　（35）	4%　（9）	0.4%　（1）	19%　（45）
IIa + IIc（n = 125）	20%　（25）	12%　（15）	4%　（5）	36%　（45）
IIc・IIb（n = 897）	13%　（117）	3%　（25）	13%　（116）	29%　（258）
UL の有無				
UL −（n = 762）	15%　（112）	3%　（26）	3%　（26）	22%　（164）
UL +（n = 496）	13%　（65）	5%　（23）	19%　（96）	37%　（184）
部位				
U 領域（n = 230）	23%　（53）	4%　（10）	5%　（12）	33%　（75）
M 領域（n = 407）	16%　（64）	1%　（6）	7%　（27）	24%　（97）
L 領域（n = 621）	10%　（60）	5%　（33）	13%　（83）	28%　（176）
腫瘍径				
10mm 以下（n = 275）	6%　（15）	0.4%　（1）	1%　（3）	7%　（19）
11 〜 20mm（n = 357）	19%　（66）	0.8%　（3）	8%　（29）	28%　（98）
21mm 以上（n = 626）	15%　（96）	7%　（45）	14%　（90）	37%　（231）
組織型				
分化型（n = 911）	15%　（137）	3%　（24）	5%　（41）	22%　（202）
未分化型（n = 347）	12%　（40）	7%　（25）	23%　（81）	42%　（146）
計（n = 1258）	14%　（177）	4%　（49）	10%　（122）	28%　（348）

て不十分な治療につながる可能性がある．

定型手術あるいは縮小手術の選択において，深達度に関しては，T1（早期癌）あるいは T2 以上（進行癌）の鑑別が問題となる[1]．今回の検討において，早期癌と進行癌の正診率は 95％ と 86％ であり，当院の 1997 年から 2001 年までの検討[4]の成績（95％ と 85％）と比し大きな向上はなかったが，臨床的に妥当な成績と考えられた．

内視鏡切除の適応決定には，M と SM との鑑別が重要となる．今回の検討において，M の正診率は 85％ と 1997 年から 2001 年までの検討[4]の成績（84％）とほぼ同様であったが，SM の正診率は 46％ で，1997 年から 2001 年までの検討[4]の成績（66％）と比べ 20％ 低下していた．そのうち，pSM を cM に浅読みしたのが 42％，pSM を cMP 以上に深読みしたのが 12％ と，1997 年から 2001 年までの検討[4]の成績（20％ と 14％）に比し浅読みが高率であった．これは内視鏡切除が内視鏡的粘膜切除術（EMR）[10]~[12]から内視鏡的粘膜下層剥離術（ESD）[13]~[16]の時代へと移り変わり，

正確な病理学診断が可能となり，pM を cSM 以上と深読みすることによる過剰な治療（ESD で根治可能な病変を手術する）を防ぐため，ESD を診断的側面として利用しているためと思われる．つまり，当院では①生検で分化型，②cM，③UL−病変は腫瘍径に制限なし，UL＋病変は腫瘍径 30mm 以下を ESD 前の適応基準とし，ESD 後に Table 5 に示す治癒切除基準に基づき病理評価を行い，追加の外科的切除の必要性を判断している．ESD 前の適応基準のうち，特に②の cM に関しては，pM を cSM 以上と深読みすることにより過剰な治療となることを防ぐため，明らかな cSM 所見のない場合は cM と判断し，診断的意義を含めた ESD を行っているためと推測される．早期癌の誤診例の内訳において，pM を cSM 以上と深読みした症例が，ESD の対象となり得る分化型において未分化型に比し少なかったことも上記を示唆していると考えられる．また，ESD の対象が多く含まれる UL−，小さな症例において深読みした症例が少なかったことも同

Table 5. ESD 治癒切除基準

1. 分化型腺癌
2. 脈管侵襲陰性
3. M 癌, UL − 　 or M 癌, UL ＋, 腫瘍径 30mm 以下 　 or SM1 癌, 腫瘍径 30mm 以下, 浸潤部低分化型腺癌成分陰性
4. 水平断端陰性, 垂直断端陰性

様に上記を示唆していると考えられる．実際に当院外科的胃切除例で，結果的に胃癌学会ガイドラインのEMR適応基準内[1]であった症例の頻度は，EMR時代には3.8%（52/1369）であったのに対し，ESD時代には0.2%（2/954）に減少していた[17]．

以上のように，pMをcSM以上と深読みすることによる過剰な治療を防ぐため，pSMをcMと浅読みした症例が増加していたと推測されるが，ESD自体を診断過程の1つのモダリティーととらえると臨床的には許容されると考える．しかし，一方でそのような浅読み症例でESD後に仮に適切な追加外科的胃切除が行われない場合は，根治的治療として不十分な治療となる可能性がある．実際に当院で内視鏡切除後，結果的に非治癒切除であった226症例のうち，約35%は追加外科的胃切除が行われていなかった[18]．その理由の半数は手術リスクや他臓器癌などであったが，残りの半数は患者選択であった[18]．ESD後結果的に非治癒切除となった場合の外科的胃切除の必要性については，ESD前より十分に説明しておく必要があると思われる．そのほか，ESD偶発症の可能性，コストの観点からも本来的には内視鏡診断によりMとSMの鑑別が行われ，適切な治療へと適応が決定されることがより望ましいことはいうまでもなく，超音波内視鏡，拡大内視鏡,特殊光観察も含め,今後の改善が必要である．

近年，外科手術例における検討[19]より，Table5に示すように分化型のSM1癌も腫瘍径3cm以下，浸潤部低分化型腺癌成分なし，脈管侵襲なしであれば，リンパ節転移が0%（95%信頼区間：0〜2.5%）であり，内視鏡切除にて根治可能な病変として扱われつつある．しかし，SM1に対す

る確立された内視鏡診断基準はないため，日常臨床においてはcSM1と積極的に臨床診断しているのではなく，cMあるいはcSMと臨床診断しているのが現状である．今回対象のpSM1，pSM2別の検討（Table 3）によると，pSM1病変は65%においてcM，30%でcSMと，pSM2病変のcMが29%，cSMが56%であった成績とは異なり，臨床的にはcMと判断されていることが多かった．しかし，pSM1病変のcMが65%，cSMが30%（Table 3）は，pM病変のcMが85%，cSMが14%（Table 2）の成績とも相違があり，pSM1病変の臨床診断は，pM病変とpSM2病変の臨床診断の中間に位置していた．SM1に対する内視鏡診断基準を持たない現状においても，結果的にこのようにpMとpSM2の中間にpSM1が位置していたことは，SM1の内視鏡診断基準を作成できる可能性があることを示唆している．拡大内視鏡や特殊光観察を含め，今後の検討に期待したい．

早期胃癌における誤診例の検討により，肉眼型，UL有無，部位，腫瘍径，組織型ごとにそれぞれの因子ごとにその誤診率や浅読みが多い病変，深読みが多い病変の内訳が明らかになった．この点に関しても，拡大内視鏡や特殊光観察を含めた，さらなる検討が必要である．

結　語
内視鏡的診断学および機器の進歩した現時点においても，胃癌に対する深達度診断成績はいまだ十分とはいえず，その課題が浮き彫りとなった．通常内視鏡，超音波内視鏡に加えて，近年では有用性が期待されている拡大内視鏡や特殊光観察も含め，今後のさらなる検討が必要である．

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Endoscopic diagnosis of gastric cancer invasion depth

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Accurate endoscopic diagnosis of gastric cancer invasion depth is essential in making a proper treatment strategy decision. We investigated the accuracy of diagnostic depth invasion in 1846 gastric cancers resected by surgery or endoscopy from 2001 to 2003 at our hospital. Diagnostic accuracy was 95% for early cancer and 86% for advanced cancer; and 85% for mucosal cancer and 46% for submucosal cancer. The rate of diagnostic inaccuracy was significantly higher in IIa + IIc type than in other macroscopic types; and lesions with UL than without UL; lesions >20mm and those ≤20mm; as well as in undifferentiated type than in differentiated type, respectively. Endoscopic diagnosis of gastric cancer invasion depth was not always accurate and improved diagnosis for submucosal cancer in particular is necessary.

Original article

Pilot study to assess the safety of local lidocaine injections during endoscopic submucosal dissection for early gastric cancer

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Abstract

Background. In Japan, endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is performed by endoscopists on patients under sedation. There is an increased risk of anesthesia-related complications due to the higher sedative doses required during lengthier ESDs, so we sought to determine whether a local pain control method could safely reduce such doses.

Methods. Twenty EGC patients enrolled in this study received local lidocaine injections during ESDs at our hospital (lidocaine group; LG). Electrocardiography, heart rate, oxygen saturation, and blood pressure were monitored during and after the ESDs, along with the doses of midazolam and pentazocine. Pain assessments were recorded for LG patients on the day of their ESDs and the following day.

Results. The mean volume of lidocaine injection solution was 55.4 ml and the mean dose of lidocaine was 236 mg (range, 100–300 mg). The mean size of the resected specimens was 39.3 mm and mean procedure time was 66.0 min. There were no lidocaine-related complications, and electrocardiography, heart rate, oxygen saturation and blood pressure measurements were normal. In comparison to 157 consecutive patients (control group; CG), who had similar characteristics and had undergone ESDs previously with submucosal injections of conventional normal saline solution, the mean ± SD pentazocine dose of 15.8 ± 10.3 mg in the LG was significantly lower ($P < 0.01$) than the dose of 23.1 ± 9.5 mg in the CG, and none of the LG patients complained of abdominal pain on the day of their ESDs, whereas such pain was reported by 17% (27/157) of the CG.

Conclusion. Local lidocaine injections into the submucosal layer were safe when administered during ESDs performed on EGC patients under sedation.

Key words Lidocaine · Endoscopic submucosal dissection (ESD) · Early gastric cancer · Local anesthesia · Submucosal injection

Introduction

Although endoscopic submucosal dissection (ESD) is less invasive for early gastric cancer (EGC) than gastrectomy, the classical open surgical procedure, some ESD patients suffer considerable postoperative pain. Localized pain both during and after ESD for large EGCs is probably caused by ulcer defects and/or electrical thermal burns extending from the submucosal (sm) layer to the serosa.

There is a problem not only with pain management but also with sedation management during the ESD procedure. In a previous report, 41% of ESDs took longer than 1 h [1]. As a result of such increased procedure times, therefore, higher doses of sedative drugs such as midazolam have become necessary, and endoscopists performing ESDs must be even more careful about the depth of patient sedation, because deep sedation can occur during endoscopic procedures [2]. Because there is an increased risk of anesthesia-related complications with the higher sedative drug doses required during lengthier ESDs, we decided to determine whether a local pain control method could safely reduce such doses.

By controlling localized pain during ESD, we thought that it might be possible to reduce the dose of the sedative drug administered during the actual procedure. In addition, administering local analgesia for pain during ESD would amount to providing preemptive analgesia for patient pain that might otherwise be experienced the day after the procedure [3].

Local anesthesia is commonly used in surgery, including laparoscopic surgery [4, 5], but there have been no previous reports on the use of lidocaine for local pain control either during or after ESD. This study intended to assess the safety of local lidocaine injections into the sm layer of EGC lesions in controlling localized pain both during and subsequent to ESD procedures performed on patients under sedation.

Patients and methods

Patients

A total of 20 EGC patients were enrolled in this study (lidocaine group; LG) between September 2005 and April 2007 at the National Cancer Center Hospital in Tokyo, Japan. These subjects were scheduled for gastric ESDs based on endoscopic mucosal resection (EMR) guideline criteria [6, 7] and had their given informed consent before undergoing the procedures. Patients with: (1) an allergy to lidocaine or other amide-type local anesthesia; (2) severe liver disease, heart disease, or renal dysfunction; (3) a gastric or duodenal ulcer; (4) atherosclerotic disease; (5) hyperthyroidism; or (6) an American Society of Anesthesiologists (ASA) physical status higher than class 2 were excluded from the study. This study was performed in accordance with the Helsinki Declaration as revised in 1989.

ESD procedures

ESDs were performed following a standard protocol, and procedure times were recorded for all LG patients. Lesion margins were delineated beforehand by using 0.2% indigo-carmine dye spraying. After the marking dots were made with a needle knife (KD-1L-1; Olympus Medical Systems, Tokyo, Japan), 0.5% lidocaine solution was injected into the sm layer to lift the lesion. A circumferential incision in the mucosa was then completed using the needle knife, an insulation-tipped knife (IT knife; KD-610L, Olympus) [7–10], and a high-frequency current electrical generator (ICC 200; ERBE, Tubingen, Germany) and, finally, the thickened sm layer was dissected using the same two endoscopic knives.

Injection solutions

As previously noted, we used 0.5% lidocaine solution consisting of 10 ml of Xylocaine Polyamp 1%, containing 100 mg of lidocaine hydrochloride (HCl; AstraZeneca, Osaka, Japan), 9.7 ml of normal saline, 0.2 ml of 0.4% indigo-carmine dye, and 0.1 ml of 0.1%

epinephrine (Table 1) for the LG in this study. The maximum volume of 0.5% lidocaine solution per LG patient was 60 ml, which contained 300 mg of lidocaine HCl [11–13].

For the purpose of lifting an EGC lesion, the lidocaine injection solution was injected into the sm layer under and around the lesion, as determined by the endoscopist, using a 23-gauge needle injection catheter (NM-200L-0423; Olympus). Once the needle was inserted into the sm layer, the endoscopist's assistant would aspirate the syringe, particularly for those patients suffering from hypertension or diabetes mellitus, thereby creating negative pressure. If no blood reflex appeared, the assistant would begin injecting the solution and would stop when the lesion was sufficiently lifted and became slightly blue in color, with the total volume of the injection solution being recorded at that time.

Patient monitoring during and following ESD procedures

Electrocardiography, heart rate, oxygen saturation, and blood pressure were automatically monitored during and after each ESD; lidocaine-related complications were recorded, as were any complications resulting from the ESD itself, such as a perforation. In addition, the patient's white blood cell count and C-reactive protein level were checked on the first day following the ESD.

Sedation during ESDs

All ESDs on LG patients were performed following standard sedation procedures. Sedation was induced with 0.06 mg/kg of midazolam. Incremental 2-mg doses of midazolam were given if a patient demonstrated signs of discomfort, restlessness, or agitation, or responded to verbal commands. When additional midazolam was ineffective, 15 mg of pentazocine was infused as an analgesic agent. Each patient received oxygen by nasal cannula from the start of the ESD for a maximum period of 3 h after the procedure.

Table 1. Composition of injection solutions

	Lidocaine solution	Conventional solution
1% Lidocaine (ml) (Lidocaine 100 mg/10 ml)	10	0
Normal saline (ml)	9.7	19.7
0.4% Indigo-Carmine (ml)	0.2	0.2
0.1% Epinephrine (ml)	0.1	0.1
Lidocaine concentration (%)	0.5	0
Maximum lidocaine injection	300 mg/60 ml	