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ORIGINAL ARTICLE

Determining factors for dexmedetomidine sedation in endoscopic submucosal dissection for early-stage gastric cancer

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Key words
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Abstract

Background and Aim: Although no specific sedation recommendations exist in early-stage gastric cancer (ESGC) for endoscopic submucosal dissection (ESD), dexmedetomidine (DEX) is useful along with benzodiazepines and analgesics. Furthermore, DEX is used for endoscopic treatment requiring lengthy sedation. However, it is unclear which patients should be administered DEX. We examined the factors that determine when DEX should be added for sedation during ESD for ESGC.

Methods: Of 316 patients undergoing ESD for ESGC at our hospital between January 2017 and December 2020, we examined 310 receiving intravenous anesthesia. Preoperative patient factors and treatment outcomes were retrospectively examined according to the sedation method.

Results: Among patients with ESGC undergoing ESD at our hospital, DEX was more frequently used alongside sedation in men, those undergoing gastrectomy, those with a lesion diameter ≥20 mm, and those with preoperative ulcers. In the standard group, patients whose treatment duration exceeded 120 min typically had a lesion diameter ≥20 mm, preoperative ulcers, lesions located outside the L region, and were treated by junior physicians.

Conclusion: It is important to evaluate specific preoperative factors (lesion diameter ≥20 mm, preoperative ulcers, lesion located outside the L region, and having a junior physician as the treating physician) in patients undergoing ESD for ESGC to determine whether the combined use of DEX in sedation is necessary.

Introduction

In endoscopic submucosal dissection (ESD) for early-stage gastric cancer (ESGC), treatment duration varies depending on the lesion diameter and the presence or absence of ulcers. Furthermore, these surgeries can take more than 120 min. Additionally, there are reports that the postoperative pneumonia risk increases in elderly patients because of the longer ESD times.[1] Therefore, treatment under appropriate sedation is essential to perform a safe and reliable procedure in a short time. However, various sedatives are available, including benzodiazepines, analgesics, dexmedetomidine hydrochloride (DEX), propofol, and general anesthesia. Although no specific sedation recommendations exist for ESD in ESGC, DEX is considered useful with benzodiazepines as well as analgesics. Furthermore, DEX is used for endoscopic treatment requiring lengthy sedation. However, it is unclear which patients should be administered DEX. Since 2017, we have used DEX with midazolam and pethidine in patients whose treatment time is expected to be at least 120 min. However, the factors determining the need for DEX-based combinations have not been clarified.

In this study, we examined the factors that determine the need for adding DEX to sedation during ESD for ESGC.

Methods

Of the 316 patients undergoing ESD for ESGC at our hospital between January 2017 and December 2020, 310 received intravenous anesthesia and were examined. The preoperative case factors and treatment outcomes were retrospectively examined using the sedation method. Consent for ESD was obtained from all case documents, and the study was approved by the Showa University Ethics Committee (Approval No. 22-269-B). Informed consent was obtained via an opt-out method, and the ESD indications were determined using the fifth edition of the *Gastric Cancer Treatment Guidelines*. ESD was performed by two supervising physicians of the Society of Gastroenterological Endoscopy and two specialists. The Olympus ITknife2 was used

as the treatment device, and the local injection solution was concentrated glycerin mixed with indigo carmine. A pathologist at our hospital evaluated the resected specimens according to the gastric cancer handling rules (15th edition).

Sedation method during ESD. In our hospital, a combination of midazolam and pethidine hydrochloride is used as standard ESD sedation regimen for ESGC. Although no clear criteria exist, the estimated ESD treatment time is based on the lesion diameter, lesion site, and the presence or absence of ulcers. Additionally, DEX was used with the standard method (DEX group) for patients who were expected to have an estimated ESD treatment time of ≥120 min based on the lesion diameter, lesion site, and presence or absence of ulcers; required a combination of midazolam and pethidine hydrochloride for sedation during preoperative endoscopy; and for whom bed rest during ESD could not be maintained using standard sedation methods. Before ESD, a conference was held with four upper gastrointestinal tract specialists to estimate the procedure time.

When combined, DEX was administered at 3 μg/kg/h for 15 min, followed by continuous administration at 0.4 μg/kg/h. Midazolam and pethidine hydrochloride were administered as boluses. Additionally, in a prospective endoscopic resection cohort study of ESGC using a web registration system (J-WEB/EGC), the median resection time was 76 min.[2] Furthermore, when treatment is expected to take 120 min, which is approximately twice the median resection time, DEX is recommended for long-term ESD, with 120 min as the cut-off. In addition, blood pressure, electrocardiogram, and blood oxygen saturation monitors were used to monitor vital signs by surgeons and caregivers during ESD.

Evaluation items. The following items were evaluated: age, sex, lesion site, postoperative gastric surgery, macroscopic type, preoperative lesion diameter, preoperative depth (M, SM1, SM2), preoperative ulceration (UL0, UL1), and preoperative pathology (adenoma, differentiated, or undifferentiated).

The ESD treatment outcome variables were post-resection lesion diameter, postoperative pathology (adenoma, differentiated type, undifferentiated type), ulceration on pathology (UL0, UL1), postoperative depth (M, SM1, SM2), endoscopic radical cure (A, B, C-1, C-2), R0 resection rate, treating physician (senior physician with >6 years of experience, or junior doctor with <5 years of experience), treatment time, amount of sedative used (midazolam, pethidine, DEX), adverse events (postoperative bleeding, intraoperative perforation, delayed perforation, aspiration pneumonia), adverse events of sedation, and length of hospitalization.

We compared the case backgrounds between the standard and DEX groups to examine factors influencing the need for DEX. Furthermore, patients were divided into two groups to examine factors leading to DEX use with the standard regimen based on the treatment time (cutoff of 120 min). The case background was compared among patients in the standard group according to the treatment duration.

Statistical analysis. Statistical analysis was performed using JMP Pro 16. For comparisons between the two groups, univariate analysis was performed using the chi-square test and the Mann–Whitney *U*-test for categorical and continuous data, respectively. Logistic regression analysis was performed on several factors to identify the significant independent variables. Statistical significance was set at $P < 0.01$.

Results

Case background. As shown in Figure 1, the standard and DEX groups included 270 and 40 patients, respectively. Table 1 shows that the sex ratios (male/female) were 74%/26% and 93%/7% in the standard and DEX groups, respectively. The percentages of patients undergoing postoperative gastric surgery were 1.5% and 10% in the standard and DEX groups, respectively. The median preoperative lesion diameters were 12 and 20 mm in the standard and DEX groups, respectively. The preoperative ulceration rates (UL0/UL1) were 93% and 7% in the

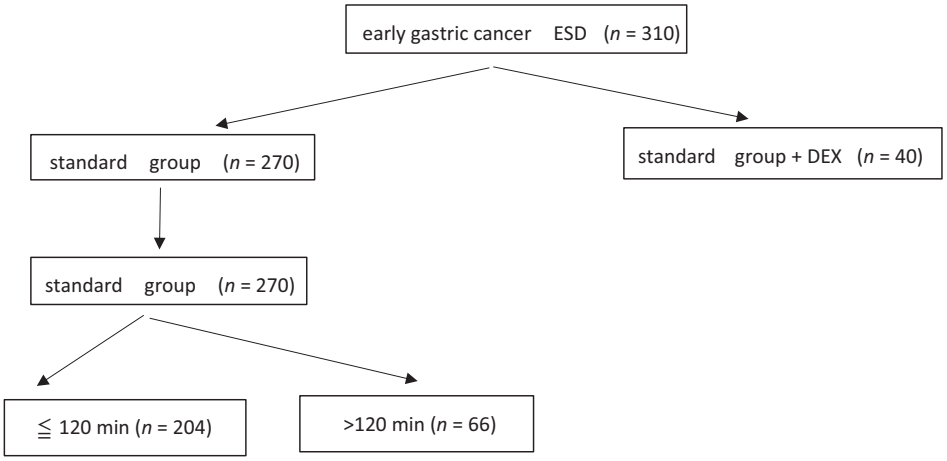

Figure 1 Standard and dexmedetomidine (DEX) groups; included 270 and 40 patients (six patients who received general anesthesia were excluded).

Table 1 Case background

	Standard group (270 patients)	DEX group (40 patients)	*P*-value
Age (median)	75 (40–89)	77 (45–88)	0.76
Sex (male/female) (patients [%])	201 (74)/69 (26)	37 (93)/3 (7)	0.01
Lesion site (L/M/U) (patients [%])	128 (47)/108 (40)/34 (13)	13 (33)/19 (48)/8 (19)	0.09
Postoperative (patients [%])	4 (1.5)	4 (10)	0.01
Median preoperative lesion diameter (mm)	12 (2–50)	20 (8–45)	<0.01
Preoperative depth (M-SM1; SM2) (patients [%])	270 (100); 0 (0)	40 (100); 0 (0)	—
Preoperative UL (0; 1) (patients [%])	252 (93); 18 (7)	31 (78); 9 (22)	<0.01
Preoperative pathology (adenoma: differentiated type: undifferentiated type) (patients [%])	34 (13); 217 (80); 19 (7)	3 (8); 33 (82); 4 (10)	0.52

DEX, dexmedetomidine.

Table 2 Endoscopic submucosal dissection treatment outcomes

	Standard group (270 patients)	DEX group (40 patients)	*P*-value
Median lesion diameter (mm)	12 (2–57)	18 (5–50)	<0.01
Postoperative pathology (adenoma: differentiated type: undifferentiated type) (patients [%])	0 (0); 251 (93); 19 (7)	0 (0); 36 (90); 4 (10)	0.617
Pathology UL (0; 1) (patients [%])	248 (92); 22 (8)	31 (78); 9 (22)	<0.01
Postoperative depth (M–SM1; SM2) (patients [%])	263 (97); 7 (3)	39 (97); 1 (3)	0.352
Endoscopic radical cure (A; B; C-1; C-2) (patients [%])	226 (84); 29 (11); 0 (0); 15 (5)	30 (74); 5 (13); 0 (0); 5 (13)	0.518
R0 resection (%)	94	88	
Treating physician (senior physician: junior doctor) (patients [%])	136 (51); 134 (49)	29 (73); 11 (27)	<0.01
Median treatment time (min)	70 (5–343)	111 (25–431)	<0.01
Dormicum; pethidine hydrochloride (mg)	6 (2–135); 70 (7.5–175)	5 (3–19); 105 (15–210)	
Dexmedetomidine (μg)		78.8 (14.2–366)	
Postoperative bleeding, intraoperative perforation, delayed perforation, aspiration pneumonia (patients [%])	13 (5); 1 (0.3); 0 (0); 3 (1)	6 (15); 0 (0); 0 (0); 1 (3)	0.06/0.059/0/0.745
Median length of hospitalization (day)	7 (6–20)	7 (7–13)	0.028

DEX, dexmedetomidine.

standard group and 78% and 22% in the DEX group, respectively. All the variables described differed significantly between the groups ($P < 0.01$).

Treatment outcomes. Table 2 describes the ESD treatment outcomes. The median lesion diameters were 12 and 18 mm in the standard and DEX groups, respectively. The ulceration rates on pathology (UL0/UL1) were 92% and 8% in the standard group and 78% and 22% in the DEX group, respectively. The attending physician was a senior physician in 51% and 73% cases in the standard and DEX groups, respectively. The median treatment times were 70 and 111 min in the standard and DEX groups, respectively (Fig. 2).

Subsequently, we included the items that significantly differed between the standard and DEX groups in the multivariate analysis, namely sex, the postoperative gastric surgery rate, the median preoperative lesion diameter, and preoperative ulceration. Table 3 shows that sex (male), the need for postoperative gastric surgery, the preoperative lesion diameter (20 mm or more), and preoperative ulceration were independent factors for adding DEX. Additionally, we compared adverse events related to anesthesia between the groups. Table 4 shows the adverse event rates

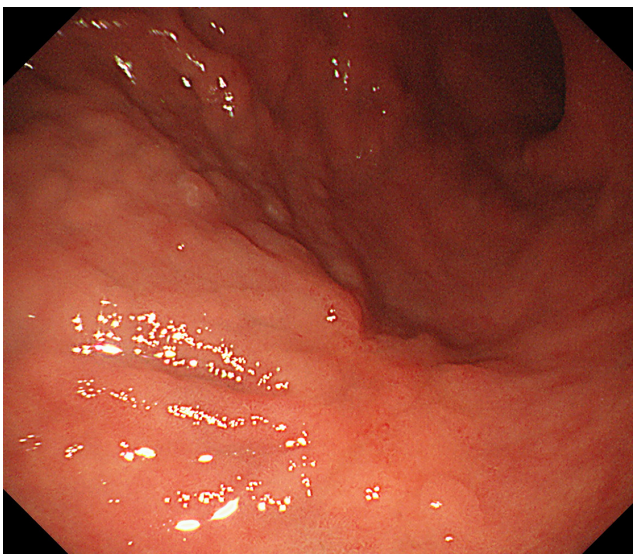

Figure 2 Endoscopic image of a case of early gastric cancer with long-duration ESD —a case with UL1.

Table 3 Multivariate analysis results in standard and dexmedetomidine (DEX) groups

	Standard group (270 patients)	DEX group (40 patients)	*P*-value	Multivariate *P*-value	Multivariate odds ratio
Age (median)	75 (40–89)	77 (45–88)	0.76		
Sex (male/female) (patients [%])	201 (74)/69 (26)	37 (93)/3 (7)	0.01	0.01	M:4.01
Lesion site (L/M/U) (patients [%])	128 (47)/142 (53)	13 (33)/27 (67)	0.09		
Postoperative (patients [%])	4 (1.5)	4 (10)	0.01	<0.01	Postoperative: 11.3
Macroscopic type (raised, flat and concave) (patients [%])	100 (37), 170 (63)	18 (45), 22 (55)	0.38		
Median preoperative lesion diameter (mm)	12 (2–50)	20 (8–45)	<0.01	0.01	20 mm≧:2.59
Preoperative depth (M–SM1; SM2) (patients [%])	270 (100); 0 (0)	40 (100); 0 (0)	—		
Preoperative UL (0; 1) (patients [%])	252 (93); 18 (7)	31 (78); 9 (22)	<0.01	0.01	UL1:3.59
Preoperative pathology (adenoma: differentiated type: undifferentiated type) (patients [%])	34 (13); 217 (80); 19 (7)	3 (8); 33 (82); 4 (10)	0.52		
Treating physician (senior physician: junior doctor) (patients [%])	136 (50), 134 (50)	29 (73), 11 (27)	0.01	0.07	

Table 4 Adverse events related to anesthesia in the standard and dexmedetomidine (DEX) groups

Adverse events	Standard group ($n = 270$)	DEX group ($n = 40$)	*P*-value
With adverse events (%)	13 (5)	9 (23)	<0.01
Breakdown	Grade 2[†]: 13 (5)	Grade 2[†]: 1 (3)	
• Bradycardia	(atropine administration)	(DEX reduction)	
• Decreased blood pressure		Grade 1[†]: 5 (13)	
		Grade 2[†]: 3 (7)	
		(ephedrine administration)	

[†]Common Terminology Criteria for Adverse Events [CTCAE] version 5.0.

as 5% and 23% in the standard and DEX groups, respectively. These rates were significantly higher in the DEX group ($P < 0.01$). However, adverse events were grade 2 or lower in all cases, and no events precluded completing ESD.

In addition, there were three cases of aspiration pneumonia in the standard group and one case in the DEX group; the average treatment time for the standard group was 81 min (56–88 min) and the DEX group was 222 min.

Furthermore, univariate and multivariate analyses were performed for patients in the standard group with a treatment time of at least 120 min. As seen from Table 5, the lesion site (other than L), the preoperative lesion diameter (20 mm or more), preoperative ulceration, and the treating physician (junior physician) were independent factors for longer treatment duration.

Discussion

Appropriate sedation is essential to perform ESD quickly and safely for ESGC. In Japan, the combination of benzodiazepine sedatives and analgesics is commonly used as a sedation regimen for ESD; however, sedation may be difficult because of benzodiazepine tolerance. The *Guidelines on Sedation in Endoscopic Practice* (second edition, Japan Gastroenterological Endoscopy Society, 2020) state that the addition of DEX is useful for ESD in ESGC if a long duration of sedation is required.[3] We used DEX with standard sedatives in cases where the ESD treatment time was estimated to be at least 120 min, based on the preoperative lesion diameter, lesion site, presence or absence of ulcers, and other variables. Because the factors necessitating the addition of DEX have not been clarified, we retrospectively examined ESD cases performed at our hospital and analyzed these factors.

At our hospital, we typically estimate the duration of ESD for ESGC preoperatively. However, in some cases, the treatment time is expected to be at least 120 min. The combined use of DEX was significantly more common in patients who were men, were undergoing gastrectomy, had a lesion diameter of ≥20 mm, and had preoperative ulcers. Furthermore, the treatment time was 120 min or longer in some cases in the standard group, and the treatment time was more frequently longer in patients treated by a junior physician (excluding patients undergoing surgery of the L region), with a lesion diameter of ≥20 mm, and with preoperative ulcers. These findings suggest that future cases may require ESD durations of 120 min or longer. Preoperative factors influencing the necessity of DEX include male sex, gastrectomy, a lesion diameter of ≥20 mm, preoperative ulceration, the lesion site (other than L), and the experience of the treating physician (junior doctor).

For patients undergoing ESD for ESGC, sedation with 0.06 mg/kg midazolam with pethidine hydrochloride may be insufficient at the time of preoperative examination for those younger than 60 years, with a lesion diameter of at least 30 mm, and with a total midazolam dose of ≧0.06 mg/kg during the preoperative examination.[4] Additionally, the ESD treatment time for

Table 5 Multivariate analysis results in the standard group (≥120 min, <120 min)

	Treatment time less than 120 min (204 patients)	Treatment time 120 min or more (66 patients)	*P*-value	Multivariate *P*-value	Multivariate odds ratio
Age (median)	75 (40–89)	73.5 (46–88)	0.35		
Sex (male/female) (patients [%])	148 (73)/56 (27)	53 (80)/13 (20)	0.2		
Lesion site (L/M/U) (patients [%])	104 (51):100 (49)	24 (36):42 (64)	0.04	<0.01	M + U:2.9
Postoperative (patients [%])	1 (1)	1 (1)	0.97		
Macroscopic type (raised, flat and concave) (patients [%])	79 (39),125 (61)	21 (32),45 (68)	0.3		
Median preoperative lesion diameter (mm)	10 (2–40)	15 (5–50)	<0.01	<0.01	20 mm≦:2.98
Preoperative depth (M–SM1; SM2) (patients [%])	204 (100),0	66 (100),0	—		
Preoperative UL (0; 1) (patients [%])	195 (96),9 (4)	57 (86), 9 (14)	0.02	0.04	UL1:3.2
Preoperative pathology (adenoma: differentiated type: undifferentiated type) (patients [%])	193 (95):11 (5)	58 (88):8 (12)	0.08		
Treating physician (senior physician: junior doctor) (patients [%])	111 (54),93 (46)	25 (38), 41 (62)	0.02	<0.01	Junior doctor:3.4

ESGC is significantly longer in the UL1 group than in the UL0 group.[5] Furthermore, ESD for ESGC has been reported to be complicated by scarring and may require a longer treatment time.[6] In our study, the preoperative lesion diameter and preoperative ulceration significantly influenced the need for sedation with DEX.

Adverse events associated with DEX include decreased blood pressure, bradycardia, and coronary artery spasm. As respiratory depression is difficult to treat, caution should be exercised during deep sedation and when using DEX with other sedatives and analgesics because respiratory depression and upper respiratory tract obstruction may occur when the dose is increased.[7] This study considered the adverse events associated with DEX up to Grade 2 severity acceptable. But, side effects of DEX that affect circulatory dynamics, such as bradycardia and lowering of blood pressure, have been reported, and it is necessary to consider reducing the dose, such as introduction of DEX at 3 to 2.7 μg/kg/h for 15 min in elderly patients and patients with heart disease, and then continuous administration at 0.4 to 0.36 μg/kg/h.

A limitation of this study is that the number of cases was insufficient because it was a single-center retrospective study, and the selection of DEX with midazolam included a case selection bias. A prospective multicenter study is needed to clarify the factors that should be considered when assessing the use of DEX in ESD for gastric cancer. This study provides important ideas for designing prospective studies.

In patients with ESGC undergoing ESD at our hospital, DEX was more commonly used for patients who were men, undergoing gastrectomy, had a lesion diameter of ≥20 mm, and had preoperative ulcers. In the standard group, patients with a treatment duration exceeding 120 min typically had a lesion diameter of ≥20 mm, preoperative ulceration, a lesion site other than the L region, or a junior physician as the treating physician. Evaluating these preoperative factors is important among patients undergoing ESD for ESGC to determine the need for the combined use of DEX for sedation.

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Patient consent

Consent for ESD was obtained in all case documents.

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