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ORIGINAL ARTICLE—ALIMENTARY TRACT

Comparison of propofol with midazolam in endoscopic submucosal dissection for esophageal squamous cell carcinoma: a randomized controlled trial

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Abstract

Background Interruption of sedation due to a poor response to modified neuroleptanalgesia (m-NLA) with midazolam often occurs during endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma (ESCC) because most patients have a history of heavy alcohol intake. Recently, propofol has been used feasibly and safely during endoscopic procedures. The aim of this study was to clarify the efficacy and safety of propofol compared with that of midazolam during ESD for ESCC.

Methods This was a single-blind, randomized controlled trial in a single center. Patients with ESCC scheduled for ESD were included in the study. Patients were randomly assigned to one of two groups: the propofol group and the midazolam group. The main outcome was the incidence of discontinuation of the procedure due to a poor response to sedation. Secondary outcomes included risk factors for a poor response to sedation.

Results Between April 2014 and October 2015, 132 patients ($n = 66$ per group) who underwent ESD for ESCC were enrolled in this study. The incidence of discontinuation due to a poor response to sedation in the propofol and midazolam groups was 0% (0/66) and 37.9% (25/66), respectively ($p < 0.01$). Multivariate analyses revealed that use of midazolam [Odds ratio (OR), 7.61; 95% confidence interval (CI), 2.64–21.92; $p < 0.01$] and age (OR, 0.93; 95% CI, 0.86–0.98; $p < 0.01$) were risk factors for a poor response to sedation.

Conclusions Our study indicates that, compared with midazolam, propofol is a more efficient sedative for m-NLA during ESD for ESCC.

Keywords Sedation · Propofol · Midazolam · Alcohol · Endoscopic submucosal dissection · Esophageal cancer

Introduction

Endoscopic submucosal dissection (ESD) is an accepted treatment for superficial esophageal squamous cell carcinoma (ESCC) that can lead to a cure regardless of lesion size and location [1, 2]. However, ESD is more difficult in the esophagus than in the stomach, and severe adverse events can occur, as the esophageal lumen is narrow and its wall is very thin, lacking a serosal membrane [1, 2]. Therefore, maintenance of an adequate level of sedation during ESD is very important. Modified neuroleptanalgesia (m-NLA) using midazolam is often the preferred protocol for ESD of gastrointestinal (GI) neoplasia [3]. However, we observed frequent interruptions in anesthesia due to a poor response to m-NLA with midazolam during ESD for ESCC, because most patients with ESCC have a history of heavy alcohol intake [4]. The American Society for Gastrointestinal Endoscopy (ASGE)'s guidelines for sedation and anesthesia in GI endoscopy indicate that patients with long-term use of narcotics, benzodiazepines, alcohol, or neuropsychiatric medications are expected to have a poor response to sedation [5].

Recently, several studies reported that propofol was a reasonable alternative for sedation during endoscopic procedures such as endoscopic retrograde

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cholangiopancreatography (ERCP) [6–8], endoscopic ultrasonography (EUS) [9, 10], and ESD for early gastric cancer [11–13]. However, most studies excluded patients with a history of heavy alcohol intake. In addition, the incidence of poor response to midazolam is higher during ESD for ESCC (65.0–66.2%) [4, 14], than during ESD for early gastric cancer (0–26.6%) [11, 12, 15]. Most patients with ESCC have a history of heavy alcohol intake, and this may be the risk factor of the poor response to sedation during ESD for ESCC [4]. Therefore, it is vitally necessary to clarify the efficacy and safety of propofol during ESD for ESCC. To our knowledge, there have been no studies that compared propofol and midazolam during ESD for ESCC. In addition, it is unclear which method of sedation is most effective and safest during ESD for ESCC in patients with a history of heavy alcohol intake.

We hypothesized that propofol would be more effective than midazolam during ESD for ESCC. Therefore, we conducted this study to clarify the efficacy and safety of propofol as compared to that of midazolam during ESD for ESCC.

Patients and methods

Patients

This was a single-blind, randomized controlled trial conducted at Osaka City University Hospital. The enrolled patients ($n = 132$) met the following inclusion criteria: (1) age >20 years; (2) a diagnosis of ESCC requiring ESD; and (3) provision of written informed consent regarding study participation. The exclusion criteria were as follows: (1) pregnancy; (2) history of egg, soybean, or propofol allergy; (3) mental incompetency, (4) severe liver disorder (serum liver transaminase >100 IU/l); (5) severe renal failure (serum creatinine >2 mg/dl); (6) severe heart disease (New York Heart Association Class III or IV); (7) severe lung disease (chronic obstructive pulmonary disease with dependency on oxygen administered by nasal cannula); and (8) patients considered to be inappropriate for inclusion in this study.

The study was performed in accordance with the Helsinki Declaration as revised in 1989. The study protocol was approved by the Institutional Review Board of the Osaka City University Graduate School of Medicine (clinical trial registration number: UMIN 000013601). All patients provided written informed consent prior to enrollment, and were blinded because they were under sedation.

Sample size

Sample size calculation was based on the rate of a poor response to sedation in a previous report (10.0% in the propofol group and 32.6% in the midazolam group) [15, 16]. Power calculation ($\alpha = 0.05$; $\beta = 0.10$) indicated a required sample size of $n = 120$ ($n = 60$ vs. $n = 60$) using a two-tailed Chi-square test. Projecting a 10% drop out rate for enrolled patients, the target sample size was 132 patients.

Study protocol

The patients were simply randomly divided into a propofol group (P-group) and a midazolam group (M-group) by allocation center. Midazolam was used as the standard arm in the present study, because it was the most commonly used sedative during endoscopic procedures prior to the spread of propofol [3]. The main outcome was the incidence of discontinuation of the ESD procedure due to a poor response to sedation. Secondary outcomes included risk factors for a poor response to sedation; post-anesthesia recovery score (PARS); satisfaction scores of the endoscopist, nurse, and patient; and the clinical outcomes of sedation and ESD including sedation time, procedure time, *en bloc* resection rate, and incidence of adverse events.

Medication

All medications were administered by physicians who were neither endoscopists nor assistants of the ESD procedures, and who had received anesthesiology training for at least 3 months. The physicians had all attended the immediate cardiac life support course [17].

Local pharyngeal anesthesia was performed using 4% lidocaine. In the P-group, 1% propofol (AstraZeneca Inc., Osaka, Japan) was administered continuously using a target-controlled infusion (TCI) system (TE-371; Terumo Co., Tokyo, Japan). Use of the TCI system, which is based on the pharmacokinetics of propofol, along with a computer-assisted infusion algorithm, is appropriate. A steady plasma concentration of propofol was achieved by adjusting the titration automatically. The initial target blood concentration of propofol was set at 1.2 μg/ml [18, 19]. To reach and maintain an adequate level of sedation defined as Ramsay Sedation Score (RSS) 5–6 [20], the titration speed of propofol was adjusted by increasing or decreasing the target blood concentration of propofol by 0.2 μg/ml. In the M-group, an initial bolus of 3 mg of midazolam (Astellas Pharma Inc., Tokyo, Japan) for patients with a body weight <50 kg, or 4 mg for patients with a body weight ≥50 kg was administered intravenously. Midazolam was added in increments of 2 mg until RSS 5–6 was achieved and maintained throughout the procedure. For analgesia, all patients in both groups received 50 mg of pethidine hydrochloride at the time of induction of sedation. The same medication was administered at a dose of 25 mg

60 min later as well as every 30 min thereafter for the remainder of the procedure. The sedation level according to the RSS was as follows: (1) patient is anxious and agitated or restless or both, (2) patient is cooperative, orientated and tranquil, (3) patient responds to commands only, (4) drowsiness: patient exhibits a brisk response to light glabellar tap or loud auditory stimulus, (5) drowsiness: patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, and (6) patient exhibits no response [21].

The procedure was discontinued when the patient was agitated or restless (RSS level 1). After failure of the primary outcome, additional drugs were administered as needed to maintain RSS 5–6. In the M-group, flunitrazepam (Chugai Pharmaceutical Co., Tokyo, Japan) was added in increments of 0.4–0.6 mg. If flunitrazepam was not effective in maintaining an adequate level of sedation, propofol was administered as described above. In the P-group, first midazolam and then flunitrazepam was administered as needed to maintain RSS 5–6. A poor response to sedation was defined as RSS 1 or 2.

To confirm patient safety immediately after the ESD procedure, 0.2 mg of naloxone (Daiichi Sankyo Co., Tokyo, Japan) was administered to both groups, and 0.5 mg of flumazenil (Fuji Pharma Co., Tokyo, Japan) was administered to the M-group as the reversal agent.

Monitoring and management of adverse events

During the procedure, blood pressure, oxygen saturation, and heart rate were continuously monitored and recorded every 5 min using automatic blood pressure monitoring equipment, pulse oximetry, and a three-lead electrocardiogram. The sedation level was assessed every 5 and 10 min after induction of sedation using the bispectral index (BIS) and RSS, respectively. Hypotension as a decrease in systolic blood pressure to less than 90 mmHg, hypoxia as oxygen saturation to less than 94% [22, 23], and bradycardia as pulse rate to less than 50 beats/min were considered adverse events of sedation, respectively. The nurses positioned themselves behind the patients and performed preventive interventions such as chin lifts, oral suction, and adjustment of oxygen supply when the patients showed snoring, paradoxical chest wall motion, or aspiration.

ESD procedure

Three experienced endoscopists conducted the procedures. After an adequate level of sedation was achieved, the endoscope was inserted. The ESD procedure has been previously described in detail [24]: (1) mark the lesion, (2) submucosal injection with a hyaluronic acid solution, (3) circumferential mucosal incision, and (4) submucosal dissection. All procedures were performed with carbon dioxide insufflation; no patients were intubated for airway protection. The total procedure time is defined as the time elapsed from submucosal injection to removal of the tumor. An *en bloc* resection was defined as a tumor resection in one piece that included all markings. Aspiration pneumonia was defined as evidence of consolidation on chest radiographs or computed tomographic scan with pulmonary symptoms including cough or sputum. Esophageal perforation was defined as a visible hole in the esophageal wall that exposed the mediastinal cavity. Delayed bleeding was defined as bleeding with hematemesis or melena that required endoscopic re-intervention or transfusion after the ESD procedure.

Recovery phase

To estimate the awakening state of patients after ESD, PARS [25, 26] were assessed immediately after the procedure and at 30, 60, 90, and 120 min, as well as the next morning. Scores ranged from 0 (under anesthesia) to 10 (fully awake).

Satisfaction score

After the procedure, satisfaction scores for sedation during the ESD procedure were assessed by the endoscopist, nurse, and patient using a five-point grading system: (1) poor, (2) fair, (3) good, (4) very good, (5) excellent.

Statistical analyses

Continuous variables are reported as mean ± standard deviation (SD) and compared using the *t* test. Categorical variables were compared using the Chi-square test (or Fisher's exact test when necessary because of small sample sizes). Multiple logistic regression analysis was used to evaluate the simultaneous effects of age, gender, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS) classification, cumulative alcohol intake, Brinkman index, regular benzodiazepine and psychiatric medicine use, and the number, location, and total area of the lesions. Cumulative alcohol intake was calculated as follows: quantity of ethanol the subject usually consumed per day × 365 days × duration in years of alcohol drinking [4]. The Brinkman index was defined as number of cigarettes per day × duration in years of smoking [27]. The area of the lesion was defined as the

approximate oval area (mm^2) of the lesion calculated as follows: 3.14 × 0.25 × major axis × minor axis [28]. When the patient had multiple lesions, the total area of all the lesions was calculated. The risk of a poor response to sedation was estimated by calculating the odds ratio (OR) and 95% confidence interval (CI). A p value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS version 21.0 for Windows (SPSS, Tokyo, Japan).

Results

Patient characteristics

Between April 2014 and October 2015, 177 patients with 263 ESCC lesions underwent ESD at our hospital. Of these patients, 45 were excluded (Fig. 1). A total of 132 patients with 186 lesions were enrolled and ended in this prospective study; each 66 patients were randomly assigned. There were no significant differences between the two groups in patient characteristics (Table 1).

The incidence of discontinuation of the ESD procedure due to a poor response to sedation

Discontinuation of the procedure due to a poor response to sedation did not occur in the P-group (0%; 0/66). This was a significantly lower incidence than in the M-group (37.9%; 25/66) ($p < 0.01$) (Fig. 2).

Risk factors for a poor response to sedation

We evaluated the risk factors for a poor response to sedation (Table 2). Younger age (OR, 0.94; 95% CI, 0.89–0.99; $p = 0.01$), total area of the lesions (OR, 0.99; 95% CI, 0.99–1.00; $p = 0.02$), and the use of midazolam (OR, 6.10; 95% CI, 2.30–16.17; $p < 0.01$) increased the risk of a poor response to sedation as determined by crude logistic regression analysis. Multivariate logistic regression analysis showed that younger age (OR, 0.93; 95% CI: 0.86–0.98, $p < 0.01$) and use of midazolam (OR, 7.61; 95% CI: 2.64–21.92, $p < 0.01$) were independent risk factors for a poor response to sedation.

Outcomes of sedation and ESD

Sedation time was not significantly different between the two groups (Table 3). Hypotension occurred more frequently in the P-group (47.0%, 31/66) than in the M-group (28.8%, 19/66; $p = 0.048$). The rates of hypoxia and bradycardia in the P-group (93.9%, 62/66; and 19.7%, 13/66, respectively) were similar to those in the M-group (89.4%, 59/66; and 19.7%, 13/66, respectively). All patients recovered from the adverse events related to sedation with conservative treatment, and discontinuation of the procedure was not required. There were no significant differences in procedural time for ESD, *en bloc* resection rate, or adverse events related to the procedure.

Post anesthetic recovery score

The patients whom PARS was not assessed, were excluded from these calculations. Immediately after ESD, PARS was significantly higher in the M-group (8.3 ± 1.3) than in the P-group (6.5 ± 1.9) ($p < 0.01$) (Table 4). It was significantly higher 120 min after the procedure in the P-group (9.4 ± 0.7) than in the M-group (9.0 ± 1.4) ($p = 0.02$) (Table 4). There were no significant differences between the two groups for PARS at any other time point.

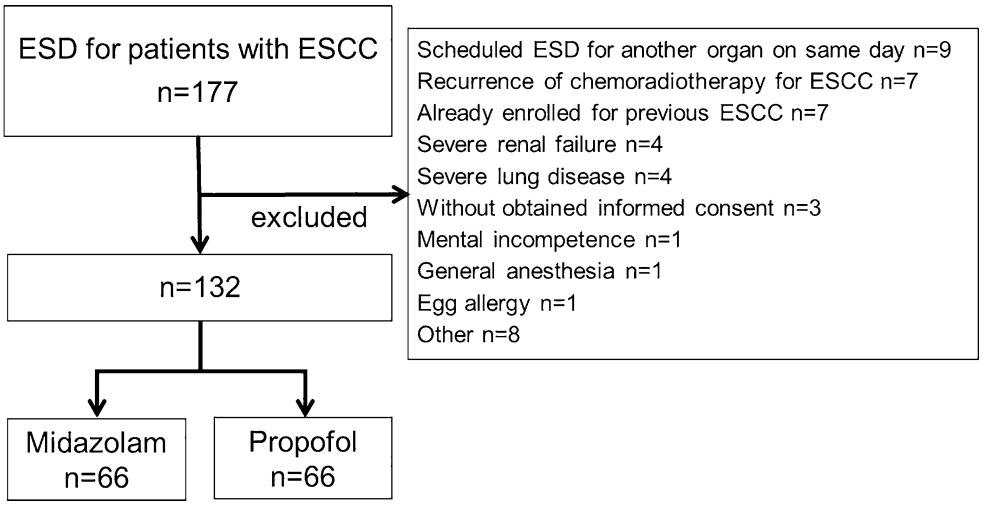

Fig. 1 Diagram of the study design. *ESD* endoscopic submucosal dissection, *ESCC* esophageal squamous cell carcinoma

Table 1 Patient characteristics

	Midazolam	Propofol	*p* value
Number of cases	66	66	
Age, years, mean ± SD	70.1 ± 8.8	69.5 ± 8.2	0.69
Gender			
Female	12 (18.2%)	14 (21.2%)	0.66
Male	54 (81.8%)	52 (78.8%)	
BMI, mean ± SD	22.4 ± 3.3	22.0 ± 3.0	0.48
ASA-PS classification			
1	7 (10.6%)	7 (10.6%)	0.97
2	49 (74.2%)	50 (75.8%)	
3	10 (15.2%)	9 (13.6%)	
Cumulative alcohol intake, kg, mean ± SD	972.6 ± 983.7	1051.2 ± 871.8	0.63
Brinkman index, mean ± SD	795.8 ± 667.9	913.3 ± 744.0	0.34
Regular benzodiazepine and psychiatric medicine use			
No	52 (78.8%)	50 (75.8%)	0.68
Yes	14 (21.2%)	16 (24.2%)	
Number of lesions			
1	43 (65.2%)	48 (72.7%)	0.31
2	15 (22.7%)	14 (21.2%)	
3	8 (12.1%)	3 (4.5%)	
4	0 (0%)	1 (1.6%)	
Location			
Ce, Ut	10 (15.1%)	11 (16.7%)	0.67
Mt	38 (57.6%)	33 (50.0%)	
Lt, Ae	18 (27.3%)	22 (33.3%)	
Total area of lesions, mm^2, mean ± SD	597.6 ± 994.7	431.4 ± 612.4	0.25

BMI body mass index, *ASA-PS* American Society of Anesthesiologists-physical status, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *Ae* abdominal esophagus, *SD* standard deviation

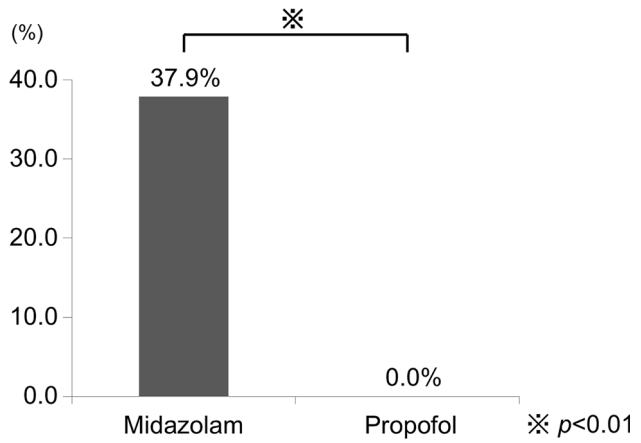

Fig. 2 The incidence of discontinuation of the procedure due to a poor response to sedation

Satisfaction score

The satisfaction scores of the endoscopist and nurse were significantly higher in the P-group than in the M-group ($p < 0.01$ and $p < 0.01$, respectively) (Table 5). The satisfaction score of the patients was similar between the two groups ($p = 0.30$).

Discussion

In the present study, none of the patients who underwent ESD for ESCC using propofol sedation required discontinuation of the procedure due to a poor response to sedation. By contrast, 37.9% of the M-group required discontinuation of the procedure. Multivariate analysis showed that the use of midazolam was an independent risk factor for a poor response to sedation. In addition, PARS 120 min after ESD was significantly higher in the P-group. Propofol was superior to midazolam as determined by the satisfaction scores of the endoscopist and nurse.

The present study had three main strengths as compared to previous studies. First, this is the first randomized controlled trial to compare propofol and midazolam during ESD for ESCC that includes patients with a history of

Table 2 The risk factors for poor response to sedation by multivariate logistic regression analysis

	n	Cases	%	Crude-OR		Multiple-adjusted OR	
				OR (95% CI)	*p* value	OR (95% CI)	*p* value
Number of cases	132	31	23.5				
Age	132	31	23.5	0.94 (0.89–0.99)	0.01	0.93 (0.86–0.98)	<0.01
Gender							
Female	26	4	15.4	1.00			
Male	106	27	25.5	1.88 (0.59–5.95)	0.28		
BMI	132	31	23.5	1.02 (0.90–1.16)	0.79		
ASA-PS classification							
1	14	4	28.6	1.00			
2	99	25	25.3	0.85 (0.63–2.93)	0.79		
3	19	2	10.5	0.29 (0.45–1.91)	0.20		
Cumulative alcohol intake	132	31	23.5	0.99 (0.99–1.00)	0.18	0.99 (0.99–1.00)	0.52
Brinkman index	132	31	23.5	0.99 (0.99–1.00)	0.11	0.99 (0.99–1.00)	0.15
Regular benzodiazepine and psychiatric medicine use							
No	102	22	21.6	1.00			
Yes	30	9	30.0	1.56 (0.63–3.88)	0.34		
Number of lesions							
1	91	22	24.2	1.00			
2	29	4	13.8	0.50 (0.16–1.60)	0.24		
3	11	5	45.5	2.61 (0.73–9.40)	0.14		
4	1	0	0.0	0.00 (0.00–)	1.00		
Location							
Ce, Ut	21	4	19.0	1.00			
Mt	71	19	26.8	1.55 (0.46–5.20)	0.48		
Lt, Ae	40	8	20.0	1.06 (0.28–4.04)	0.93		
Total area of lesions	132	31	23.5	0.99 (0.99–1.00)	0.02	0.99 (0.99–1.00)	0.10
Sedation method							
Propofol	66	6	9.1	1.00			
Midazolam	66	25	37.9	6.10 (2.30–16.17)	<0.01	7.61 (2.64–21.92)	<0.01

BMI body mass index, *ASA-PS* American Society of Anesthesiologists-physical status, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *Ae* abdominal esophagus, *OR* odds ratio, CI confidence interval

heavy alcohol intake. Second, the increased efficacy of propofol as compared to midazolam during an endoscopic procedure was proven. Third, propofol was administrated with the BIS/TCI system and its effects were evaluated with RSS by a non-anesthesiologist.

Recently, several studies reported that propofol was as safe and effective as midazolam during ESD for early gastric cancer [11]. There was no significant difference in the likelihood of a poor response to sedation between propofol and midazolam with pentazocine (10 and 27%, respectively) [15]. However, these studies excluded patients with a history of heavy alcohol intake. In the present study, 33.3% of the patients had a history of heavy alcohol intake. Previous studies have shown that a poor response to treatment with benzodiazepines is often encountered in patients with cumulative alcohol intake >1188 kg [4]. The incidence of a poor response to midazolam was 37.9% in the present study, which was lower than that observed in previous studies (65.0–66.2%) [4, 14]. Our results may have been affected by the regular administration of pethidine hydrochloride as an analgesic agent and the strict control of sedation level using BIS and RSS. In patients whose procedure was discontinued due to poor response to sedation, the ESD procedure could not be completed using midazolam alone. However, it could be accomplished after additional sedative drugs were administered. It follows that propofol was a more efficient sedation method than midazolam during ESD for ESCC, because the substantial completion rate in the M-group was actually 62.1%. On the other hand, the total procedure time is defined as the time elapsed from submucosal injection to tumor removal, including the time after administration of sedative. In the M-group, most discontinuations due to poor response to sedation occurred in the early phase, and the

Table 3 Outcomes of sedation and ESD

	Midazolam	Propofol	*p* value
Number of cases	66	66	
Sedation			
Sedation time, min, mean ± SD	152.0 ± 79.6	144.5 ± 68.6	0.56
Adverse events of sedation, *n* (%)			
Hypotension	19 (28.8%)	31 (47.0%)	0.04
Hypoxia	59 (89.4%)	62 (93.9%)	0.53
Bradycardia	13 (19.7%)	13 (19.7%)	1.00
ESD			
Procedure time, min, mean ± SD	89.0 ± 55.2	81.5 ± 52.5	0.43
En bloc resection, *n* (%)	66 (100%)	66 (100%)	–
Adverse events of ESD procedure, *n* (%)			
Pneumonia	2 (3.0%)	2 (3.0%)	1.00
Perforation	0 (0%)	1 (1.5%)	0.32
Delayed bleeding	1 (1.5%)	0 (0%)	0.32

SD standard deviation, *ESD* endoscopic submucosal dissection

Table 4 Post-anesthetic recovery scores after ESD

Minutes after ESD	Midazolam ($n = 61$)	Propofol ($n = 66$)	*p* value
0, mean ± SD	8.3 ± 1.3	6.5 ± 1.9	<0.01
30, mean ± SD	8.7 ± 1.6	8.7 ± 1.6	0.89
60 mean ± SD	8.7 ± 1.4	9.1 ± 1.2	0.06
90, mean ± SD	8.8 ± 1.5	9.2 ± 0.9	0.08
120, mean ± SD	9.0 ± 1.4	9.4 ± 0.7	0.02
Next morning, mean ± SD	9.5 ± 0.5	9.5 ± 0.5	0.38

SD standard deviation, *ESD* endoscopic submucosal dissection

Table 5 Satisfaction for sedation

	Midazolam ($n = 66$)	Propofol ($n = 66$)	*p* value
Endoscopist, mean ± SD	3.0 ± 1.4	4.2 ± 0.9	<0.01
Nurse, mean ± SD	3.7 ± 1.0	4.3 ± 0.9	<0.01
Patient, mean ± SD	4.4 ± 0.9	4.6 ± 0.7	0.30

SD standard deviation

ESD procedure could be accomplished as usual. For this reason, no significant difference was observed in procedure time between the two groups.

Our study showed that propofol was more efficient for sedation during ESD for ESCC than midazolam. Midazolam was one of the independent risk factors for a poor response to sedation. Propofol is associated with less cross-tolerance with alcohol than are benzodiazepines [29]. Propofol exerts its actions through agonism of gamma-amino-butyric acid (GABA) receptors at a binding site different from that of benzodiazepines, and reduces glutamatergic activity through *N*-methyl-D-aspartase (NMDA) receptor blockade. Alcohol enhances the inhibitory tone of the GABA receptor complex and inhibits the excitatory effect of glutamate on NMDA. The chronic consumption of alcohol leads to a decrease in endogenous GABA release as well as conformational changes in the GABA receptors that reduce their sensitivity to benzodiazepines. In addition, the chronic consumption of alcohol also leads to an up-regulation of NMDA receptors, and the increased production of glutamate [30–32]. Propofol can directly activate the GABA receptor's chloride channel at higher concentrations [29]. Furthermore, propofol has NMDA antagonistic properties that benzodiazepines do not have [33]. Propofol and midazolam are metabolized by the cytochrome P450 (CYP) enzymes CYP2B6 and CYP 3A4, respectively [4, 34]. Alcohol is metabolized by CYP2E1, CYP3A4, and CYP1A2 [35]. Because CYP3A4 metabolism is shared by midazolam and alcohol and is enhanced in

patients with high alcohol consumption, a poor response to midazolam during ESD for ESCC is likely to occur. Younger age was also a risk factor for poor response to sedation. Differences in metabolism and underlying disease between younger and older patients are considered to be the reason for this.

Because propofol has a narrow therapeutic window, it is difficult to maintain an adequate level of sedation with this drug and dose-related side-effects are sometimes encountered [36]. However, it has been reported that it is possible for non-anesthesiologists to maintain a stable level of sedation during ESD using the BIS/TCI system [19, 37]. Similar results were found in the present study. There were no severe adverse events related to sedation in either group. This study emphasized the efficacy and safety of propofol suggested by previous studies because ESD for ESCC takes longer and is more likely to be performed on patients with a history of heavy alcohol intake as compared to other endoscopic procedures. Although hypoxia was observed more frequently in this study than in previous ones (0–27%) [11, 15], this was likely because of a difference in the definition of hypoxia. In the present study, hypoxia was defined as a decrease in oxygen saturation to less than 94%; this definition is internationally recommended by the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [22, 23]. Despite this, most previous studies have defined hypoxia as an oxygen saturation of less than 90%, although some recent reports have defined it as less than 94% [12]. In addition, patients received supplemental oxygen (2 L/min) from the beginning of sedation in previous studies, whereas we began without supplemental oxygen. However, because about 90% of the patients in this study ended up requiring supplemental oxygen, its use from the time of induction is recommended. Although hypotension occurred frequently in the P-group, all patients recovered after conservative treatments or dose adjustment of sedation drugs. In this regard, some studies have shown that propofol is associated with hypotension. However, a meta-analysis showed that the associated risk of cardiopulmonary adverse events does not differ significantly between propofol and traditional sedative agents such as midazolam [38].

Propofol is a short acting sedative with a rapid onset of action. The recovery of consciousness after sedation with propofol was superior to that after sedation with midazolam in ESD for early gastric cancer [11]. However, no significant difference was noted 60 min after the procedure. In the present study, PARS immediately after ESD was significantly better in the M-group. This score was affected by the administration of flumazenil that was used as a reversal agent for midazolam for all cases in the M-group. By contrast, an antagonist to propofol does not exist. After 60 min PARS was higher in the P-group; and after 120 min PARS was significantly higher in the P-group. These scores were influenced by the shorter elimination half-life of propofol versus midazolam. The half-life of flumazenil is also shorter (approximately 50 min) than that of midazolam. The scores may also be influenced by the fact that the total amount of pethidine hydrochloride used in our study was greater than that used in previous studies, although we did use naloxone as a reversal agent. At any rate, our study suggested that propofol was safe after ESD.

In our study, the endoscopist and nurse expressed more satisfaction with the P-group because, for them, satisfaction was related to the frequency of a poor response to sedation. No difference in patient satisfaction was recorded, which could be due to the fact that both agents induced post-procedural amnesia. Similar results were previously reported [39]. Modified neuroleptanalgesia with propofol provided suitable sedation for the endoscopist and nurse during ESD for ESCC regardless of the length of the procedure and including patients with a heavy alcohol habit.

Recently, other sedation methods using dexmedetomidine and hybrid sedation during the ESD procedure have been described. A poor response to the administration of dexmedetomidine combined with pentazocine was observed in 2% of the patients, which is significantly lower than that observed with propofol administered without a TCI system (10%) [15]. Hypoxia was observed less often with dexmedetomidine than with propofol. Nonaka et al. reported that a poor response to sedation with a combination of propofol administered without a TCI system and dexmedetomidine was encountered in 25% of patients. This was significantly lower than the incidence observed with the administration of midazolam or flunitrazepam (65%) during ESD for ESCC ($p = 0.025$) [14]. However, hypotension and bradycardia were encountered significantly more often with the use of combination sedation than with the use of conventional sedation. In the present study, the procedure did not need to be discontinued in any patient due to a poor response to propofol administered with a TCI system, and the occurrence of adverse events was comparable to that of midazolam. Therefore, our method is suitable for sedation during ESD for ESCC, but prospective randomized studies are still needed.

There are several limitations to this study. First, this was a single center study. Therefore, the generalizability of the results is uncertain. Second, this was a single-blind study because the endoscopist and nurse could not be blinded. This may have resulted in a bias in the assessment of satisfaction. Third, the cost of propofol sedation, when it includes the price of monitoring and instruments such as the BIS/TCI system, is more expensive than that of midazolam sedation. However,

because many patients show a poor response to sedation during ESD for ESCC, we recommend propofol sedation with the BIS/TCI system and without discontinuation for this procedure.

In conclusion, propofol was a more efficient sedation method than m-NLA with midazolam during ESD for ESCC. Furthermore, the safety profile of the two drugs is similar, although hypotension may be more frequent when using propofol. Propofol administrated with the BIS/TCI system by a non-anesthesiologist might be a suitable sedation regimen during ESD for ESCC.

Compliance with ethical standards

Conflict of interest Toshio Watanabe received a consulting fee from Eisai Co. Ltd.; Yasuhiro Fujiwara received a consulting fee from Ono Pharmaceutical Co. Ltd.; Tetsuo Arawaka received consulting fees from Eisai Co. Ltd., Otsuka Pharmaceutical Co. Ltd, Astra-Zeneca Co. Ltd. and Tsumura Co. Ltd.

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