

# Efficacy and safety of sedation during endoscopic submucosal dissection of gastric cancers using a comparative trial of propofol versus midazolam

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submitted 22.1.2017

accepted after revision 11.9.2017

## Bibliography

DOI <https://doi.org/10.1055/s-0043-122225> |  
Endoscopy International Open 2018; 06: E51–E57  
© Georg Thieme Verlag KG Stuttgart · New York  
ISSN 2364-3722

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## ABSTRACT

**Background and study aims** Proper sedation is necessary for the safe and satisfactory completion of endoscopic submucosal dissection (ESD) for early gastric cancer. This study was conducted as a comparative trial of efficacy and safety,

comparing propofol-based sedation and midazolam-based sedation during ESD of early gastric cancer patients.

**Patients and methods** This study examined 64 lesions in 58 patients treated using ESD with midazolam plus pentazocine between July 2013 and January 2014 (group M) and 237 lesions in 216 patients treated by ESD using propofol plus pentazocine between February 2014 and December 2015 (group P). The two groups were compared in terms of the frequency of body movement during ESD as the primary outcome and in terms of the procedure time, en bloc resection rate, intraoperative change in cardiorespiratory dynamics, and postoperative awareness as the secondary outcomes. Body movement was defined as movement by a patient that required interruption of the procedure or restraint of the patient's body trunk, and addition of a sedative agent.

**Results** The median frequency of body movement during ESD was significantly lower in group P (0 times) than in group M (3 times) ( $P < 0.001$ ). No significant difference was found for the mean procedure time (117 min in group P; 127 min in group M). Although no significant difference was found in the incidence of hypoxemia, bradycardia, or bradypnea, the incidence of hypotension was significantly higher in group P (31.5%) than in group M (6.9%) ( $P = 0.004$ ). Patients in group P had significantly higher postoperative awareness immediately after ESD and at 1 hour after ESD ( $P = 0.002$  and  $0.022$ , respectively).

**Conclusion** These results demonstrate the efficacy and safety of propofol-based sedation for gastric ESD.

## Introduction

Endoscopic submucosal dissection (ESD) for early gastric cancer, a minimally invasive technique that enables en bloc tumor resection, has become a standard treatment for early gastric cancer in Japan [1, 2]. It has allowed endoscopic treatment to be applied to large lesions and lesions with an ulcer scar [3, 4], provided that the lesions are localized in the mucosa. Because

ESD is a technically demanding [5] and lengthy procedure, the need exists for a sedation method that provides a consistent level of sedation during ESD for the safe and satisfactory completion of the procedure [6].

Increasing attention has been given to the use of propofol-based sedation in ESD. Propofol is known to have a narrow therapeutic range and an appreciable effect on cardiorespiratory dynamics [7–9]. Propofol use is also characterized by a rapid

onset and short duration of action [10], thereby providing stable anesthesia and good postoperative awareness [6, 11]. Results of some studies have suggested that the use of propofol leads to substantial improvement in patient acceptance of and satisfaction with endoscopic examination [12–17]. Since the introduction of ESD, we have used midazolam-based sedation. Moreover, we have experienced cases in which body movement could not be controlled and the operation had to be discontinued. We have therefore introduced propofol-based sedation into our ESD protocol since February 2014. This study was conducted to compare the efficacy and safety of propofol-based sedation to that of midazolam-based sedation in ESD for early gastric cancer patients.

## Patients and methods

### Patients

This study assessed 64 lesions in 58 patients treated by gastric ESD using midazolam-based sedation between July 2013 and January 2014 (group M) and 237 lesions in 216 patients treated by gastric ESD using propofol-based sedation between February 2014 and December 2015 (group P). All patients underwent chest radiography, electrocardiography, spirometry, and blood analysis, including liver and renal function tests, before the treatment. All patients provided written informed consent before the procedures. This study was conducted with the approval of the Ethics Committee of Fukushima Medical University (approval No. 2058).

### Sedation and monitoring protocols

In group M, anesthesia was induced by a bolus intravenous (IV) infusion of 15 mg pentazocine plus 2.5–5 mg midazolam. In the event of body movement, an additional bolus IV infusion of 2.5 mg midazolam or 7.5 mg pentazocine was given. If the patient did not respond to the additional sedative, then more sedative was administered equally while carefully monitoring cardiorespiratory dynamics. After the completion of ESD, patients recovered from anesthesia with the administration of 0.5 mg flumazenil. In group P, anesthesia was induced using a bolus IV infusion of 15 mg pentazocine plus 20 mg propofol, followed by the continuous infusion of propofol using an infusion pump. The continuous infusion rate was set initially at 10 mg/kg/h and was gradually tapered every 1 minute (min) to 5, 4, and 3 mg/kg/h. The rate was maintained at 3–5 mg/kg/h during ESD. In addition, 7.5 mg pentazocine was administered every 30 min during ESD. In the event of body movement, a bolus IV infusion of 20 mg propofol was given. Also, the continuous infusion rate was increased. After the completion of ESD, the continuous propofol infusion was stopped to allow the patient to recover from anesthesia. The depth of sedation was adjusted to “deep sedation” without using the bispectral index monitoring, under which spontaneous breathing is maintained, according to the “Practice guidelines for sedation and analgesia by non-anesthesiologists” published by the American Society of Anesthesiologists (ASA) [18].

During ESD, patients received oxygen via a nasal cannula at a rate of 2 L/min. The blood pressure (BP) was measured immedi-

ately after sedation and then every minute until the insertion of the endoscope and every 5 min thereafter. The heart rate (HR), respiratory rate (RR), and SpO<sub>2</sub> were monitored continuously. The RR was measured using an acoustic respiration monitor (Rad-87™; Masimo, Tokyo, Japan). In addition to the physician, sedation was managed exclusively by an endoscopist with expertise in anesthesia. The endoscopist evaluated the frequency of body movement and decided to administer bolus midazolam, propofol, or pentazocine. The endoscopist who administered sedation was in the same room at all times during ESD procedures. A nurse checked the vital signs of the patients and recorded the data. The nurse who checked the vital signs recorded the frequency of body movement during ESD, as directed by a previously established protocol. Therefore, although this study is retrospective, we were able to obtain these data. The nurse recording the vital signs had no other duties. She devoted herself to monitoring the patient's condition. Body movement was defined as a patient's movement that required interrupting the procedure or restraining the patient's body trunk and adding the sedative agent. All patients were restrained with simple restraining bands.

### ESD procedure

ESD was performed using a Dual Knife (KD-650L; Olympus Medical Systems Corp., Tokyo, Japan), a Flex Knife (KD-630L; Olympus Medical Systems Corp.), an IT Knife (KD-610L; Olympus Medical Systems Corp.) or an IT Knife 2 (KD-611L; Olympus Medical Systems Corp.). For the submucosal injection solution, a 1:1 solution of 0.4% sodium hyaluronate (MucoUp; Johnson & Johnson K. K., Tokyo, Japan) and glycerol (Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) was injected into the submucosa using a 25-G injection needle (ImpactFlow; TOP Corp., Tokyo, Japan). A hemostatic forceps (Coagrasper; FD410LR; Olympus Medical Systems Corp.) was used for the prophylactic coagulation of blood vessels and hemostasis for intraoperative bleeding. A VIO300D or ICC200 (ERBE Elektromedizin GmbH, Tübingen, Germany) was used as the high-frequency generator. All ESDs were performed by expert physicians who were board-certified gastroenterological endoscopists of the Japan Gastroenterological Endoscopy Society or by less-experienced physicians (i.e., those who had performed fewer than 50 ESD procedures) under the supervision of the expert physicians. An expert endoscopist took over when the procedural time was expected to exceed 2 hours or when complications such as perforation or respiratory depression occurred.

### Outcomes

The primary outcome was the frequency of body movement during ESD. The secondary outcomes were procedure time, en bloc resection rate, cardiorespiratory dynamics during ESD, and postoperative awareness. The procedure time was defined as the time from the insertion of endoscope to the withdrawal of endoscope after the completion of tumor resection. For cardiorespiratory dynamics, systolic blood pressure (sBP) <90 mmHg was defined as hypotension, HR <50 beats/min as bradycardia, RR <8 breaths/min as bradypnea, and SpO<sub>2</sub> <90% as hypoxemia. Postoperative awareness was evaluated immediately,

► **Table 1** Patient characteristics.

	Group M (n=58)	Group P (n=216)	95 % CI	P value
Age, mean ± SD, yr.	74.3 ± 8.4	72.9 ± 8.7	–.130 – 3.925	0.277
Gender, n (%)			0.480 – 1.811	0.836
▪ Male	43 (74.1)	163 (75.5)		
▪ Female	15 (25.9)	53 (25.5)		
Body weight, mean ± SD, kg	58.3 ± 12.9	59.3 ± 10.5	–4.238 – 2.197	0.533
ASA classification, n (%)			0.592 – 35.127	0.111
▪ I/II	57 (98.3)	200 (92.6)		
▪ III	1 (1.7)	16 (7.4)		
Vital signs before sedation, median (range)				
Systolic BP, mmHg	145 (113 – 186)	139 (97 – 217)		0.052
HR, beats/min	69 (46 – 98)	67 (46 – 99)		0.052
SpO <sub>2</sub> , %	98 (94 – 100)	98 (93 – 100)		0.218
RR, breaths/min	16 (9 – 24)	16 (7 – 30)		0.229
Data are analyzed using the $\chi^2$ -test, the Student's <i>t</i> -test and the Mann-Whitney <i>U</i> -test. ASA, American Society of Anesthesiologists; BP, blood pressure; HR, heart rate; SpO <sub>2</sub> , oxygen saturation; RR, respiration rate.				

1 hour, and 3 hours after ESD according to the Observer's Assessment of Awareness/Sedation (OAA/S) scale, and the percentage of patients with an OAA/S score of 5 (awake or responding immediately to quiet name calling) was determined. Doctors of the ESD team, including the physician, checked the recovery time after ESD.

### Statistical analyses

Continuous data were expressed as the mean ± standard deviation, median, and range. Differences were analyzed for statistical significance using  $\chi^2$  test, Student's *t*-test and Mann-Whitney *U*-test; differences were considered significant when the *P* value was less than 5%. Analyses were performed using Statcel 2 software (OMS Publishing Inc., Tokorozawa, Japan).

## Results

No significant difference was found between the two groups in terms of patient data including age, sex, body weight, ASA score, pretreatment sBP, HR, SpO<sub>2</sub>, and RR (► **Table 1**). One patient in group P and 16 patients in group M were assigned an ASA score of III. All of these patients had cardiovascular disease (angina pectoris or old myocardial infarction). However, their disease conditions were stable. Therefore, we confirmed them as suitable candidates to undergo ESD. The ESD procedure outcomes were also similar between the two groups, with no significant difference in terms of histological type, invasion depth, specimen diameter, tumor diameter, procedure time (117 min in group P; 127 min in group M), or en bloc resection rate (► **Table 2**).

In group P, the median total amount of propofol was 454.5 mg. The median total amount of pentazocine was

37.5 mg. In contrast, in group M, the median total amount of midazolam was 15 mg. The median total amount of pentazocine was 30 mg. During ESD, significantly more bolus injections were made of midazolam (5 times) than of propofol (1 time) ( $P < 0.001$ ; ► **Table 3**).

The median frequency of body movement during ESD was significantly lower in group P (0 times) than in group M (3 times) ( $P < 0.001$ ; ► **Table 4**). One patient in group M had body movement that required interruption of ESD because of difficulty in continuing the procedure; that patient underwent ESD under general anesthesia in an operation room 2 days later. The minimum values of sBP, HR, and RR during ESD were significantly lower in group P than in group M ( $P < 0.001$ ,  $P < 0.001$  and  $P = 0.005$ , respectively; ► **Table 4**). These abnormalities were rapidly reversed by modifying the propofol infusion rate and/or increasing the oxygen flow. Therefore, they did not affect the continuation of the procedure. A significantly higher percentage of patients in group P experienced hypotension during ESD ( $P = 0.004$ ), although no significant difference was found between the two groups in the incidence of bradycardia, hypoxemia, and bradypnea during ESD (► **Table 4**). The use of an acoustic respiration monitor for the precise measurement of the respiratory rate also enabled the detection of hypoxemia before any decrease in SpO<sub>2</sub> was observed. No patient in any group required any medication to rectify sedation-induced hemodynamic derangement.

Fifty-two patients in group M and 189 patients in group P had procedure times longer than one hour. The percentages of patients in group P who experienced hypotension, bradycardia, and bradypnea during ESD were significantly higher than those in group M ( $P < 0.001$ ,  $P = 0.043$ , and  $P = 0.015$ , respectively), al-

► **Table 2** Lesion characteristics and procedure outcomes.

	Group M (n = 64)	Group P (n = 237)	95 % CI	P value
Tumor location, n (%)			0.364 – 1.624	0.611 <sup>1</sup>
▪ Upper	10 (15.6)	46 (19.4)		
▪ Middle	26 (40.6)	99 (41.8)		
▪ Lower	28 (43.8)	92 (38.8)		
Histological type, n (%) <sup>2</sup>			0.176 – 1.989	0.610
▪ Differentiated type	60 (93.7)	228 (96.2)		
▪ Undifferentiated type	4 (6.3)	9 (3.8)		
Depth of invasion, n (%)			0.317 – 1.522	0.360 <sup>3</sup>
▪ M	54 (84.4)	210 (88.6)		
▪ SM1	5 (7.8)	9 (3.8)		
▪ SM2	5 (7.8)	18 (7.6)		
Specimen diameter, mean ± SD, mm	42.0 ± 13.2	39.6 ± 13.2	–1.319 – 6.145	0.204
Tumor diameter, mean ± SD, mm	18.3 ± 13.0	17.8 ± 13.0	–3.063 – 4.123	0.772
Procedure time, mean ± SD, min	127.0 ± 67.0	117.3 ± 63.0	–8.968 – 28.205	0.309
Procedure time each location, mean ± SD, min				
▪ Upper	145.8 ± 52.9	149.6 ± 81.9	–58.195 – 50.708	0.891
▪ Middle	149.2 ± 82.3	121.7 ± 58.8	–0.531 – 55.522	0.054
▪ Lower	104.6 ± 39.6	103.8 ± 49.1	–19.239 – 21.003	0.931
En bloc resection rate, n (%)	62 (96.9)	236 (99.6)	0.012 – 1.472	0.053

Data are analyzed using the  $\chi^2$ -test and the Student's *t*-test.

Depth of invasion: M, mucosal cancer; SM1, minimally invasive submucosal cancer, invasion depth <500  $\mu$ M from the muscularis mucosa; SM2, invasive submucosal cancer, invasion depth  $\geq$ 500  $\mu$ M from the muscularis mucosa.

<sup>1</sup> Upper vs Middle + Lower

<sup>2</sup> When the tumor exhibited a mixture of differentiated and undifferentiated types, the histological type was classified according to the major component of the tumor.

<sup>3</sup> M vs SM1 + SM2

► **Table 3** The total dose and the number of bolus injection of the drug.

	Group M (n = 58)	Group P (n = 216)	P value
Total amount of midazolam or propofol, median (range), mg	15 (5 – 67.5)	454.5 (103 – 1830)	
Total dose of midazolam or propofol, median (range), mg/kg/h	0.14 (0.05 – 0.36)	4.39 (0.52 – 14.35)	
The number of bolus injection of midazolam or propofol, median (range), times	5 (1 – 24)	1 (0 – 9)	<0.001
Total amount of pentazocine, median (range), mg	30 (15 – 75)	37.5 (22.5 – 75)	<0.001
Total dose of pentazocine, median (range), mg/kg/h	0.25 (0.10 – 0.72)	0.36 (0.14 – 1.00)	<0.001
The number of bolus injection of pentazocine, median (range), times	1 (0 – 6)	3 (1 – 8)	<0.001

Data are analyzed using the Mann-Whitney *U*-test.

though no significant difference was found between the two groups for the incidence of hypoxemia (► **Table 5**).

In terms of awareness after ESD, the percentages of patients in group P who had an OAA/S score of 5 immediately and 1 hour after ESD were significantly higher than those in group M ( $P=0.002$  and  $0.022$ , respectively; ► **Table 6**). One patient in group

M experienced nocturnal delirium. This patient, who had no dementia or cerebrovascular disease, showed no vital sign abnormalities during ESD.

► **Table 4** Body movement and cardiorespiratory data during the ESD procedure.

	Group M (n=58)	Group P (n=216)	P value
Body movement, median (range), times	3 (0–10)	0 (0–10)	<0.001
Minimum values, median (range)			
▪ Minimum sBP, mmHg	120.5 (76–158)	100.5 (57–151)	<0.001
▪ Minimum HR, beats/min	66 (41–90)	56 (37–83)	<0.001
▪ Minimum SpO <sub>2</sub> , %	97 (79–100)	97 (79–100)	0.948
▪ Minimum RR, breaths/min	13 (6–19)	10 (3–19)	0.005
Abnormal vital signs, n (%)			
▪ Hypotension (sBP<90 mmHg)	4 (6.9)	68 (31.5)	0.004
▪ Bradycardia (HR<50 /min)	4 (6.9)	40 (18.5)	0.174
▪ Hypoxemia (SpO <sub>2</sub> <90 %)	2 (3.4)	15 (6.9)	0.683
▪ Bradypnea, (RR<8 /min)	3 (5.2)	39 (18.1)	0.132

Data are analyzed using the Mann-Whitney *U*-test.  
sBP, systolic blood pressure; HR, heart rate; SpO<sub>2</sub>, oxygen saturation; RR, respiration rate.

► **Table 5** Body movement and cardiorespiratory data during the ESD procedure among the patients with long procedure time (>1 hr).

	Group M (n=52)	Group P (n=189)	P value
Body movement, median (range), times	3.5 (0–10)	0 (0–10)	<0.001
Minimum values, median (range)			
▪ Minimum sBP, mmHg	118.5 (76–158)	101 (57–151)	<0.001
▪ Minimum HR, beats/min	64 (41–82)	56 (37–83)	<0.001
▪ Minimum SpO <sub>2</sub> , %	96.5 (79–100)	97 (79–100)	0.396
▪ Minimum RR, breaths/min	12 (6–19)	10 (3–15)	0.024
Abnormal vital signs, n (%)			
▪ Hypotension (sBP<90 mmHg)	4 (7.7)	57 (30.2)	<0.001
▪ Bradycardia (HR<50 /min)	4 (7.7)	37 (19.6)	0.043
▪ Hypoxemia (SpO <sub>2</sub> <90 %)	2 (3.8)	10 (5.3)	0.671
▪ Bradypnea, (RR<8 /min)	3 (5.8)	38 (20.1)	0.015

Data are analyzed using the Mann-Whitney *U*-test.  
sBP, systolic blood pressure; HR, heart rate; SpO<sub>2</sub>, oxygen saturation; RR, respiration rate.

► **Table 6** Awareness after ESD.

	Group M (n=58)	Group P (n=216)	95 % CI	P value
Immediately after ESD, n (%)	13 (22.4)	96 (44.4)	0.184–0.708	0.002
One hour after ESD, n (%)	26 (44.8)	133 (61.6)	0.282–0.311	0.022
Three hours after ESD, n (%)	43 (74.1)	179 (82.9)	0.298–1.177	0.132

Data are analyzed using  $\chi^2$ -test.  
ESD, endoscopic submucosal dissection

## Discussion

Non-anesthesiologists are using propofol increasingly for sedation during gastrointestinal endoscopy [19]. Propofol-based sedation can be achieved safely with minimal complication even by non-anesthesiologists, provided that the non-anesthesiologists are trained in its proper use and in response to emergency situations [20]. The efficacy and safety of propofol-based sedation have been demonstrated for endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography [21–23]. The present study demonstrated the safety and efficacy of propofol-based sedation in ESD.

The present data also suggest greater effects on cardiorespiratory dynamics in propofol-based sedation. However, propofol-related hypotension, bradycardia, and hypopnea were only observed immediately after sedation induction. No change in cardiorespiratory dynamics requiring treatment was observed during ESD. Reducing the dose of continuous propofol infusion reversed hypotension and bradycardia; hypopnea and hypoxemia were corrected rapidly by increasing the oxygen dose temporarily. Although propofol has some advantages such as rapid onset and shorter duration of action [10], its narrow therapeutic range and appreciable effect on cardiorespiratory dynamics are regarded as disadvantageous [7–9]. To group M patients, a bolus IV infusion of midazolam or pentazocine was given in the event of body movement, which was generally followed by changes in cardiorespiratory dynamics. However, no patient required ESD to be discontinued as a result of cardiorespiratory dynamic change.

Sedation with continuous propofol infusion has been associated with a significantly lower frequency of body movement during ESD compared to bolus IV infusion of midazolam or propofol [24]. This reported association is consistent with the present study's findings: during ESD, a significantly higher frequency of body movement was observed in group M. For targeting deep sedation, propofol has an effect with continuous infusion; midazolam has an effect with bolus IV infusion because of its half-life. Fundamentally, the two drugs have different uses. We suggest that the continuous infusion is not the reason for effectiveness. Body movements were observed between sedation induction and the start of the ESD procedure in both groups. In group M, body movements requiring trunk restraint were also observed during ESD in many cases. One patient in group M had severe body movement that required discontinuation of the procedure. This patient had diabetes, hypertension, dyslipidemia, and mild liver dysfunction, but had no history of heavy alcohol use or regular use of benzodiazepines.

Patients in group P had better postoperative awareness immediately and at 1 hour after ESD. Propofol has a short duration of action [10] and therefore engenders good postoperative awareness, which might lead to lower incidence of secondary complications such as unrest and subsequent falls and/or a fall from a bed.

This study has several limitations. First, this study was not a randomized controlled trial for which patients were retrospectively assigned to study groups at different time points. Sec-

ond, the study was conducted at a single center with a small sample size.

## Conclusion

During ESD for gastric cancer, propofol-based sedation provided stable sedation with a lower frequency of body movement and better postoperative awareness than those of midazolam-based sedation. Continued monitoring of the respiratory rate allowed us to understand the patient's respiratory condition immediately. The need remains to verify these findings further in a multicenter, randomized controlled trial.

## Acknowledgements

We express our gratitude to all endoscopy medical staff for their collaboration and assistance with the endoscopic procedures.

## Competing interests

None

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