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ORIGINAL ARTICLE

Diazepam during endoscopic submucosal dissection of gastric epithelial neoplasias

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Abstract

AIM: To investigate risk factors and adverse events related to high-dose diazepam administration during endoscopic submucosal dissection for gastric neoplasias.

METHODS: Between February 2002 and December 2009, a total of 286 patients with gastric epithelial neoplasia underwent endoscopic submucosal dissection in our hospital. To achieve moderate sedation, 5-7.5 mg of diazepam was administered intravenously by non-anesthesiologists. Intermittent additional administration of 2.5-5 mg diazepam was performed if uncontrollable body movement of the patient was observed. All patients were classified into groups based on the required diazepam dose: low-dose ($\leqslant$ 17.5 mg, n = 252) and high-dose (> 17.5 mg, n = 79).

RESULTS: Differences between the low- and high-dose diazepam groups were observed in lifetime alcohol consumption (0.30 ± 0.48 *vs* 0.44 ± 0.52 tons, P = 0.032), body weight (58.4 ± 10.3 *vs* 62.0 ± 9.9 kg, P = 0.006), tumor size (15 ± 10 *vs* 23 ± 18 mm, P < 0.001), lesion location (P < 0.001) and the presence of ulcerative findings (14/238 *vs* 18/61, P < 0.001). Multivariate analysis identified all five variables as independently related to required diazepam dosage. In terms of adverse reactions to diazepam administration, paradoxical excitement was significantly more frequent in the high-dose diazepam group (P < 0.001).

CONCLUSION: Intermittent administration of diazepam enabled safe completion of gastric endoscopic submucosal dissection except in patients who were alcohol abusers or obese, or who showed complicated lesions.

Key words: Diazepam; Endoscopic submucosal dissection; Gastric epithelial neoplasias; Moderate sedation; Non-anesthesiologists

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is a novel and minimally invasive procedure for the treatment of gastric epithelial neoplasia. As this technique permits en bloc resection of lesions, ESD has the advantages of enabling accurate pathological assessment and reducing the risk of local recurrence[1]. However, in comparison to conventional endoscopic mucosal resection (EMR), ESD requires a high level of endoscopic competence and a longer resection time[2-4]. In addition, many cases of early gastric cancer occur in elderly patients, who also display increased sensitivity to sedatives and a higher risk of adverse reactions, including respiratory and cardiovascular depression[5]. Suitable sedatives that do not cause complications and permit safe completion of ESD thus need to be identified.

The American Society of Anesthesiologists (ASA) classifies the degree of sedation into four levels: minimal sedation; moderate or conscious sedation; deep sedation; and general anesthesia[6]. Given that deep sedation or even general anesthesia can be achieved with propofol, the ASA suggests that care must be taken even if aiming for moderate sedation[6]. In addition, due to the narrow therapeutic window[7-9], the American Society for Gastrointestinal Endoscopy has recommended the presence of trained personnel dedicated to the administration of propofol[10]. To date, the safety and efficacy of sedation using propofol have been reported in esophagogastroduodenoscopy, colonoscopy, endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography[11-15]. In contrast, due to the risk of cardiorespiratory complications, particularly in the elderly, the Japan Gastroenterological Endoscopy Society does not recommend sedation using propofol for endoscopic procedures. Thus, there is an in-principle requirement in Japan that propofol be administered by an anesthesiologist. As a result, not many institutions use propofol for sedation during ESD[16,17].

Of the available sedatives, benzodiazepines are generally considered to have a broad safety margin as they do not activate the gamma-aminobutyric acid $(GABA)_A$ receptor in the absence of endogenous GABA[18]. Diazepam is the least potent injectable benzodiazepine sedative, with a long history of clinical use, even by non-anesthesiologists. Moreover, unlike in the case of propofol administration, if a patient falls into deep sedation while being treated with diazepam, a pharmacological antagonist (flumazenil) can be administered to counter this effect[19,20]. Fujishiro *et al*[21] reported that, in principle, ESD for esophageal squamous cell neoplasms could be performed with the patient under conscious sedation induced by intermittent administration of diazepam and pentazocine. However, administration methods have yet to be clearly established for safe and effective sedative use during the gastric ESD procedure.

The objectives in this retrospective study were to evaluate variables relating to the diazepam dosage during ESD for gastric epithelial neoplasia and to investigate the characteristics and adverse events of patients administered high-dose diazepam.

MATERIALS AND METHODS

Patients

Between February 2002 and December 2009, we performed ESD for 446 gastric epithelial neoplastic lesions in 342 consecutive patients treated at Wakayama Medical University Hospital. ESD was indicated for patients with adenomas suspected of being malignant on the basis of endoscopic findings or biopsy. In addition, ESD was indicated for patients with early gastric cancers that were considered to have a nominal risk of lymph node metastasis according to the criteria of Gotoda *et al*[22], excluding undifferentiated cancers. For this study, we retrospectively analyzed ESDs that had been performed for 331 lesions in 286 patients (mean age, 69.5 years; range, 42-90 years). Excluded lesions comprised 77 cases for which multiple lesions had been simultaneously dissected by ESD, 26 cases for which diazepam had not been administered, 7 lesions in which other investigations had been carried out, and 7 lesions for which the intraoperative records were unclear (with an overlap of 2 lesions). All patients underwent blood tests, chest X-rays and electrocardiographic testing before treatment. ESD was indicated for patients with an ASA classification of 1-3[23]. This study was approved by the ethics committee of Wakayama Medical University, and all patients provided written informed consent prior to undergoing ESD.

ESD procedures

ESD was performed by one of four experienced therapeutic endoscopists, each of whom had performed ESD for more than 50 cases of early gastric cancer or gastric adenoma. We predominantly used a flex electrosurgical knife (KD-630L; Olympus, Tokyo, Japan)[2,24], along with a hook knife (KD-620LR; Olympus) when necessary[25]. Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan)[26-28] were used to reduce bleeding during ESD.

Diazepam administration

We aimed to achieve moderate sedation during ESD. For introduction, we intravenously administered diazepam (Cercine®; Takeda Pharmaceutical, Osaka, Japan) at 5-7.5 mg/body (5 mg/body for patients $\geqslant$ 75 years old or weighing $\leqslant$ 50 kg) prior to insertion of the endoscope; in principle, administration of diazepam was continued

up to 10 mg during ESD. When the sedative effect of 10 mg diazepam was judged sufficient, administration of the drug was continued without any change, and additional administration was performed in intermittent doses of 2.5-5 mg/body each, only when uncontrollable body movement was observed (maximal dose: 40 mg). When the sedative effect of 10 mg diazepam was judged to be insufficient and patient distress was considered great, diazepam was switched to midazolam (Dormicum®; Astellas Pharmaceutical, Tokyo, Japan) for rescue, administered intermittently at 1-2 mg/body. Intermittent sedative administration was performed by non-anesthesiologists (i.e., gastroenterologists) at the direction of the operator. For the purposes of pain relief, 15 mg of pentazocine (Sosegon®; Astellas Pharmaceutical) was administered intramuscularly to all patients at the start of ESD. When the level of anesthesia reached deep sedation, flumazenil (Anexate®; Astellas Pharmaceutical) was administered as deemed necessary.

Patient monitoring

Blood pressure, heart rate, electrocardiography (ECG), and peripheral oxygen saturation (SpO_2) were monitored during the procedure. Blood pressure was measured at 5-min intervals, while heart rate, ECG tracing and SpO_2 were measured continuously. Supplementary oxygen was administered to patients with SpO_2 below 90%. Administered dosages of sedatives and analgesics, all adverse events (such as decreases in SpO_2 below 90% and blood pressure below 90 mmHg), and uncontrollable body movements were recorded by trained nurses.

Patients were instructed to rest in bed for 3 h following ESD, and to remain under strict observation until the next morning. All ESD procedures were performed on an inpatient basis, and patients were discharged within 10 days after ESD if no problems were encountered.

Parameters assessed

Since several reports have indicated that it is advisable that ESD requiring around 1.5 h or more should be carried out under general anesthesia[21], patients were stratified into two groups according to procedure time (≤ 1.5 h or > 1.5 h) and then compared in terms of the following variables: age; sex; lifetime alcohol consumption; smoking habit; body weight (BW); tumor size (maximal diameter of the lesion); location (upper-third, middle-third, or lower-third of the stomach); gross morphological type (0-Ⅰ/Ⅱa, 0-Ⅱb/Ⅱc or combined type); tumor depth (mucosal or submucosal tumor); histological type (cancer or adenoma); ulcerative findings in the submucosal layer; and diazepam dosage.

Patients were also stratified into two groups according to diazepam dose: low-dose diazepam (≤ 17.5 mg, n = 252) and high-dose diazepam (> 17.5 mg, n = 79). These two groups were then compared in terms of age, sex, lifetime alcohol consumption, smoking habit, BW, use of anxiolytic agents, ASA classification, comorbidities (hypertension, diabetes mellitus, heart disease, respiratory disease, chronic renal failure, or liver cirrhosis), tumor size, tumor location, gross morphological type, tumor depth, histological type, ulcerative findings, type of resection (en bloc or piecemeal), postoperative bleeding, perforation, use of midazolam, and sedative-related adverse events such as oxygen desaturation (SpO_2 below 90%), hypotension (blood pressure below 90 mmHg), delayed awakening and paradoxical excitement.

Statistical analysis

Univariate analysis was performed using an unpaired t-test for numerical data and Fisher's exact test or the chi-squared test for categorical data. Variables that differed significantly between groups in univariate analysis were then subjected to multivariate analysis using a logistic regression model. All tests were two-sided, with values of $P < 0.05$ being considered statistically significant. All analyses were performed using SPSS software (SPSS, Chicago, IL, United States).

RESULTS

Comparison of clinicopathological features according to procedure time

The outcome of univariate analyses comparing variables according to the ESD procedure time (i.e., ≤ 1.5 h *vs* > 1.5 h) is outlined in Table 1. Significant differences were found between the two groups in relation to tumor size, location, ulcerative findings and diazepam dosage ($P < 0.001$, respectively). Specifically, mean diazepam dosage among patients with an ESD procedure time of > 1.5 h was 17.5 mg.

Comparison of clinicopathological features according to diazepam dose

Based on the above results, patients were divided into a low-dose (≤ 17.5 mg) diazepam group and a high-dose (> 17.5 mg) diazepam group. Results of univariate analyses of patient variables in relation to diazepam dosage are shown in Table 2. Significant differences in lifetime alcohol consumption and BW ($P = 0.032$ and $P = 0.006$, respectively) were found between the dosage groups. The results of univariate analyses for clinicopathological features of the lesion and clinical outcomes in relation to diazepam dosage are shown in Table 3. Significant differences in tumor size, location, ulcerative findings and resection style ($P = 0.001$ for each) were found between the two dosage groups.

Multivariate logistic analysis was performed including lifetime alcohol consumption, BW, tumor size, location and ulcerative findings in the prediction of the diazepam dosage. Each variable included in the model was shown to be independently associated with a need for high diazepam dosage (Table 4).

Patients were stratified into two groups on the basis of lifetime alcohol consumption (alcohol), using > 0.4 and ≤ 0.4 t as the strata. Finally, a second stratification was performed on the basis of BWs of > 60 kg and ≤

Table 1 Clinicopathological features of study subjects with a low (≤ 1.5 h) or high (> 1.5 h) procedure time

Variables	Procedure time ≤ 1.5 h (*n* = 180)	Procedure time > 1.5 h (*n* = 151)	*P* value
Age (yr) (mean ± SD)	69.9 ± 9.1	69.0 ± 9.6	NS
Sex (male/female)	136/44	125/26	NS
Lifetime alcohol consumption (t) (mean ± SD)	0.30 ± 0.50	0.37 ± 0.48	NS
Smoking habit (Brinkman index) (mean ± SD)	655.1 ± 777.7	563.0 ± 666.9	NS
Body weight (kg) (mean ± SD)	58.5 ± 10.9	60.1 ± 9.6	NS
Tumor size (mm) (mean ± SD)	13.3 ± 7.7	22.3 ± 16.0	< 0.001
Tumor location in stomach (U + M/L)	54/126	94/57	< 0.001
Gross morphological type (0-I / IIa *vs* 0-IIb / IIc *vs* combined)	92/68/20	76/66/9	NS
Tumor depth (mucosa/submucosa)	168/12	134/17	NS
Histological type (cancer /adenoma)	124/56	108/43	NS
Ulcerative findings, *n* (%)	2 (1.1)	30 (19.9)	< 0.001
Diazepam (mg) (mean ± SD)	9.9 ± 3.3	17.5 ± 7.8	< 0.001

SD: Standard deviation; NS: Not significant; U: Upper-third of the stomach; M: Middle-third of the stomach; L: Lower-third of the stomach.

Table 2 Clinical features of study subjects administered low- or high-dose of diazepam

Variables	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	*P* value
Age (yr) (mean ± SD)	69.8 ± 9.1	68.3 ± 10.1	NS
Sex (male / female)	194/58	67/12	NS
Lifetime alcohol consumption (t) (mean ± SD)	0.30 ± 0.48	0.44 ± 0.52	0.032
Smoking habit (Brinkman index) (mean ± SD)	649.5 ± 767.7	497.8 ± 582.5	NS
Body weight (kg) (mean ± SD)	58.4 ± 10.3	62.0 ± 9.9	0.006
Anxiolytic agents (used/not used)	46/206	7/72	NS
ASA classification (ASA 1/ ASA 2 / ASA 3)	48/151/53	20/47/12	NS
Comorbidities			
Hypertension, *n* (%)	127 (50.3)	39 (49.4)	NS
Diabetes mellitus, *n* (%)	44 (17.5)	11 (13.9)	NS
Heart disease, *n* (%)	58 (23.0)	18 (22.8)	NS
Respiratory disease, *n* (%)	30 (11.9)	4 (5.1)	NS
Chronic renal failure, *n* (%)	4 (1.6)	0 (0)	NS
Liver cirrhosis, *n* (%)	21 (8.3)	5 (6.3)	NS

SD: Standard deviation; NS: Not significant; ASA: American Society of Anesthesiologists.

60 kg. Thus, four subgroups were created and analyzed in relation to the diazepam dosage. The odds ratios of this logistic regression analysis are shown in Table 5. The combination of alcohol ≤ 0.4 t and BW ≤ 60 kg was defined as the standard subgroup. Odds ratios for the other three subgroups were found to increase in a stepwise fashion, with the greatest risk of high diazepam dose among patients with both alcohol > 0.4 t and BW > 60 kg (odds ratio = 4.52, 95% CI: 2.07 to 9.86).

Table 3 Clinicopathological features and clinical outcomes of subjects administered low- or high-dose of diazepam

Variables	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	*P* value
Tumor size (mm) (mean ± SD)	15.4 ± 10.1	23.9 ± 18.2	< 0.001
Tumor location in stomach (U and M/L)	96/156	52/27	< 0.001
Gross morphological type (0-I / IIa *vs* 0-IIb / IIc *vs* combined)	129/100/23	39/34/6	NS
Tumor depth (mucosa/submucosa)	233/19	69/10	NS
Histological type (cancer/ adenoma)	176/76	56/23	NS
Ulcerative findings, *n* (%)	14 (5.6)	18 (22.8)	< 0.001
Resection style (en bloc/ piecemeal)	246/6	63/16	< 0.001
Postoperative bleeding, *n* (%)	1 (0.4)	1 (1.3)	NS
Perforation, *n* (%)	8 (3.2)	6 (7.6)	NS
Midazolam (added / not added)	43/209	20/59	NS

SD: Standard deviation; NS: Not significant; U: Upper-third of the stomach; M: Middle-third of the stomach; L: Lower-third of the stomach.

Table 4 Factors associated with the need for high doses of diazepam: Results of multivariate logistic analysis

Variable	*P* value	Odds ratio	95% CI
Lifetime alcohol consumption	0.041	1.74	1.02-2.97
Body weight	0.034	1.03	1.00-1.06
Tumor size	0	1.05	1.03-1.08
Location in stomach	0	2.87	1.61-5.12
Ulcerative findings	0.001	4.45	1.92-10.34

CI: Confidence interval.

Adverse events

Comparisons of adverse events according to diazepam dosage are included in Table 6. The incidence of paradoxical excitement was significantly higher in the high-dose diazepam group ($P < 0.001$). However, no other significant differences in adverse events were found.

DISCUSSION

This retrospective study revealed that gastric ESD can be performed in nearly 80% of patients under sedation achieved using a low dosage of diazepam. Patients with a long ESD procedure time were characterized by large-diameter tumors, lesions located in the upper- or middle-third of the stomach, and those accompanied by ulcerative findings. Outcomes found to be predictive of

Table 5 Comparison of need for high diazepam dose between subgroups stratified for lifetime alcohol consumption and body weight

Subgroup	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	Odds ratio	95% CI
Alcohol > 0.4 t, BW > 60 kg	31	20	4.52	2.07-9.86
Alcohol > 0.4 t, BW ≤ 60 kg	38	17	3.13	1.43-6.88
Alcohol ≤ 0.4 t, BW > 60 kg	72	27	2.63	1.31-5.28
Alcohol ≤ 0.4 t, BW ≤ 60 kg	105	15	1	Referent

CI: Confidence interval. Alcohol: Lifetime alcohol consumption; BW: Body weight.

Table 6 Adverse events in patients administered a low *vs* high dose of diazepam

Variables	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	*P* value
SpO2 < 90%, *n* (%)	70 (27.8)	18 (22.8)	NS
Blood pressure < 90 mmHg, *n* (%)	8 (3.2)	2 (2.5)	NS
Delayed awakening (flumazenil used/not used)	4/248	0/79	NS
Paradoxical excitement, *n* (%)	6 (2.4)	13 (16.5)	< 0.001

NS: Not significant.

a long ESD procedure time in the current study agreed with those previously reported by Goto *et al*[29]. To the best of our knowledge, no previous reports have confirmed that the sedative dose used during gastric ESD is increased in special patient groups (e.g., alcoholics or patients with higher BW). However, we found that a number of lesion-specific findings, as well as lifetime alcohol consumption and BW, were also associated with high-dose diazepam administration. In particular, lifetime alcohol consumption > 0.4 t and BW > 60 kg were additive risk factors for increased diazepam dosage. Specifically, patients with both a lifetime alcohol consumption > 0.4 t and a BW > 60 kg showed the greatest risk of needing a high diazepam dosage during ESD. While habitual alcohol consumption may increase the clearance of diazepam, the high lipid-solubility of diazepam may also result in rapid removal from the plasma and uptake by adipose tissue[30,31]. Therefore, when predicting diazepam dosages prior to starting gastric ESD, it is important to take into account not only the difficulty of the ESD procedure, but also the alcohol history and BW of the patient.

Although both respiratory and cardiovascular depression are common adverse events of diazepam administration, we encountered no serious events in the current study. For example, while oxygen saturation < 90% was observed in approximately 26% of patients, all recovered quickly in response to intraoperative supplemental oxygen administration and none required endotracheal intubation.

Debate is continuing regarding the proper depth of anesthesia required to perform lengthy endoscopic procedures such as ESD. We consider moderate sedation, which does not appear to cause respiratory depression, as the appropriate level of sedation. If the aim is to maintain the patient under moderate sedation with intermittent administration of a benzodiazepine, long-acting drugs such as diazepam are thought to be suitable in treatments requiring a relatively long time. Indeed, ESD procedures in almost all Japanese institutions are performed by an endoscopist who not only performs the ESD, but is also responsible for sedation during the operation. Due to a long half-life, diazepam is more suitable for intermittent than for continuous administration. Furthermore, intermittent administration in response to uncontrollable body movement is easy for a single operator to manage. The current analysis did not find any significant differences in the incidence of oxygen desaturation (SpO_2 below 90%) or hypotension (blood pressure below 90 mmHg) as a function of the administered diazepam dosage. These findings not only indicate the safety of diazepam, but also the suitability of its administration method.

Due to deep sedation in response to diazepam in the low-dosage diazepam group, flumazenil had to be administered to 4 patients (1.2%). Three of those patients had been coadministered 10 mg of midazolam, while another was an 85-year-old patient with a BW of only 42 kg. Kiriyama *et al*[17] reported that post-ESD recovery from sedation was faster with propofol than with midazolam. The present study did not perform scoring to investigate the recovery from sedation, but almost all patients were awake after returning to their hospital room following completion of the ESD procedure. Also, no cases showed carry-over of the sedative effect to the following morning. All patients who were administered flumazenil also showed rapid awakening, and no problems due to re-sedation were noted. Nevertheless, since ESD in Japan is currently performed as an inpatient treatment, as long as sufficient postoperative management is carried out, there may be no need for quick recovery of wakefulness.

Paradoxical excitement represents restless motion that occurs during diazepam administration. This reaction is reportedly caused, at least in part, by the toxicity of propylene glycol, an included diazepam solvent[32]. Propylene glycol is also a solvent that causes local irritation of veins. Some patients in the present study complained of transient vascular pain, but phlebitis was not seen in any patients. However, a notable increase in restlessness was observed with increasing diazepam dosages. Such reactions made the operation difficult to continue. Accordingly, in cases where preoperative prediction shows a strong possibility that a large dose of diazepam will be required, a different approach to sedation may be advisable. Examples include continuously administering propofol or dexmedetomidine from the start of the

operation, a technique that has recently been reported as useful during ESD[17,33].

The present study has several limitations. First, data generated from only a single hospital were reviewed retrospectively. Second, the decision to administer additional diazepam was left up to the operator, and the timing of such administration was not consistent across patients. However, the most important aspect of this study was the evaluation of the suitability of intermittent administration of diazepam prior to ESD. Further studies at multiple institutions should be conducted using different benzodiazepines and concomitant drugs, with different methods of administration.

In conclusion, among patients who are predicted to require only a low dosage of diazepam during ESD, intermittent administration of diazepam for sedation during gastric ESD will enable safe completion of the surgery. The need for high-dose diazepam can be expected in patients with lifetime alcohol consumption > 0.4 t, BW > 60 kg, or requiring a technically difficult ESD procedure. Given the present results, further randomized trials performed in a prospective manner with clear inclusion criteria and a clear injection protocol should be conducted for such patients.

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COMMENTS

Background

Endoscopic submucosal dissection (ESD) is a curative treatment for gastric epithelial neoplasia. Many cases of gastric epithelial neoplasia occur in elderly patients, who show increased sensitivity to sedatives and a higher risk of adverse reactions. Suitable methods for the administration of sedatives during ESD thus need to be established.

Research frontiers

This study can help us to understand the diazepam dosage required during ESD for gastric epithelial neoplasia and the characteristics of and adverse events encountered by patients administered high-dose diazepam.

Innovations and breakthroughs

Diazepam is the least potent injectable benzodiazepine sedative, with a long history of clinical use. However, administration methods have yet to be clearly established for safe and effective sedative use during gastric ESD procedures.

Applications

The results have demonstrated that intermittent administration of diazepam enabled safe completion of gastric ESD except for patients who are alcohol abusers or obese, or those with complicated lesions.

Peer review

This retrospective study investigated risk factors and adverse events related to high-dose diazepam administration during ESD for gastric neoplasias. Based on the present results, further randomized trials performed prospectively with clear inclusion criteria and a clear injection protocol should be conducted.

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