Title; Propofol sedation with target-controlled infusion pump and bispectral index monitoring system in elderly patients during complex upper endoscopy procedure

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ABSTRACT

Background and Aims: Although the usefulness of propofol sedation during endoscopic submucosal dissection (ESD) for gastric neoplasms was reported previously, information is limited on its use in elderly patients. We investigated the safety and efficacy of propofol sedation with a target controlled infusion (TCI) pump and bispectral index (BIS) monitoring system (TCI/BIS system) in elderly patients during gastric ESD.

Methods: Included were 413 consecutive gastric ESD procedures involving 455 lesions (379 patients) under propofol sedation with a TCI/BIS system between October 2009 and September 2013. Patients were divided into 3 groups: group A, age <70 (N=162); group

B, age ≥70 and <80 (N=171); and group C, age ≥80 (N=80). We compared the propofol dose and adverse events (e.g., hypotension and hypoxemia) during ESD.

Results: Older groups required a lower target concentration of propofol (Group A: median 2.1 μg/mL (interquartile range [IQR] 1.9-2.3); Group B: median 1.6 μg/mL (IQR 1.3 -1.8); and Group C: median 1.4 μg/mL (IQR 1.2-1.6); p<0.0001). Hypotension tended to occur in the younger group and hypoxemia occurred at a significantly higher ratio in the older groups although the number of cases was small. Low preoperative systolic blood pressure (≤125 mmHg) presented a risk for hypotension (OR=1.73 [CI 1.12–2.70], p=0.013) and abnormal pulmonary function was a risk for hypoxemia in Groups B and C (OR=4.54 [CI 1.01–31.5], p=0.048).

Conclusions: Elderly patients required lower doses of propofol with the TCI/BIS system than younger patients. Attention to hypoxemia is necessary in elderly patients, particularly patients with abnormal pulmonary function.

INTRODUCTION

In recent years with the increasingly aging society, the number of endoscopic examinations for elderly persons has increased in Japan. As the number of elderly persons developing upper gastrointestinal diseases has increased so has the number of elderly patients who received complex endoscopic procedures. Endoscopic submucosal dissection (ESD) is one of the complex upper endoscopic procedures. ESD is very useful and effective in treating early gastric cancer mainly because it is a less invasive treatment for achieving curative resection, as has been reported in the literature [1-5]. In addition, its usefulness in elderly patients has been recognized recently [6-9].

Since ESD is more time-consuming than conventional endoscopic mucosal resection multiple doses of medication are usually required to provide an adequate level of sedation [10]. Propofol is a short-acting sedative with a rapid recovery profile, and its use is associated with a number of additional advantages, including relative ease in safely maintaining an appropriately depressed level of consciousness and a suitable amnesic state [11]. These advantages have resulted in an increased use of propofol worldwide for standard endoscopy procedures. However, oxygen desaturation and hypotension are drawbacks of propofol sedation. When treating older patients, attention is necessary to avoid sedation-related adverse events because elderly individuals generally have one or more underlying diseases.

It can be hypothesized that elderly patients require lower doses of sedation to achieve similar pharmacological effects compared with younger patients. A target-controlled infusion (TCI) system enables automatic control of the dose of sedative drugs by a computer-assisted infusion algorithm of pharmacokinetics for calculating the effect-site concentration [12, 13]. However, the pharmacokinetic model in the TCI may not be optimal when considering the age of and comorbidities in individual patients [14]. Bispectral index (BIS) monitoring is an EEG-based method that quantifies the depth of anesthesia by analyzing the EEG and uses a complex algorithm to generate an index score, providing an objective measurement of the level of consciousness in sedated patients [15-17]. Recently, the utility of the combination of a TCI pump and BIS monitoring system (TCI/BIS system) for endoscopic treatment was reported [18].

However, there is limited information on the outcome of endoscopic treatment and the sedation used in elderly patients [19]. This study aimed to evaluate the safety and efficacy of propofol sedation with appropriate amounts of propofol with the use of the TCI/BIS system for elderly patients during gastric ESD.

METHODS

Patients

A total of 449 consecutive ESD procedures for 491 early gastric neoplasms (412 patients) were performed at Okayama University Hospital using propofol sedation with a TCI/BIS system between October 2009 and September 2013 and were included in this study. Thirty-three patients accounting for 36 procedures involving 36 lesions were excluded from the analysis because the lesions were in the gastric remnant and gastric tube. Thus, 379 patients who underwent 413 procedures for 455 lesions were evaluated (Figure 1). ESD was conducted as one of the treatment options for lesions with a preoperative diagnosis of gastric adenoma or possible node-negative early gastric cancer based on the expanded criteria proposed by Gotoda et al [20]. The study was approved by the Okayama University School of Medicine Clinical Ethics Committee on Human Experiments in accordance with the Helsinki Declaration.

Study design

The patients were divided into 3 groups according to age: group A, <70 years old, 162 procedures (39%); group B, ≥70 and <80 years old, 171 procedures (41%); and group C, ≥80 years old, 80 procedures (20%). Associations between the age group and the propofol dose or sedation-related adverse events during the ESD procedure were examined.

As for the target blood concentration and propofol dosage, the setting of target blood concentration (μg/ml), and the total infusion dose of propofol (mg) during the ESD procedure were recorded. Minimum target blood concentration (μg/ml) and maximum target blood concentration (μg/ml) were reviewed and the average target blood concentration (μg/ml) and average maintenance dose (mg/kg/h) were calculated. The major adverse events concerning propofol sedation were defined as follows: hypoxemia (peripheral capillary oxygen saturation <90%) and hypotension (systolic blood pressure (SBP) <80 mmHg) [19]. Subsequently, we assessed those adverse events that occurred during 3 periods in each procedure: induction period, maintenance period, and recovery period. The induction period was defined as from the time of the start of propofol infusion to insertion of the endoscope. The maintenance period was defined from insertion of the endoscope to the end of the dissection and the recovery period was from the end of dissection to the time the patient left the endoscopy room. All patients left the endoscopy room after ESD when it was confirmed that they were fully awake and could respond to questions and the BIS score went above 90. Infusion of propofol was continued until the end of the dissection. Endoscopic hemostasis was carried out after the discontinuation of propofol infusion.

Additional data concerning the patients and their gastric neoplasms were examined as background factors. Gender, body mass index, American Society of Anesthesiologists (ASA) classifications, results of lung function testing, preoperative SBP, preoperative peripheral capillary oxygen saturation (preoperative SpO2), chronic concomitant diseases, and location and size of tumors were recorded. All patients received a lung function test before the operation. The % SBP change from the preoperative value and % SpO2 change from the preoperative value were defined as follows: (preoperative SBP-operative lower SBP）× 100/preoperative SBP and (preoperative SpO2- operative lower SpO2）× 100/preoperative SpO2. Differences in these background factors among the 3 age groups and the associations between adverse events and background factors were examined. Chronic concomitant diseases were classified as hypertension, diabetes mellitus, cardiovascular conditions (ischemic and valvular heart disease, congestive heart failure, significant cardiac arrhythmia), neurological diseases (cerebral vascular disorder), pulmonary diseases (chronic obstructive pulmonary disease), and renal failure (dialysis). Patients with a history of sulfite, egg, soybean, or propofol allergies were excluded.

Medication and monitoring

Local pharyngeal anesthesia was performed by an 8% topical lidocaine spray prior to intravenous infusion of the sedative drugs. Propofol was administered intravenously using the Diprifusor™ system (TE-371; Terumo, Tokyo, Japan), which is a target-controlled infusion system using the pharmacokinetic parameter set according to the Marsh model. The initial setting of the target blood concentration of propofol (1% Diprivan Injection-kit; AstraZeneca, Osaka, Japan) was set at 2.0 μg/ml for the nonelderly (<70 y) patients [21]. The initial setting for the elderly patients (≥70 y) was 1.0 μg/ml, which was chosen for moderate sedation on the basis of a previous study [18, 22]. The predicted blood concentration of propofol at each time point was calculated automatically and was shown on the monitor of the TCI pump. For the objective measurement of the level of consciousness in sedated patients, the A2000 BIS monitor (Aspect Medical Systems, Newton, MA) was used. The BIS score was managed between 40 and 80. In the induction period, if the BIS score went below 80 before the initial setting of the target blood concentration was obtained, the maintenance dose was set at the predicted blood concentration for that time and endoscopic treatment was started. However, if the BIS score was over 80 after the initial setting of the target blood concentration was reached, the blood concentration of propofol was increased by 0.2 μg/ml until the BIS score reached less than 80. During the maintenance period, if the BIS score went over 80 or the patient began to move, the target blood concentration of propofol was increased by 0.2 μg/ml. An additional bolus of 1-2 ml of propofol was given if the patient's movements were frequent. When the BIS score was less than 40 or an adverse event (SBP <80 mmHg or SpO2 <90%) occurred, the target blood concentration of propofol was reduced by 0.2 μg/ml with an immediate increase in the intravenous drip or oxygen dosage. All patients received 15 mg of pentazocine as an analgesic agent just before insertion of the endoscope. All patients received supplemental oxygen (2 L/min) by nasal cannula during sedation and were kept in the lateral decubitus position. If hypoxemia occurred during the sedation, we performed chin lift on the patient and increased the oxygen dosage.

The patients' pulse rate, blood pressure, electrocardiogram, and SpO2 were monitored with a bedside monitor (BSM-2301; Nihon Kohden Wellness Corporation, Tokyo, Japan) during the procedure. The signal averaging time of the pulse oximeter was

8 seconds. Blood pressure was recorded every 5 minutes. SpO2 and heart rate were recorded continuously. All adverse events, including hypoxemia (SpO2 <90%) and hypotension (SBP <80 mmHg), and the total propofol dose were recorded during the ESD.

All medications were given by a gastroenterologist who did not participate directly in gastric ESD procedures. We consulted with the anesthesia department before the operation, and an anesthesiologist was on standby in case of an emergency.

Endoscopic procedure

The ESD procedure for gastric neoplasm was performed using a dual knife (KD-650L/Q; Olympus Optical Co.) for marking and precutting, an insulated-tipped (IT) knife (Olympus) for circumferential mucosal incision, and an IT knife or a Mucosectom (Pentax Corp, Tokyo, Japan) for submucosal resection. Glycerol (10% glycerol and 5% fructose; Chugai Pharmaceutical Co., Tokyo, Japan) with small amounts of epinephrine and indigo carmine or Muco up (0.4% sodium hyaluronate; Johnson & Johnson K.K., Tokyo, Japan) were injected into the submucosal layer to lift the mucosa. High-frequency generators (ICC200 or VIO 300D; ERBE Elektromedizin GmbH, Tübingen, Germany) were used during marking, incision of the gastric mucosa, and exfoliation of the gastric submucosa.

Statistical analysis

Continuous variables are presented as the median and range or interquartile range (IQR). Comparison of continuous variables was performed by the Mann-Whitney U test, and comparison of dichotomous variables was made using the Fisher’s exact test and logistic regression. In order to extract significant factors for each of the major adverse events concerning propofol sedation (hypotension or hypoxemia), multivariate analyses were done using logistic regression analysis. For variable selection, backward stepwise selection (P=0.15 as the level for including variables, and P=0.10 for exclusion of variables) with direct selection for the age groups was used. The significance level was set at $P < 0.05$. The resultant data were evaluated using JMP software version 11 (SAS Institute, Cary, NC, USA).

RESULTS

The median ages of patients in the 3 groups were as follows: Group A, 63 y (range 35-69 y); Group B, 75 y (range 70-79 y); and Group C, 83 y (range 80-91 y). There were statistically significant differences between the 3 groups in terms of ASA classifications, pulmonary malfunction, underlying cardiovascular disease, neurological disease, and hypertension. There were no statistically significant differences between groups in gender, BMI, preoperative SpO_2 (%), pulmonary disease, chronic renal failure, diabetes mellitus, location of the lesions, and mean tumor diameter (Table 1).

There were no statistically significant differences between groups in the procedure times for gastric ESD (Group A: 84.5 min, range 54.8-124.3 min; Group B: 78.0 min, range 58.0-118.0 min; Group C: 83.0 min, range 57.0-107.8 min; p=0.96), and there were no statistically significant differences between groups in the time of the induction period for gastric ESD (Group A, 4.5±2.7 min; Group B, 5.3±3.6 min; Group C, 5.1±3.1 min;

p=0.26). There was a moderate correlation between age and the amount of target concentration (minimum target concentration: r= -0.573, p<0.0001; maximum target concentration: r= -0.576, p<0.0001; average target concentration: r= -0.648, p<0.0001). The older age groups needed a lower median amount of each target concentration (minimum target concentration: Group A, 1.8 µg/mL (IQR 1.4-2.0); Group B, 1.2 µg/mL (IQR 1.0-1.4); Group C, 1.0 µg/mL (IQR 1.0-1.2), p<0.0001; maximum target concentration: Group A, 2.4 µg/mL (IQR 2.2-2.8); Group B, 2.0 µg/mL (IQR 1.6-2.2); Group C, 1.6 µg/mL (IQR 1.4-2.0), p<0.0001; average target concentration: Group A, 2.1 µg/mL (IQR 1.9-2.3); Group B, 1.6 µg/mL (IQR 1.3 -1.8); Group C, 1.4 µg/mL (IQR 1.2-1.6), p<0.0001) (Figure 2).

The older were the age groups, the lower was the requirement for the total infusion doses of propofol (Group A: median 430 mg, (IQR 300-633); Group B: median 300 mg, IQR 200-450); Group C: median 280 mg, IQR 180-388; p<0.0001, p-value for trend <0.0001); also lower average maintenance doses of propofol were needed in the older age groups (Group A: median 5.1 mg/kg/h, IQR 4.2-6.4; Group B: median 4.1 mg/kg/h, IQR 3.2-5.0; Group C: median 3.6 mg/kg/h, IQR 3.1-4.6; p<0.0001, p-value for trend=0.0002).

As for the adverse events related to propofol sedation during ESD, there were no statistically significant differences between groups in the percentages of SBP change from the preoperative value (Group A: median 27.9% (range -8.3-71.3); Group B: median 26.6% (range -11.6-74.7); Group C: median 25.2% (range -16.4-51.2); p=0.306). In addition, there were no statistically significant differences between groups in the percentages of SpO2 from the preoperative value (Group A: median 2.1% (IQR 1.0-4.2); Group B: median 2.1% (IQR 0-4.1); Group C: median 2.1% (IQR 0-4.2); p=0.92). Hypotension (as defined by SBP <80mmHg) tended to occur more often in the younger groups, but the difference was not significant (Group A: 57/162, 35.2%; Group B: 47/171, 27.5%; Group C: 17/80, 21.3%, p=0.062). Hypoxemia occurred significantly more often in the older group but the prevalence was low (Group A: 0/162, 0%; Group B: 4/171, 2.3%; Group C: 4/80, 5.0%, p=0.01). Almost all events resolved immediately after decreasing the amount of propofol and increasing the per-nasal oxygen dosage. All patients recovered from hypoxemia within 30 seconds. Only 4 patients needed vasopressor drugs to recover from hypotension, and no patient needed more than 5 L/min of per-nasal dosage. In addition, all patients were stable under good sedation after hypotension was improved. There were no significant differences between groups in major adverse events related to the ESD procedure such as postoperative bleeding and perforation. All cases of postoperative bleeding were treated by endoscopic hemostasis without blood transfusion, and no cases required surgical therapy for adverse events (Table 2).

When the occurrence of adverse events with the use of propofol was evaluated for 3 periods within the procedure, we found that hypotension occurred most frequently in the maintenance period and that the ratio tended to be highest in Group A. In addition, hypoxemia occurred at a significantly higher ratio in the oldest group (Group C) in the maintenance period (Table 3).

Table 4 summarizes the results of the univariate and multivariate analyses for risk factors associated with hypotension or hypoxemia. Multivariate analysis showed that in Group C the risk of hypotension was decreased; however, when the preoperative SBP ≤125 mmHg the risk of hypotension was increased (Group C: OR=0.53 [CI 0.28–0.98], p=0.042; preoperative SBP ≤125 mmHg, OR=1.73 [CI 1.12–2.70], p=0.013). Also, abnormal pulmonary function increased the risk of hypoxemia in Groups B and C (abnormal pulmonary function, OR=4.54 [CI 1.01–31.5], p=0.048).

DISCUSSION

Although deep sedation in general endoscopic treatment has been reported, data are limited on the monitoring of deep sedation in older patients [18, 19, 23]. This report suggests the efficacy of the TCI/BIS system for propofol sedation during gastric ESD by comparing older and younger patients. In our study, there was an inverse correlation between age and target concentration of propofol. The older the age group was, the lower was the required total infusion dose and the lower was the required average maintenance dose of propofol under the TCI/BIS system of sedation. As for adverse events, the ratio of those with hypotension was highest in Group A, which was the youngest age group, and that with hypoxemia was significantly higher in the older groups (Groups B and C), although the number of cases with this adverse event was small. Possibly the cause of hypoxemia in Group C was that those patients had more frequent episodes of hypoxemia during natural sleep than those in Group A. Hypotension mostly occurred in the maintenance period, while hypoxemia occurred in both the maintenance and recovery periods. Preoperative low SBP was associated with hypotension, and abnormal pulmonary function was associated with hypoxemia in the older patient groups. All events were resolved immediately and no significant differences in major adverse events concerning the ESD procedure, such as preoperative bleeding and perforation, were seen between the 3 groups. Propofol sedation in the elderly patients during ESD with the TCI/BIS system was as safe as in the younger patient group.

Propofol has increasingly replaced benzodiazepines as a sedative because of its short-acting and early awakening pharmacokinetic characteristics [24-27]. The usefulness of propofol sedation in endoscopy has been reported [28-31]. It was reported that propofol was superior to midazolam in a randomized controlled trial of endoscopic examinations [32-37].

In addition, the safety of propofol sedation for elderly patients in endoscopy was also reported [38-41]. Gotoda et al [19] reported that gastroenterologist-guided propofol sedation during gastric ESD may be acceptable even in the elderly with ASA classification I/II under careful monitoring of vital signs and oxygen saturation.

However, propofol may cause cardiorespiratory inhibition. Once cardiorespiratory inhibition has occurred by excessive propofol injection, it is necessary to provide cardiorespiratory supportive care with a ventilator until propofol is metabolized because there are no antagonists available. To avoid excessive infusion of propofol, we used the BIS monitoring system, which makes possible the objective evaluation of the sedation depth. BIS evaluates the association among the different parts of the electroencephalogram at various stages. Since the BIS value is generally set at 45 to 65 during surgical operations under general anesthesia, we set BIS values at 40 to 80 during ESD [42]. Several studies of BIS monitoring for propofol sedation during endoscopic procedures showed its effectiveness for stable sedation [15-17, 43]. But the efficacy of a BIS monitor for propofol sedation concerning the amount of propofol has not been shown clearly. With a TCI/BIS system, Imagawa et al reported that a lower blood concentration of propofol is needed to maintain stable sedation during a lengthy endoscopic procedure [18]. In our examination, there was an inverse correlation between age and the target concentration of propofol to maintain BIS values <80. As a result, it was possible to maintain stable sedation by a lower amount of propofol for elderly patients in comparison with younger patients through control by the TCI/BIS system. That elderly patients require a lower amount of propofol to reach similar levels of sedation than younger patients undergoing complex upper endoscopic procedures was shown [40]. This result suggests that strict control of infusion by the TCI pump adjusted by titration of the individual sedative depth by BIS monitoring could decrease the dose of propofol in elderly patients.

In our study, hypotension events occurred most frequently in the maintenance period. Especially, patients with low preoperative SBP had a high risk of hypotension independent of the age group. A previous study showed that propofol has weaker respiratory suppression and stronger circulatory suppression with a 36% incidence of hypotension compared with 14% with midazolam [35]. Because of the short-acting characteristic of propofol, almost all patients recovered immediately with decreases in the dosage of propofol without using a vasopressor drug. But special attention is needed for patients with low preoperative SBP. Contrary to our expectation, hypotension occurred at a higher ratio in the younger patient group. It was previously shown that propofol-induced hypotension was more prominent in elderly patients when the propofol dose was identical between elderly and young patients. The incidence of hypotension in the younger patients might be explained by the more rapid rate of increase in propofol concentrations [44]. A BIS monitoring system was recommended to avoid hypotension in the elderly [45]. We thought that our finding was due to the stability of the sedative state in the older groups through the BIS/TCI system and the higher preoperative SBP in the aged groups.

Our study has some limitations. First, it was retrospective. However, bias was minimized by accumulating consecutive cases with the same protocol. Second, the initial target concentrations of propofol differed among Group A, Group B, and Group C. The difference in the initial setting might have resulted in an increased propofol dose in Group A and caused hypotension in patients in that group. However, the BIS maintenance target score was the same among groups, and the target doses were adjusted to the predicted concentration at the time when the BIS score fell below 80. Furthermore, no adverse events occurred in the induction period. Third, our study sample size was not determined a priori, therefore false negative outcomes due to a possible under-powered study may have occurred. Fourth, the synergic action of opioid drugs might have resulted in the occurrence of adverse events. We used pentazocine in our study; therefore, the synergic action of pentazocine might explain the occurrence of this adverse event, although to our knowledge there are no previous data on this topic. It might preferable to use propofol combined with low-dose fentanyl or a remifentanil. However, we were not able to examine this issue.

In conclusion, our study revealed that propofol sedation with a TCI/BIS system is very effective in performing ESD in elderly persons safely with a lower dose of propofol. However, there is not yet a standard method for propofol sedation in endoscopic treatment especially in elderly persons. Further studies on a larger scale with a prospective controlled design are needed to standardize sedation with propofol.

FIGURE LEGENDS

Figure 1.

Flowchart of study selection.

Figure 2.

Correlation between age and the target blood concentration.

There was a moderate inverse correlation between age and the target blood concentration (A, B, C). The older age groups needed a lower target blood concentration (C, D, E). Age groups: group A, age <70 (N=162); group B, age ≥ 70 and <80 (N=171); and group C, age ≥ 80 (N=80)

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Table 1. Baseline characteristics of study patients

	All	Group A (<70)	Group B (≥70, <80)	Group C (≥80)	p-Value
N (procedures)	413	162	171	80	
Age (years), median, range	72 (35-91)	63 (35-69)	75 (70-79)	83 (80-91)	
Gender M/F	327/86	136/26	129/42	62/18	0.14
BMI (kg/m2) , median, IQR	22.4 (20.5-24.4)	22.9 (20.8-25.3)	22.2 (20.4-24.5)	21.7(20.0-23.7)	0.062
ASA classification, n (%)					
1	**168 (40.7)**	**103 (63.6)**	**65 (38.0)**	**0 (0)**	**<0.0001**
2	**154 (37.3)**	**32 (19.8)**	**67 (39.2)**	**55 (68.8)**	
3	**91 (22.0)**	**27 (16.6)**	**39 (22.8)**	**25 (31.2)**	
Abnormal pulmonary function, n (%)	**129/385 (33.5)**	**36/153 (23.5)**	**59/156 (37.8)**	**34/76 (44.7)**	**0.0018**
Obstructive	99	34	40	25	
Restrictive	14	2	9	3	
Combined	16	0	10	6	
Preoperative SBP (mmHg), median, IQR	**124 (113-137)**	**121 (110-135)**	**126 (116-137)**	**127 (114-141)**	**0.020**
Preoperative SpO2 (%), median, IQR	97 (93-100)	97 (94-100)	98 (93-100)	97 (95-100)	0.27
Chronic concomitant diseases					
Cardiovascular disease, n (%)	**60 (14.5)**	**15 (9.3)**	**31(18.1)**	**14 (17.5)**	**0.043**
Neurological disease, n (%)	**39 (9.4)**	**8 (4.9)**	**18 (10.5)**	**13 (16.3)**	**0.015**
Pulmonary disease, n (%)	22 (5.3)	9 (5.6)	5 (2.9)	8 (10.0)	0.077
Chronic renal failure, n (%)	18 (4.4)	5 (3.1)	8 (4.7)	5 (6.3)	0.51
Hypertension, n (%)	**141 (34.1)**	**33 (20.4)**	**73 (42.7)**	**35 (43.8)**	**<0.0001**
Diabetes mellitus, n (%)	67 (16.2)	20 (12.4)	32 (18.7)	15 (18.8)	0.22
Number of lesions	455	175	187	93	
Location: n (%)					
Upper	67 (14.7)	25（14.3）	29（15.5）	13（14.0）	0.52
Middle	219 (48.1)	93（53.1）	84（44.9）	42（45.2）	
Lower	169 (37.2)	57（32.6）	74（39.6）	38（40.8）	
Lesion size (mm) , median, IQR	13.0 (8.0-22.0)	13.0 (7.0-25.0)	13.0 (8.0-22.0)	12.0 (7.5-20.0)	0.71

N, number of procedures; M, male; F, female; BMI, body mass index; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; IQR, interquartile range; SpO2, blood oxygen saturation;

Table 2. Characteristics of procedures and adverse events

	Group A (<70)	**Group B (≥70, <80)**	**Group C (≥80)**	**p-Value**
N (procedures)	**162**	**171**	**80**	
Procedure time (min), median, IQR	84.5 (54.8-124.3)	78.0 (58.0-118.0)	83.0 (57.0-107.8)	0.96
Induction period time (mg), mean±SD	4.5±2.7	5.3±3.6	5.1±3.1	0.26
Target blood concentration of propofol				
Minimum target blood concentration (μg/ml), median, IQR	**1.8 (1.4-2.0)**	**1.2 (1.0-1.4)**	**1.0 (1.0-1.2)**	**<0.0001**
Maximum target blood concentration (μg/ml), median, IQR	**2.4 (2.2-2.8)**	**2.0 (1.6-2.2)**	**1.6 (1.4-2.0)**	**<0.0001**
Average target blood concentration (μg/ml), median, IQR	**2.1 (1.9-2.3)**	**1.6 (1.3-1.8)**	**1.4 (1.2-1.6)**	**<0.0001**
Total infusion dose (mg) , median, IQR	**430 (300-633)**	**300 (200-450)**	**280 (180-388)**	**<0.0001** **(p<0.0001 for trend)**
Average maintenance dose (mg/kg/h) , median, IQR	**5.1 (4.2-6.4)**	**4.1 (3.2-5.0)**	**3.6 (3.1-4.6)**	**<0.0001** **(p=0.0002 for trend)**
% SBP change from preoperative value (%), median, IQR	27.9 (-8.3-71.3)	26.6 (-11.6-74.7)	25.2 (-16.4-51.2)	0.306
% SpO2 change from preoperative value (%), median, IQR	2.1 (1.0-4.2)	2.1 (0-4.1)	2.1 (0-4.2)	0.92
Hypotension (SBP <80 mmHg), n (%)	57 (35.2)	47 (27.5)	17 (21.3)	0.062
Needs vasopressor drug	2 (1.2)	0 (0.0)	2 (2.5)	0.15
Hypoxemia (SpO2 <90%), n (%)	**0 (0)**	**4 (2.3)**	**4 (5.0)**	**0.01**
Needs per-nasal oxygen dosage >5l/min	0	0	0	-

Perforation, n (%)	12 (7.5)	8 (4.7)	4 (5.0)	0.53
Postoperative bleeding, n (%)	9 (5.6)	5 (3.0)	3 (3.8)	0.48

N, number of procedures; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; SpO2, blood oxygen saturation

Table 3. Adverse events related to sedative during three periods

		Group A (<70)	Group B (≥70, <80)	Group C (≥80)	p-Value
N (procedures)		**162**	**171**	**80**	
Hypotension (SBP <80 mmHg)	Induction period, n (%)	4 (2.5)	2 (1.2)	0 (0)	0.18
	Maintenance period, n (%)	57 (35.2)	46 (26.9)	17 (21.3)	0.056
	Recovery period, n (%)	3 (1.9)	3 (1.8)	0 (0)	0.27
Hypoxemia (SpO2 <90%)	Induction period, n (%)	0 (0)	0 (0)	0 (0)	-
	Maintenance period, n (%)	**0 (0)**	**2 (1.2)**	**3 (3.8)**	**0.034**
	Recovery period, n (%)	0 (0)	3 (1.8)	2 (2.5)	0.075

N, number of procedures; SBP, systolic blood pressure; SpO2, blood oxygen saturation

Table 4. Risk factors for hypotension and hypoxemia

	Hypotension				Hypoxemia			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-Value	OR (95%CI)	p-Value	OR (95%CI)	p-Value	OR (95%CI)	p-Value
Group A	1 (ref.)		1 (ref.)		0.0 (incalculable)		0.0 (incalculable)	
B	0.69 (0.44-1.11)	0.13	0.73 (0.46-1.17)	0.20	1 (ref.)		1 (ref.)	
C	**0.50 (0.26-0.91)**	**0.024**	**0.53 (0.28-0.98)**	**0.042**	2.20 (0.51-9.52)	0.28	1.93 (0.44-8.49)	0.37
Gender (M/F)	1.47 (0.86-2.60)	0.17			2.26 (0.39-42.6)	0.41		
BMI >22.5 kg/m2	0.83 (0.54-1.27)	0.40			2.23 (0.53-11.05)	0.27		
ASA class 1	1 (ref.)				1 (ref.)			
class 2	**0.61 (0.37-0.99)**	**0.047**			2.74 (0.43-52.97)	0.32		
class 3	0.94 (0.53-1.61)	0.81			2.06 (0.19-45.04)	0.55		
Abnormal pulmonary function	0.88 (0.55-1.40)	0.60			**4.72 (1.06-32.73)**	**0.041**	**4.54 (1.01-31.5)**	**0.048**
Preoperative SBP ≤125 mmHg	**1.81 (1.18-2.81)**	**0.007**	**1.73 (1.12-2.70)**	**0.013**	0.64 (0.13-2.64)	0.54		
Chronic concomitant diseases								
Cardiovascular disease	1.36 (0.5-2.41)	0.30			1.55 (0.22-6.99)	0.61		
Neurological disease	0.60 (0.25-1.28)	0.19			1.01 (0.05-5.99)	0.99		
Pulmonary disease	1.13 (0.42-2.76)	0.79			0.0004 (0.0-5.15)	0.35		
Chronic renal failure	0.47 (0.11-1.45)	0.20			0.0003 (0.0-5.13)	0.35		
Hypertension	0.89 (0.56-1.38)	0.60			2.27 (0.54-11.2)	0.26		
Diabetes mellitus	0.72 (0.38-1.29)	0.28			0.61 (0.03-3.56)	0.63		

M, male; F, female; BMI, body mass index; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; OR, odds ratio

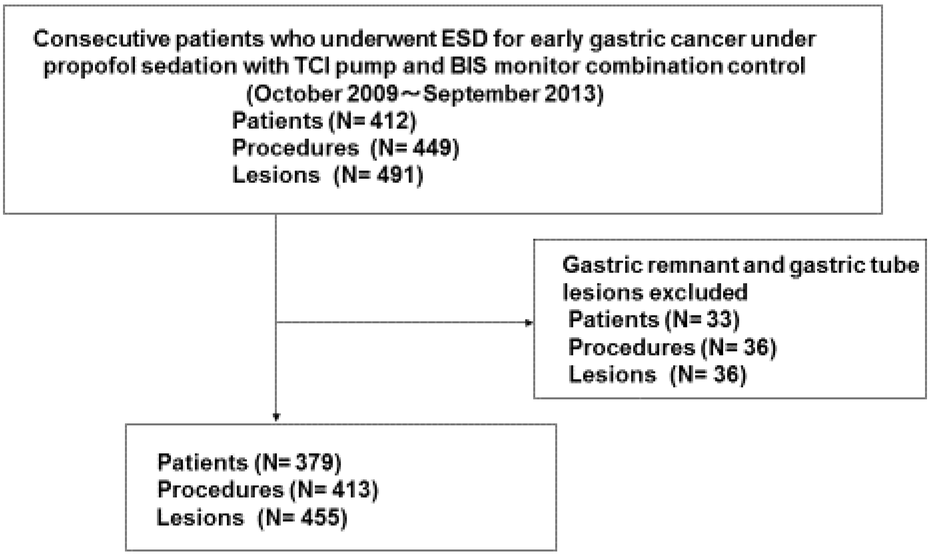

Figure 1. Flowchart of study selection. BIS, bispectral index; ESD, endoscopic submucosal dissection; TCI, target-controlled infusion.

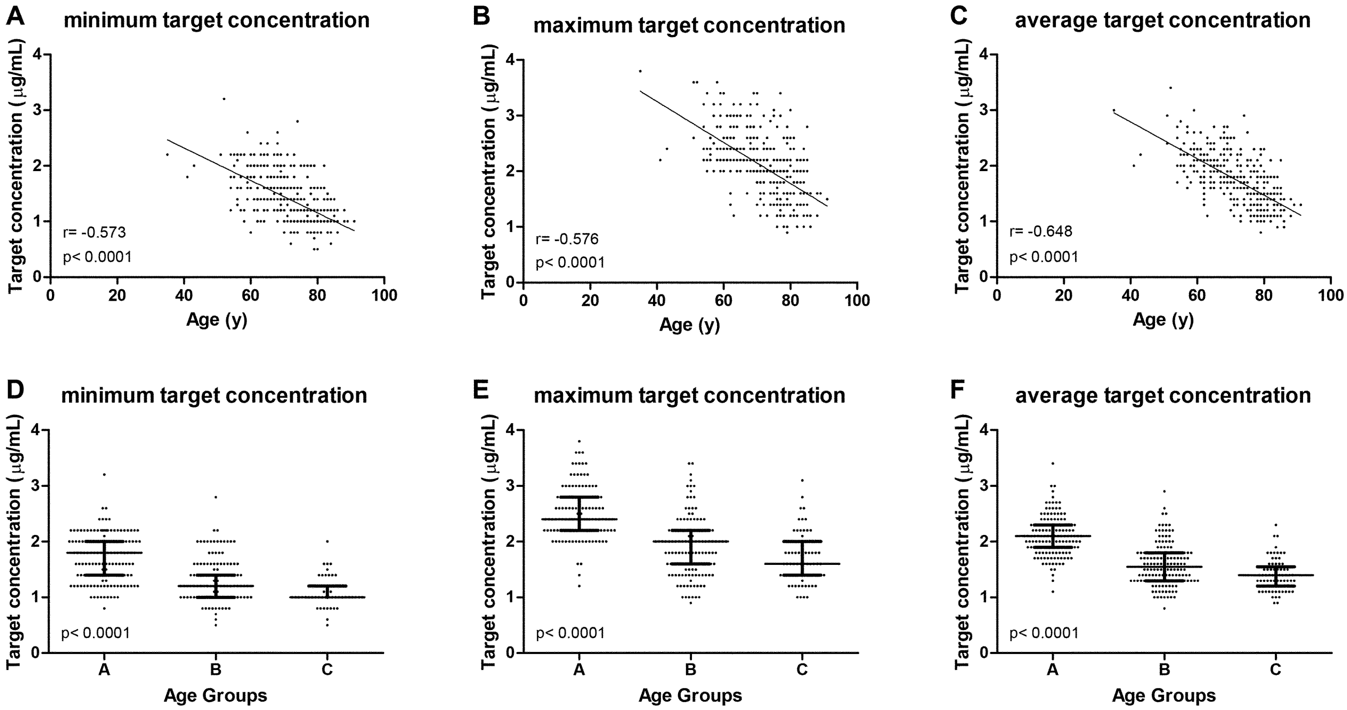

Figure 2. Correlation between age and the target blood concentration. There was a moderate inverse correlation between age and the target blood concentration (A, B, C). The older age groups needed a lower target blood concentration (D, E, F). Age groups: group A, age <70 years (n = 162); group B, age ≥70 and <80 years (n = 171); and group C, age ≥80 years (n = 80).