Title page

Title

Propofol sedation with a target-controlled infusion pump (TCI) in elderly patients undergoing endoscopic retrograde cholangiopancreatography

Key words: ERCP, TCI, elderly patients

Short title

Propofol sedation with a TCI system in ERCP

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Abbreviations

ERCP, endoscopic retrograde cholangiopancreatography; AE, adverse effect; SBP systolic blood pressure; SPO_2, peripheral oxygen saturation; eGFR, glomerular filtration rate; M, male; F, female

Author contributions

TO, TT, and HK took part in the conception, design, and drafting of the article. YA and ST participated in the analysis and interpretation of the data. HO participated in the final approval of the article.

Abstract

Background and Aims

Advanced age is an important risk factor for adverse events (AEs) during propofol sedation for endoscopic procedures. This study aimed to evaluate the safety and efficacy of non-anesthesiologist-administered propofol (NAAP) sedation with a target-controlled infusion (TCI) system in elderly patients during endoscopic retrograde cholangiopancreatography (ERCP).

Methods

This study retrospectively analyzed 482 patients who underwent ERCP under propofol sedation with a TCI system at Iwakuni Medical Center between January 2014 and October 2016. The patients were divided into three groups according to their age: Group A, <70 years (n=130); Group B, ≥70 and <85 years (n=224); and Group C, ≥85 years (n=125). We compared the propofol dose and AEs during ERCP.

Results

The median total infusion dose and minimum and maximum target blood concentrations of propofol were 336 mg, 2.2 μg/mL, and 2.2 μg/mL in Group A, 184 mg, 1.0 μg/mL, and 1.4 μg/mL in Group B, and 99 mg, 0.6 μg/mL, and 1.0 μg/mL in

Group C, respectively, with older groups requiring a lower dose ($p<0.0001$). Hypotension was observed in 23 patients (4.8%), with no significant difference between the groups (Group A: 2.3%; Group B: 6.3%; Group C: 4.8%; $p=0.24$). Hypoxemia was observed in 16 patients (3.3%), with no significant difference between the groups (Group A: 3.1%; Group B: 4.9%; Group C: 0.8%; $p=0.17$). All AEs were immediately resolved, and no procedures were aborted.

Conclusion

NAAP sedation with a TCI system during ERCP may be acceptable in elderly patients with a lower dose of propofol than that used in younger patients.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is currently indispensable for the diagnosis and treatment of diseases in the biliary-pancreatic region (1-3). Since ERCP is physically burdensome to the patient and difficult to perform without sedation, it is usually performed using a sedative. However, sedatives are known to cause serious side effects, such as a reduction in blood pressure and respiratory depression when overdosed (4).

Propofol has been used for anesthesia since 1984 (5) and is a short-acting sedative with a rapid recovery profile compared with that of other sedatives, which allows the patient to be sedated and wakened quickly. These advantages have resulted in an increased use of propofol worldwide (4), and a few reports have demonstrated the safety of propofol administration during ERCP procedures (6, 7). Moreover, recent European guidelines state that non-anesthesiologist-administered propofol (NAAP) can also be safely applied in endoscopic procedures (8).

Among the effective sedatives, propofol has a narrow safety margin and should be used with care in older patients as it reduces cardiac output and systemic vascular

resistance and leads to respiratory inhibition (9). Well-accepted risk factors for the development of cardiopulmonary complications include impaired physical status, procedure type, and older age (10-12).

A target-controlled infusion (TCI) system, which is incorporated into a conventional infusion pump, enables automatic control of the dose of sedative drugs using a computer-assisted infusion algorithm (13,14). With the TCI system, the dose of propofol is gradually reduced per unit time and the blood concentration of propofol is kept constant when the theoretical target concentration is constant (15). According to the patient's weight and age, a steady concentration of propofol can be administered. It is believed that the TCI system increases the safety of sedation during endoscopic procedures, even in elderly patients (16,17). However, considering the currently limited information, this study aimed to evaluate the safety and efficacy of NAAP sedation with an appropriate dose of propofol supplied using a TCI system in elderly patients during ERCP.

Methods

Patients

This is a single-center, retrospective observational study. Patients were identified

from our consecutive ERCP database, and data were collected from their medical records. A total of 951 consecutive ERCP procedures were performed at Iwakuni Medical Center using propofol sedation with a TCI system between January 2014 and October 2016.

Among them, we excluded 469 patients who underwent repeated ERCP during the study period. Additionally, three cases involving the use of other sedative drugs and one case in which sufficient systolic blood pressure (SBP) (80 mmHg) could not be achieved before the procedure were also excluded. Therefore, a total of 478 patients were considered eligible for inclusion. This study was approved by the Ethics Committee at the Iwakuni Medical Center in accordance with the Helsinki Declaration.

Study design

The patients were divided into three groups according to their age: group A: <70 years; group B: ≥70 and <85 years; and group C: ≥85 years. Associations between age group, and propofol dose and sedation-related adverse events (AEs) during ERCP were examined.

In addition, the established target blood concentration and total infusion dose of propofol during the ERCP procedure were recorded. The minimum and maximum target blood concentrations were reviewed.

We assessed hypotension and hypoxemia, which are major adverse events that are related to propofol sedation, that occurred during two periods of each procedure: the induction period and the maintenance period. The induction period was defined as the time from the start of propofol infusion to the insertion of the endoscope. The maintenance period was defined as the time from the endoscope insertion to endoscope removal. All patients left the endoscopy suite after ERCP when it was confirmed that they were fully awake and could respond to questions. The infusion of propofol was continued until the endoscope was removed. Moreover, ERCP-related AEs, such as post-ERCP pancreatitis, perforation, bleeding, and postoperative pneumonia, were investigated. These AEs were defined according to Cotton's criteria (18).

Additional data were examined as background factors. Sex, body mass index, American Society of Anesthesiologists (ASA) classification, heavy alcohol consumption (60 g/day for males and 48 g/day for females), indication for ERCP,

emergency endoscopy (procedure within <24 hours or scheduled), preoperative SBP, preoperative peripheral capillary oxygen saturation (preoperative blood oxygen saturation [SpO_2]), and chronic concomitant diseases were recorded prior to the ERCP procedure by the endoscopist. Differences in these background factors between the three groups were examined.

Concomitant diseases included the following: cardiovascular disease (ischemic heart disease, moderate-severe valvopathy, arrhythmia, heart failure, heart attack); neurological disease (cerebrovascular disorder, neurodegenerative disease, neurological injuries); pulmonary disease (asthma, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, pulmonary hypertension); renal failure (estimated glomerular filtration rate [eGFR] ≤29); hypertension; and diabetes mellitus.

ERCP procedure and medication

All ERCP procedures were performed with the patient in the prone or semi-prone position using the side-view endoscope (JF-260 or TJF-260V: OLYMPUS, Tokyo, Japan) with CO_2 insufflation. Local pharyngeal anesthesia was induced using an

8% topical lidocaine spray, and 15 mg of pentazocine was administered as an analgesic agent. Propofol was then administered intravenously using the diprifusor system (TE-371; Terumo, Tokyo, Japan), which is a TCI system incorporating pharmacokinetic parameters. The initial target blood concentration of propofol (1% Diprivan Injection kit; AstraZeneca, Osaka, Japan) was set at 2.2 μg/mL for Group A, 1.0 μg/mL for Group B, and 0.6 μg/mL for Group C; the initial target propofol blood concentration was determined with reference to our previous study (19). The objective was to maintain a patient sedation level between moderate (the patient responds properly to verbal commands either given alone or accompanied by light tactile stimulation) and deep (the patient cannot be easily aroused but may respond properly to repeated or painful stimulation) (20).

When the sedation level was considered insufficient even if the initial concentration had been reached, the target blood concentration was increased by 0.2 μg/mL. In addition, if the patient sedation level was appropriate even if the initial concentration had not been reached, the endoscopic procedures were started at that concentration. If the patient was awake or moving significantly during the procedure, the target blood concentration was increased by 0.2 μg/mL. If the

movement was still severe, bolus doses of 1.0 mL of propofol were given. All medications were administered by a gastroenterologist who did not directly participate in the ERCP procedures. We consulted with the anesthesiology department before the operation, and an anesthesiologist was on standby in case of emergency.

Monitoring

Patients received supplemental oxygen (2 L/min) via nasal cannula in the endoscopy room as their vital signs and oxygen saturation were continuously monitored and recorded every 5 min using a standard 3-lead electrocardiogram, pulse oximetry, and automatic blood pressure equipment. Chest excursion and respiratory rates were monitored visually, and consciousness levels were assessed initially after the induction of sedation using the stages of sedation according to the American Society of Anesthesiologists (20). After the procedure, patients were discharged from the endoscopy room at the discretion of the endoscopist when it was confirmed that they were fully awake and responding to questions and had stable vital signs. After the procedure, patients fasted until blood tests were performed the following day confirming the absence of pancreatitis or other AEs.

All patients in this study were hospitalized for at least 48 hours after the procedure for observation. We assessed patients the morning after the procedure and any time they complained of pain. Decisions regarding the evaluation of AEs following the procedure were made at the discretion of the endoscopist. All results were recorded by the endoscopist.

Management of AEs

AEs were defined as a decline in oxygen saturation to <90% (hypoxemia) for longer than 10 seconds or an SBP of <80 mmHg (hypotension). If a patient developed hypoxemia for longer than 10 seconds, we performed a chin lift, reduced the target blood concentration of propofol by 0.2 mg/mL, and supplemental oxygen was used to immediately increase the oxygen flow until the saturation level reached >95%. If the patient's oxygenation did not improve within 1 minute, the ERCP procedure and sedation were interrupted to secure the airway. In cases of hypotension, we immediately reduced the target blood concentration of propofol by 0.2 mg/mL, with an immediate increase in the intravenous drip infusion. If the patient's blood pressure did not improve within 5 minutes, a temporary vasopressor was administered.

Statistical analyses

Continuous variables are presented as the median and interquartile range (IQR). The Kruskal-Wallis test was performed to compare the continuous data, and the chi-square test was performed to evaluate non-continuous variables. $p<0.05$ was considered statistically significant. All statistical analyses were performed using JMP Pro 12 (SAS Institute Inc., Cary, NC, USA). A multivariate model was not feasible because of the low number of AEs.

Results

Patient characteristics

The baseline characteristics of the three groups are shown in Table 1. The median age of the groups was as follows: group A, 61 years (range 55–67 years); group B, 77 years (range 74–81 years); group C, 88 years (range 86–91 years). There were significant differences between the three groups in terms of sex, body mass index, ASA classifications, heavy alcohol consumption, preoperative SpO_2 (%), underlying cardiovascular disease, neurological disease, chronic renal failure, and hypertension.

Details of propofol administration

The median induction period, maintenance period, and total sedation time were 8 (range, 5–10) minutes, 43 (range, 30–65) minutes, and 52 (range, 40–47) minutes, respectively. None of the patients had insufficient sedation during the procedure. There was a significant difference in the induction period between the three groups ($p=0.01$), but there were no differences in the median maintenance period ($p=0.91$) or total sedation time ($p=0.67$) (Table 2).

There was a moderate correlation between age and total infusion dose ($r=-0.60$, $p<0.0001$) and a strong correlation between age and maximum target concentration ($r=-0.79$, $p<0.0001$) and minimum target concentration ($r=-0.79$, $p<0.0001$) (Figure 1). Overall, the older age groups needed a lower median minimum target concentration (Group A, 2.2 μg/mL; Group B, 1.0 μg/mL; Group C, 0.6 μg/mL; $p<0.0001$), maximum target concentration (Group A, 2.2 μg/mL; Group B, 1.4 μg/mL; Group C, 1.0 μg/mL; $p<0.0001$), and total infusion dose (Group A, 336 mg; Group B, 185 mg; Group C, 99 mg; $p<0.0001$) (Table 2).

There was no significant difference between the three groups in terms of the need for an additional propofol bolus injection.

Adverse events

Regarding the AEs related to propofol sedation during ERCP, hypotension was observed in 23 patients (4.8%) and tended to occur more often in Group B; however, there was no significant difference between the three groups (Group A, 3/130 [2.3%]; Group B, 14/224 [6.3%]; Group C, 6/125 [4.8%]; p=0.24). Among the 23 patients, only nine needed temporary vasopressor treatment (etilefrine hydrochloride for five patients, dopamine hydrochloride for two, and noradrenaline hydrochloride for two) to recover from hypotension, while the others were improved by reducing the target blood concentration of propofol with an immediate increase in the intravenous drip infusion.

Hypoxemia was observed in 16 patients (3.3%), with no significant difference between the three groups (Group A, 4/130 [3.1%]; Group B, 11/224 [4.9%]; Group C, 1/125 [0.8%]; p=0.17) (Table 3). These patients were treated by increasing the per-nasal oxygen dose, and 12 patients needed more than a 5 L/min per-nasal dose. All patients recovered from hypoxemia within 30 seconds, and none required endotracheal intubation. Upon evaluation of the occurrence of AEs with the use of

propofol during the induction period and the maintenance period of the procedure, we found that hypotension and hypoxemia occurred most frequently in the maintenance period.

There were no significant differences between groups in terms of AEs related to the ERCP procedure, such as postoperative pneumonia, perforation, post-ERCP pancreatitis, or bleeding (Table 3).

Discussion

We compared the safety and efficacy of the use of the TCI system for propofol sedation administered by a non-anesthesiologist during ERCP among older and younger patients in this study.

With regard to AEs, the rates of hypotension and hypoxemia were not significantly different between the groups. Propofol sedation during ERCP using the TCI system was as safe in elderly patients as it was in the younger patient group.

Advanced age is one of the risk factors for cardiopulmonary complications during propofol sedation based on current reports (15). In our study, we set different

initial target control concentrations for each group, and there was an inverse correlation between the age and the target propofol concentration. The older the age of the group, the lower was the required total infusion dose and maintenance dose of propofol using the TCI system.

Furthermore, the frequency of additional propofol bolus injections did not significantly differ between the three groups, indicating that there was no difference in the frequency of insufficient sedation level.

In a number of studies reporting the outcomes of propofol administration during ERCP (9, 21, 22), the rates of hypotension and hypoxemia related to propofol sedation were reported to range between 6.0% and 15.6% and 6.9% and 17.0%, respectively. In the present study, hypotension and hypoxemia occurred in 5.0% and 3.3% of patients, respectively, which are more favorable results compared with those in previous studies. Most previous reports used a method of administering a constant amount of propofol per minute that was not a TCI system. In fact, the blood concentration of propofol does not stay constant over several hours using this method (15); therefore, in theory, the longer the total sedation time, the higher is the likelihood of AEs. While European guidelines recommend using a TCI system

for endoscopic procedures (8), there has been limited information on the outcomes of propofol sedation using a TCI system for ERCP procedures, especially in elderly patients. In this study, fewer AEs occurred than in previous studies, which may be attributable to the effective maintenance of appropriate propofol concentrations using the TCI system.

In recent European guidelines, physical state according to the ASA classification was reported to be related to the AEs of propofol sedation (8). In our study, hypotension was observed in 16 patients (4.3%) who were ASA ≤III and four (12.2%) who were ASA IV. Hypotension was significantly more frequent in ASA IV patients than in those with ASA ≤III ($p=0.04$), but there was no difference in terms of hypoxemia (19 ASA ≤III patients (3.6%) in the ASA ≤III group and no ASA IV patients (0%); $p=0.27$). According to this result, it may be possible to further reduce the rate of the AEs by considering not only age but also ASA classification when establishing the initial target concentration of propofol. Moreover, the bolus injection dose of propofol may need to be adjusted according to age and ASA classification.

Our study has some limitations. First, this study was a single-institution retrospective study, and further multi-institutional, prospective research is necessary. Second, pentazocine was administrated before intravenous infusion of the sedative drug as an analgesic. It is possible that proper analgesia was not obtained during the procedures and that the propofol concentration was adjusted more than necessary. Third, the initial target concentrations of propofol were set for each group according to age. In our study, the rates of AEs were not significantly different between the three groups, though it remains unknown whether the initial target concentration of each group was actually optimal. We need to explore the possibility of more appropriate initial target concentrations to further decrease the occurrence of AEs. In addition, an investigation of the use of the same initial blood propofol concentration across all age groups is necessary in the future. Fourth, evaluation of the sedation level during ERCP was lacking, which may have affected the frequency of AEs.

In conclusion, NAAP sedation with a TCI system during ERCP may be acceptable in elderly patients with a lower dose of propofol than that used in younger patients.

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Table 1. Patient characteristics

	All n = 478	Group A n = 130	Group B n = 223	Group C n = 125	p-value
Age, years, median (range)	77 (69–85)	61 (55–67)	77 (74–81)	88 (86–91)	
Sex, male/female	246/232	84/46	118/105	44/81	<.0001
Body mass index, kg/m^2, median (range)	21.9 (20.0–24.5)	23.07 (21.2–26.0)	21.8 (19.8–24.5)	21.0 (19.3–23.0)	<.0001
Body mass index >35	2 (0.4)	2 (1.5)	0 (0)	0 (0)	0.068
ASA classification, n (%)					0.013
I	21 (4.4)	10 (7.7)	8 (3.6)	3 (2.4)	
II	295 (61.7)	90 (69.2)	136 (61.0)	69 (55.2)	
III	129 (27.0)	25 (19.2)	65 (29.1)	39 (31.2)	
IV	33 (6.9)	5 (3.9)	14 (6.3)	14 (11.2)	
Heavy alcohol consumption	33 (6.9)	20 (15.4)	9 (4.0)	4 (3.2)	<0.0001
Preoperative SBP, mmHg median (range)	131 (119–146)	130 (119–143)	131 (119–147)	132 (119–149)	0.48
Preoperative SpO_2, % median (range)	97 (96–98)	98 (96–98)	97 (96–98)	96 (95–98)	0.0011
Chronic concomitant diseases, n (%)					
Cardiovascular disease	110 (23.0)	12 (9.2)	59 (26.5)	39 (31.2)	<0.0001
Neurological disease	93 (19.5)	16 (12.3)	40 (17.9)	37 (29.6)	0.0017
Pulmonary disease	33 (6.9)	6 (4.6)	22 (9.9)	5 (4)	0.06
Chronic obstructive pulmonary disease	20 (4.2)	4 (3.1)	13 (5.8)	3 (2.4)	0.24
Sleep apnea syndrome	2 (0.4)	0 (0)	2 (0.9)	0 (0)	0.32
Chronic renal failure (eGFR ≤29 ml/min)	28 (5.9)	2 (1.5)	16 (7.2)	10 (8)	0.046
Hypertension	250 (52.3)	51 (39.2)	128 (57.4)	71 (56.8)	0.0022
Diabetes mellitus	100 (20.9)	34 (26.2)	43 (19.3)	23 (18.4)	0.22
Emergency endoscopy (procedure within <24 hours)	137 (28.7)	36 (27.7)	60 (26.9)	41 (32.8)	0.49

ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; SPO_2, peripheral oxygen saturation; eGFR, estimated glomerular filtration rate

Table 2. Characteristics of sedation time and propofol dose

	Group A n=130	Group B n=224	Group C n=125	p-value
Introduction time, min, median (range)	7 (5–9)	9 (5–12)	8 (5–12)	0.001
Procedure time, min, median (range)	44 (33–60)	45 (30–65)	41 (30–65)	0.91
Total sedation time, min, median (range)	50 (40–65)	55 (40–75)	50 (37–74)	0.67
Target concentration of propofol, μg/mL, median (range)				
Minimum	2.2 (1.6–2.2)	1.0 (1.0–1.0)	0.6 (0.6–0.6)	<0.0001
Maximum	2.2 (2.2–2.6)	1.4 (1.2–1.7)	1.0 (0.8–1.2)	<0.0001
Total infusion dose, mg, median (range)	336 (241–439)	185 (123–250)	99 (65–164)	<0.0001
Additional propofol bolus injection, n (%)				0.29
Total	23 (17.7)	26 (11.7)	18 (14.4)	
One time	13 (10.0)	17 (7.6)	10 (8.0)	
More than two times	10 (7.7)	9 (4.0)	8 (6.4)	

Table 3. Adverse events

	Group A n=130	Group B n=224	Group C n=125	p-value
Hypotension, n (%)	3 (2.3)	14(6.3)	6 (4.8)	0.24
Induction period	1 (0.8)	0	0	0.26
Maintenance period	2 (1.5)	14(6.3)	6 (4.8)	0.12
Hypoxemia, n (%)	4 (3.1)	11 (4.9)	1 (0.8)	0.12
Induction period	0	1 (0.5)	0	0.56
Maintenance period	4 (3.1)	10 (4.5)	1 (0.8)	0.17
Postoperative pneumonia	0	2 (0.9)	0	0.32
Perforation	1 (0.8)	1 (0.5)	0	0.63
Post-ERCP pancreatitis	6 (4.6)	9 (4.0)	1 (0.8)	0.18
Bleeding	0	1 (0.5)	0	0.57

ERCP, endoscopic retrograde cholangiopancreatography

Figure legends

Figure 1A–C: Correlation between age, and total infusion dose and target blood concentration of propofol. There was a moderate inverse correlation between age and the total infusion dose (r=−0.60) and a strong inverse correlation between age and maximum target blood concentration (r=−0.79) and minimum target blood concentration (r=−0.79).