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ORIGINAL ARTICLE

The Optimal Maintained Effective-site Concentration of Propofol under Target-controlled Infusion in Same-day Bidirectional Endoscopy

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Background: The same-day bidirectional endoscopy (BDE) under anesthesia is commonly performed for its efficacy. Until now, the optimal regimen of sedation for same-day BDE is still inconclusive. **Aim:** The aim of this study is to investigate the relationship between the effect-site concentration at loss of consciousness (Ce_{LOC}) and maximal maintained Ce (Ce_M) in patients undergoing sole propofol sedation with the targeted-controlled infusion (TCI) pump and to explore the potential factors for extra fentanyl administration for same-day BDE to improve the quality of anesthesia. **Methods:** After excluding the patients with different anesthesiologists/endoscopists and esophagogastroduodenoscopy before colonoscopy, a total of 183 patients receiving BDE with the American Society of Anesthesiologists I to III were enrolled. Anesthesia with TCI of propofol ranged from 2.5 to 5.0 μg/mL was administrated and propofol was increased in steps of 0.5 μg/mL when inadequate or too deep sedation during the procedure. If the sedation level failed to meet satisfaction after two times of Ce increments or Ce_M achieve 5.0 μg/mL, bolus of fentanyl (25 μg) would be administered. The age, height, weight, gender, Ce_{LOC}, $Ce_{M,}$ awake Ce, anesthesia time, examination time, frequency of TCI adjustments, total consumption of propofol or fentanyl, incidence of patient movements affecting the procedure, and use of ephedrine or atropine were retrieved from anesthetic charts and electronic medical record was recorded and the factors affecting the extra bolus of fentanyl or Ce_M were calculated. **Results:** One hundred and fifty-seven patients underwent procedures with only propofol sedation and 26 patients with additional fentanyl bolus 25 μg. There were three patients with hypotension, bradycardia, and transient hypoxemia in only propofol sedation, respectively. The incidence of patient movements affecting the procedure was 36.6% (67/183), 41 patients completed the procedure after increasing propofol Ce, and 26 patients required an extra bolus of fentanyl. After linear regression, the optimal formula was $Ce_M = 1.9 – (0.006 \times age) + 0.658 \times Ce_{LOC}$. After controlling for confounding covariates, only Ce_{LOC} was the most informative covariate for the demand for fentanyl. Finally, we simplified the formula as propofol $Ce_M = Ce_{LOC} + 0.7$ μg/mL to avoid patient movements affecting the procedure and adverse effects. **Conclusion:** We showed that the age and Ce_{LOC} were associated with Ce_M and only higher Ce_{LOC} (>4.5 μg/mL) was the only contributing factor for the extra bolus of fentanyl in BDE. We also provided the simplified formula as propofol $Ce_M = Ce_{LOC} + 0.7$ μg/mL to avoid patient movements affecting the procedure and adverse effects.

Key words: Propofol, target-controlled infusion, effect-site concentration, bidirectional endoscopy

INTRODUCTION

Gastrointestinal endoscopy (GIE), including esophagogastroduodenoscopy (EGD) and colonoscopy, is a common clinical technique for diagnosis and treatment of GI disease. Same-day bidirectional endoscopy (BDE), performance of both colonoscopy and EGD at the same time,

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has been widely performed during adult health examinations.[1,2] Since invasive procedures often cause anxiety and painful stimuli, adequate sedation and analgesia play important roles in endoscopic examinations. However, the optimal strategy of anesthesia during BDE remained controversial. A retrospective study had reported that co-administration of fentanyl and midazolam and/or propofol results in delayed emergence during GIE.[3] On the other hand, the use of sole propofol sedation was proved to be both effective and safe during diagnostic GIE.[4-7] In addition, propofol-based sedation under targeted-controlled infusion (TCI) might provide satisfactory cardiovascular stability, mild respiratory depression, and rapid recovery in GI endoscopic procedures.[8-15] In our clinical practice, sole propofol sedation with TCI was applied for anesthesia during same-day BDE or GIE. Iwakiri *et al*. concluded that propofol effect-site concentration at loss of consciousness (Ce_{LOC}) could be used as a guide to the anesthetic management to maintain a constant Ce.[16] Until now, there was rare research regarding sole propofol under TCI in sedated BDE.[10,15,17,18] Therefore, this retrospective cohort study aimed to investigate the relationship between the Ce_{LOC} and maximal maintained Ce (Ce_M) in patients undergoing sole propofol sedation with the TCI pump and to explore the potential factors for extra fentanyl administration for same-day BDE to improve the quality of anesthesia.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Tri-Service General Hospital and National Defense Medical Center, Taiwan (TSGHIRB No: 100-05-168) and waived the need for informed consent, retrieved information from the electronic database and anesthetic records of Tri-Service General Hospital (TSGH; Taipei, Taiwan, Republic of China). All methods were performed in accordance with the relevant guidelines and regulations by domestic IRB. A total of 183 patients (81 women and 102 men), classified as the American Society of Anesthesiologists (ASA) classification I to III, aged from 20 to 80 years, and scheduled in same-day BDE (colonoscopy followed by EGD) from January 2010 to December 2011, were enrolled in this study. Exclusion criteria were those with known neurological disorders, pregnancy, uncontrolled hypertension, recent use of psychotropic drugs or central nervous system depressants/stimulants, chronic alcohol consumption, significant obese (body mass index >30 kg/m^2), different anesthesiologists and endoscopists, EGD before colonoscopy, only performing EGD or colonoscopy, and incomplete data [Figure 1].

The standard clinical practice as followings, all fasted overnight cases were without premedication before anesthesia

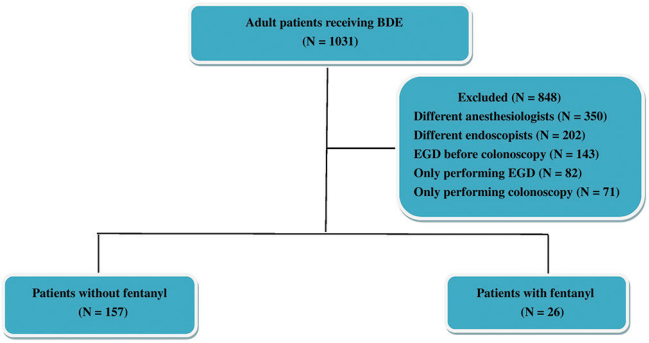

Figure 1: Flow diagram showing patient flow according to the study protocol. BDE: Bidirectional endoscopy, EGD: Esophagogastroduodenoscopy

induction. Standard monitoring, such as noninvasive blood pressure, electrocardiography (lead II), pulse oximetry (SpO_2), and end-tidal carbon dioxide pressure, were used for each case. Cases received 100% oxygen at 6 L/min using a facial mask throughout procedure. 1. Continuous infusion of propofol (Fresofol 1%)) was delivered by the TCI pump (Fresenius Orchestra Primea; Fresenius Kabi AG, Bad Homburg, Germany) with the Schnider model to keep the Ce of 2.5–5.0 μg/mL, which was determined by the anesthesiologist (Zhi-Fu Wu) based on the patient's clinical conditions to maintain mean arterial pressure (MAP) and heart rate (HR) at baseline levels ± 30% and patient comfort (adequate sedation without patient movements affecting the procedure).[19] The patients were defined as reaching level of LOC while being unable to obey verbal command and lost eyelash reflex; colonoscopy was started before EGD by one single endoscopist. If patients with insufficient sedative levels such as body movements affecting the procedure, increasing propofol Ce of 0.5 μg/mL was administrated. If adjustment of TCI device >2 times was failed to meet adequate level of sedation or Ce_M achieved 5.0 μg/mL, an extra bolus of fentanyl (25 μg) was added and reducing propofol Ce by 0.5 ng/mL would be conducted. If patients presented with signs of too deep sedative level such as hypotension (MAP <60 mmHg), or bradycardia (HR <60 bpm), or apnea with desaturation (SpO_2 <90%), reducing propofol Ce of 0.5 μg/mL was administered. When apnea with desaturation (SpO_2 <90%) occurred, we also used positive pressure mask ventilation (with 100% oxygen at 6 L/min) and jaw elevation to keep airway open. If patients with systolic blood pressure <90 mmHg or HR <50 bpm, an intravenous bolus of ephedrine 5–10 mg or atropine 0.5 mg was given. Propofol infusion was ceased when the stomach was visualized. After each patient regained consciousness by name, the patient was sent to the postoperative anesthesia care unit for further care.

Ce_{LOC} is the Ce of propofol as the time to LOC without eyelash reflex, and Ce_M is the Ce of propofol as the Ce_M

during procedures. The anesthetic time was defined as the time from anesthesia induction to the end of procedure. The examination time was measured from the successful insertion of the colonoscopy to completion of EGD. The recovery time was defined as the end of the procedure to eye-opening of patient on verbal command. The total amounts of propofol and fentanyl were defined as the total dose of propofol and fentanyl administered during the procedure. All variables including gender, age, height, weight, Ce_{LOC}, Ce_M, awake Ce, anesthetic time, examination time, frequency of TCI adjustments, total consumption of propofol or fentanyl, and other medications were retrieved from anesthetic charts and electronic medical records. Data were presented as the mean and standard deviation or as medians with the range or percentage counts, unless otherwise indicated. Demographic and perioperative variables were compared using Student's *t*-tests or the Mann–Whitney test when the data were not normally distributed. Categorical variables were compared using the Chi-square test as appropriate. A univariate analysis was performed to examine the association between demographic/clinical factors and the amount of fentanyl or Ce_M; furthermore, multivariable logistic analysis was used to examine the association between demographic/clinical factors and the amount of fentanyl or Ce_M after controlling for confounding covariates. Statistical significance was accepted for two-tailed $P < 0.05$. Statistical analysis was performed using SigmaPlot for Windows version 14.5 (Systat Software Inc., CA, USA). A simple linear regression model was used to correlate for Ce_{LOC} and Ce_M.

RESULTS

We excluded the different anesthesiologists (n = 350) or endoscopists (n = 202), EGD before colonoscopy (n = 143), and only performing EGD (n = 82) or colonoscopy (n = 71). The cohort study consisted of 183 patients who underwent same-day BDE sedation with TCI of propofol. Most patients (157 cases, 85.8%) completed endoscopic examination with sole use of propofol sedation. The incidence of patient movements affecting the procedure was 36.6% (67/183), and 41 patients completed the procedure after increasing propofol Ce. Only 26 cases (14.2%) required an extra bolus of fentanyl 25 μg for extra analgesia after two increments of Ce (1.0 μg/mL) or Ce_M reached 5.0 μg/mL due to the patient movements affecting the procedure. There were multiple significant differences in patient's characteristics between fentanyl and no-fentanyl groups [Table 1]. During sole use of propofol anesthesia with TCI (without fentanyl use), hypotension was recorded in 3 (1.9%, 3/157) patients while bradycardia was found in 3 (1.9%, 3/157) patients, without receiving, and 3 (1.9%, 3/157) patients presented with transient and mild desaturation (SpO_2 85%–90%). There was no patient requiring the use of ephedrine or atropine during the procedure. There was no respiratory or hemodynamic compromise in the fentanyl group. Ten patients received polypectomy during the colonoscopy. There were no participants experiencing awareness during whole procedures. The age (P = 0.032) was significantly lower, but the height (P = 0.025) and weight (P = 0.019) were significantly higher in the fentanyl group. In addition, the Ce_{LOC}, Ce_M, times of TCI adjustment, total propofol consumption, and the frequency of patient movements were higher in the fentanyl group ($P < 0.001$). The awake time and awake Ce were similar between the two groups. Table 2 shows that younger age (P = 0.032), higher height (P = 0.028), higher weight (P = 0.019), higher Ce_{LOC} ($P < 0.001$), and higher Ce_M ($P < 0.001$) were associated with the amount of fentanyl by univariate analysis. Table 3 reveals that only Ce_{LOC} ($P < 0.001$) was associated with the amount of fentanyl after multivariable logistic analysis for controlling for confounding covariates identified in univariate analysis. Table 4 shows that younger age ($P < 0.001$), higher height ($P < 0.001$), higher weight (P = 0.012), and higher Ce_{LOC} ($P < 0.001$) were significantly associated with Ce_M by univariate analysis. Table 5 reveals that younger age (P = 0.007) and higher Ce_{LOC} ($P < 0.001$) were associated with Ce_M after multivariable logistic analysis for controlling for confounding variables identified in univariate analysis. We calculated the linear regression between age, Ce_{LOC}, and Ce_M as followings, $Ce_M = 1.9 - (0.006 \times age) + 0.658 \times Ce_{LOC}$. In addition, the optimal formula was $Ce_M = 1.831 + (0.695 \times Ce_{LOC})$ ($R^2 = 0.64$) [Figure 2]. Finally, we simplified the formula as propofol $Ce_M = Ce_{LOC} + 0.7$ μg/mL.

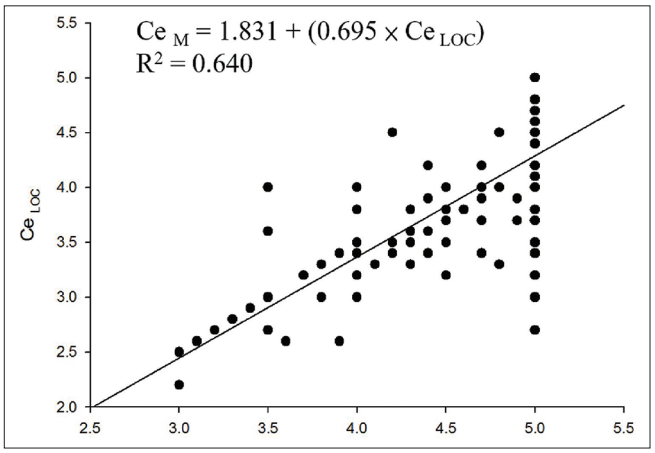

Figure 2: The linear regression between the effect-site concentration at loss of consciousness and maximal maintained concentration of propofol. Ce: Concentration, Ce_{LOC}: Concentration at loss of consciousness, Ce_M: Concentration maximal maintained

Table 1: Patients' characteristics in target-controlled infusion with propofol sedation combination with/without fentanyl

	All patients (*n*=183)	No-fentanyl group (*n*=157)	Fentanyl group (*n*=26)	*P*
Age (years)	52.9±12.9	53.8±13.3	47.9±9.4	0.032
Male, *n* (%)	102 (55.7)	84 (53.5)	18 (69.2)	0.154
Height (cm)	162.9±7.9	162.4±7.9	166.1±7.4	0.025
Weight (kg)	63.7±12.1	62.8±12.1	68.8±10.7	0.019
Ce_{LOC} (μg/mL)	3.8±0.6	3.7±0.5	4.7±0.4	<0.001
Ce_{M} (μg/mL)	4.5±0.6	4.4±0.5	5.0±0.2	<0.001
Anesthesia time (min)	18.7±5.2	18.9±5.4	17.3±3.7	0.148
Examination time (min)	15.5±5.9	15.8±6.1	14.8±4.8	0.427
Awake time (min)	3.5±1.5	3.5±1.5	3.5±1.4	0.895
Propofol (mL)	25.2±6.6	24.3±6.3	30.6±5.9	<0.001
Fentanyl (μg)	0 (0–25)	0	25 (25–25)	N/A
Awake Ce (μg/mL)	1.28±0.34	1.27±0.36	1.30±0.36	0.587
Frequency of TCI adjustments, *n* (%)				
0	137 (74.9)	124 (79.0)	13 (50)	<0.001
1	38 (20.8)	29 (18.5)	9 (34.6)	
2	6 (3.3)	4 (2.55)	2 (7.7)	
3	2 (1.1)	0	2 (7.7)	
Movements affecting the procedure, *n* (%)				
No	116 (63.4)	116 (73.9)	0	<0.001
Yes	67 (36.6)	41 (26.1)	26 (100)	

Data shown as mean±SD or median (range) or *n* (%), Ce indicated as Ce_{LOC} Ce_{M} awake Ce. TCI=Targeted-controlled infusion; Ce=Effect-site concentration; Ce_{LOC}=The effect-site concentration at loss of consciousness; Ce_{M}=The effect-site concentration at maximal maintained concentration; SD=Standard deviation

Table 2: Univariate analysis examining the association between demographic/clinical factors and the amount of fentanyl (*n*=183)

	β	SE	*P*
Age (years)	−0.004	0.002	0.032
Gender	−0.075	0.053	0.154
Height (cm)	0.007	0.003	0.028
Weight (kg)	0.005	0.002	0.019
Ce_{LOC} (μg/mL)	0.309	0.035	<0.001
Ce_{M} (μg/mL)	0.257	0.043	<0.001

Group: No fentanyl group=0, Fentanyl group=1. β=Difference between each variant using fentanyl as a dependent variable. SE=Standard error; Ce_{LOC}=The effect-site concentration at loss of consciousness; Ce_{M}=The effect-site concentration at maximal maintained concentration

DISCUSSION

The major findings in this single-center study showed that the use of sole propofol sedation under TCI was safe and effective in same-day BDE and the linear regression between age, Ce_{LOC} and Ce_{M} as followings, $Ce_{M} = 1.9 – (0.006 \times age) + 0.658 \times Ce_{LOC}$. The results were similar with two recent studies, and they also showed that the use of sole propofol sedation was safe and effective in BDE.[17,18] To our best knowledge, this was the first study to analyze the administration of formula between age, Ce_{LOC}, and Ce_{M} for deep sedation in same-day BDE. We found that patients with younger age and higher Ce_{LOC} were the potential for an extra bolus of fentanyl. In addition, higher Ce_{LOC} was the most informative factor associated with the demand for fentanyl.

We demonstrated that the patient's age was inversely correlated with Ce_{M} undergoing the BDE sedation with TCI propofol. It meant that lower propofol Ce_{M} was found in the elders.[20] Schnider and Minto reported an increased sensitivity to propofol's effect in elderly patients.[21] In addition, Kreuer *et al*.[20] also found that the propofol consumption decreased with increasing age. The data suggested that propofol dose should be reduced in elderly patients for pharmacokinetic and pharmacodynamic reasons.[22] In our previous reports, we also found that elder patients had lower propofol Ce_{LOC} and Ce of return of consciousness than younger patients.[23,24] This may be legitimately explained by the fact that the decreasing weight of the brain in an elderly patient increases sensitivity to propofol. After induction anesthesia, this innovative formula facilitates

Table 3: Multivariable logistic regression analysis examining the association between demographic/clinical factors and the demand for fentanyl after controlling for confounding covariates identified in univariate analysis (*n*=183)

	β	SE	*P*
Age (years)	0.001	0.002	0.584
Height (cm)	−0.001	0.004	0.712
Weight (kg)	0.001	0.002	0.787
Ce_{LOC} (μg/mL)	0.327	0.058	<0.001
Ce_{M} (μg/mL)	−0.062	0.066	0.345

P<0.05 was considered significant. Group: No fentanyl=0, fentanyl=1. β=Difference between each variant using fentanyl as dependent variable; SE=Standard error; Ce_{LOC}=The effect-site concentration at loss of consciousness; Ce_{M}=The effect-site concentration at maximal maintained concentration

Table 4: Univariate analysis examining the association between demographic/clinical factors and the effect-site concentration at maximal maintained concentration (*n*=183)

	β	SE	*P*
Age (years)	−0.017	0.003	<0.001
Gender	−0.151	0.083	0.072
Height (cm)	0.020	0.005	<0.001
Weight (kg)	0.009	0.003	0.012
Ce_{LOC} (μg/mL)	0.696	0.040	<0.001

P<0.05 was considered significant. Group: No fentanyl group=0, Fentanyl group=1. β=Difference between each variant using fentanyl as dependent variable; SE=Standard error; Ce_{LOC}=The effect-site concentration at loss of consciousness

Table 5: Multivariable logistic regression analysis examining the association between demographic/clinical factors and the effect-site concentration at maximal maintained concentration after controlling for confounding covariates identified in univariate analysis (*n*=183)

	β	SE	*P*
Age (years)	−0.006	0.002	0.007
Height (cm)	0.003	0.004	0.418
Weight (kg)	−0.002	0.003	0.351
Ce_{LOC} (μg/mL)	0.658	0.044	<0.001

P<0.05 was considered significant. Group: No fentanyl=0, fentanyl=1. β=Difference between each variant using fentanyl as dependent variable; SE=Standard error; Ce_{LOC}=The effect-site concentration at loss of consciousness

us to calculate Ce_{M} as maintained Ce of propofol during the BDE procedure. Accordingly, this strategy of current research might provide a simple and effective practice to facilitate sedation induction and maintenance of a same-day BDE.

We observed that patients with higher Ce_{LOC} were associated with higher Ce_{M} and required additional bolus of fentanyl. It could be attributed to those with higher Ce_{LOC} might be physically healthier that increased their propofol consumption physiologically. The finding was consistent with our previous report that patients with higher Ce_{LOC} were associated with higher awake Ce and propofol consumption during anesthesia.[16,23]

Due to the invasive and painful BDE procedures, adequate sedation and analgesia could minimize the risks of physical injury by preventing patient movements during the procedure. Previous studies reported that routine combination of opioid (e.g., fentanyl, alfentanil, and remifentanil) and propofol could provide sufficient analgesia and sedation during GIE procedures.[8,10,13,25] However, additional opioid increased the hypnotic effect of propofol in clinical practice[26] and resulted in higher incidence of respiratory depression than sole use of propofol without opioids.[27] Therefore, extra addition of opioid should be considered in deep sedation with propofol for BDE examination. In the current study, we suggested that additional use of fentanyl seemed to be indicated for the patient with higher value of Ce_{LOC} and younger age during the same-day BDE.

Several studies have shown that the traditional bolus of propofol sedation was both effective and safe during diagnostic GIE;[4,6,28,29] however, cardiovascular and respiratory functions were transiently suppressed due to sudden overshooting of propofol in clinical practice. A 2-year prospective study reported that the incidence of hypoxia was 8.0% (28/349), hypotension was 3.4% (12/349), and bradycardia was 6.6% (23/349) undergoing BDE anesthesia with the total bolus of propofol dose of 3.15 ± 1.13 mg/kg.[4] Moreover, another study demonstrated that the incidence of hypoxemia was 6.7% (1842/27500), hypotension was 1.86% (511/27500), and bradycardia was 1.7% (468/27500) under the moderate level of sedation by nonanesthesiologists.[30] Therefore, the risk of intermittent bolus of propofol for moderate/deep sedation during outpatient GIE should not be minimized. Caution is warranted regarding hypoxemia and hypotension and hence appropriate surveillance by anesthesiologists and monitoring is required in all patients (and especially ASA > III).[4] However, in this study, the anesthesiologist conducted BDE anesthesia with propofol through TCI system to achieve deep sedation under spontaneous breathing, and 85.8% (157/183) of selected patients met the clinical goals as predicted, such as no responsiveness to verbal commands, acceptable patient movements, no expressions of discomfort. However, Hsu *et al*.[10] demonstrated that a deep GIE sedation with sole use of propofol through TCI system resulted in 28% (14/50) hypotension, 16% (8/50) transient hypoxemia, and 4% (2/50) bradycardia, and 6% patient movements during GIE. Their results showed longer recovery time and higher incidences

of adverse effects (such as hypotension, transient hypoxemia, and bradycardia), but fewer patient movements compared with our results. This might be due to their higher initial propofol Ce setting compared with ours (4.0–5.0 vs. 2.5–5 μg/mL), and they kept a deeper sedation level during the procedure.

Previous research demonstrated that TCI systems might facilitate the anesthetic management in GIE.[11,15] The anesthesiologist simply set the targeted Ce and the TCI pump dealt with the infusion rate of anesthetics according to the pharmacokinetic model. Several studies reported that these TCI anesthetic techniques were associated with high satisfaction of patients and surgeons, faster recovery time, and better hemodynamic and respiratory stability.[24,31-36] However, the optimal regimen for adequate depth of sedation during GIE is still debated. Thaharavanich *et al*.[37] have investigated that the value of Ce was 3.25 ± 0.47 μg/mL for 50% of patients, who do not respond to a colonoscopy. Fanti *et al*.[9] revealed that the target plasma Ce to maintain adequate anesthesia widely ranged from 2 to 5 μg/mL during endoscopic retrograde cholangiopancreatography. Tsai *et al*.[38] have proposed that deep sedation was achieved by bispectral index (BIS) values between 40 and 60 with the Ce of 3.5 μg/mL (Marsh model) and fentanyl supplement (1 μg/kg) in the elective gastroscopic procedure. Accordingly, TCI system might provide precise control to achieve deep propofol sedation quickly; however, the depth of maintenance for endoscopic anesthesia seemed varied based on different TCI models and different endoscopic procedures.

There were some limitations in this study. First, our results only expressed the experiences of a single academic medical center. Second, lack of both patient and endoscopist's satisfactions failed to provide real feedbacks regarding clinical practice; however, there was no complaint from patients or endoscopists perioperatively. Third, lack of BIS monitoring might lead to higher infusion rates in propofol TCI compared with BIS monitoring in GIE;[39] however, the recovery time, procedure time, sedation-related adverse events, and even satisfactory outcomes were not significantly superior with BIS monitoring than without BIS monitoring.[40] Similarly, we provided the simplified formula to avoid patient movements affecting the procedure and adverse effects. Finally, this was a retrospective study with a small sample size and the same anesthesiologist or endoscopist. Large-sized prospective, randomized controlled, double-blinded trials are necessary to confirm these results.

CONCLUSION

This study demonstrated that delivery of sole propofol by TCI system is an effective and safe anesthesia in outpatient same-day BDE. We further investigated that the age and Ce_{LOC} were associated with Ce_M and only higher Ce_{LOC} (>4.5 μg/mL) was the only contributing factor for the extra bolus of fentanyl in BDE. Finally, we first simplified the formula as propofol $Ce_M = Ce_{LOC} + 0.7$ μg/mL to avoid patient movements affecting the procedure and adverse effects.

Data availability statement

The data that support the findings of this study are available from the corresponding author, HCL, upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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