Original Article

Optimal Propofol Concentration at Effect Site for Esophagogastroduodenoscopy under Moderate to Deep Sedation with Target-controlled Infusion

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Background: The target-controlled infusion (TCI) of propofol is being increasingly used for moderate-to-deep sedation during esophagogastroduodenoscopies (EGDs).

Objective: To determine the target effect-site concentration (Cet) of propofol required for EGD scope insertions during sedation using TCI.

Materials and Methods: Dixon's up-and-down sequential allocation method was used with patients scheduled for elective EGD at Srinagarind Hospital, Thailand. The patients were divided into Group A aged 18 to 64 years and Group B aged over 65 years. Anesthesia was induced with propofol via TCI (Schnider model). The propofol Cet commenced at 3 mcg/mL and 2 mcg/mL in Groups A, and B, respectively. The response during an EGD scope insertion determined the Cet for the next patient, with intervals of 0.3 mcg/mL. Calculations of the effective concentration without response during EGD scope insertion in 50% and 95% of patients (EC50 and EC95) values of propofol, with 95% confidence intervals (CIs), were performed using the isotonic regression method.

Results: Twenty-one and nineteen patients were enrolled in Groups A, and B, respectively. In Group A, the EC50 of propofol for EGD was 3.30 mcg/mL (95% CI 3.05 to 3.55), while the EC95 was 3.75 mcg/mL (95% CI 3.34 to 4.16). In the case of Group B, the EC50 was 3.05 mcg/mL (95% CI 2.75 to 3.35) and the EC95 was 3.05 mcg/mL (95% CI 2.92 to 3.18). Hypotension occurred in 52.3% and 31.5% of patients in group A, and B, respectively.

Conclusion: The appropriate Cet of propofol for anesthesia during EGD using TCI is 3.75 mcg/mL for patients aged 18 to 64 years, and 3.05 mcg/mL for patients aged 65 years and over. Hypotension is the most common adverse event of moderate-to-deep sedation with propofol using TCI.

Keywords: Sedation; Esophagogastroduodenoscopy; Propofol; Target-controlled infusion

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Esophagogastroduodenoscopy (EGD) is an endoscopic procedure with significant growth in the anesthesia service requirements. Although EGD is usually tolerated, gag reflex and retching occur in approximately 29% of the patients[1]. A combination of topical anesthesia and intravenous sedation, which ranges from minimal sedation through to general anesthesia, is generally utilized in endoscopic procedure[2]. Advantages of sedation are to reduce anxiety, relax the patient, relieve discomfort, facilitates a smooth operation for endoscopists, and improves the outcomes of the examination[3]. Disadvantages of sedation include difficulty in adjusting the depth of anesthesia, failure to achieve an appropriate level of sedation and adverse events such as respiratory and cardiovascular depression[4].

Target-controlled infusion (TCI) uses a micro-processor-controlled to administer a drug at a rate that maintains a drug blood level that is related to an individual patient's needs[5]. The infusion rate calculation is based on the patient's parameters and the desired target effect-site concentration (Cet) in the central nervous system and estimate the time to awakening after ceasing the intravenous anesthetic infusion[6] with higher levels of satisfaction and faster recovery times with TCI than manual pumps[7-9]. At

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present, the most widely used intravenous anesthetic for sedation is propofol[10], which is a short-acting anesthetic that provides faster induction and recovery than midazolam and opioids[2]. Side effects of propofol include vasodilatation, myocardial depression, and respiratory depression. As these result in hypotension, apnea, and desaturation after induction, it is essential to use propofol at a dose that is appropriate for each individual.

The current study was designed to determine the Cet of propofol that would prevent the gag reflex and retching during EGD scope insertion under moderate-to-deep sedation using propofol with TCI.

Materials and Methods

Before commencement of the present prospective descriptive study, its protocol was approved by the Ethics Committee, Khon Kaen University (HE591462). Dixon's up-and-down sequential allocation method[11] was subsequently utilized at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand between January and June 2017. The present trial was registered at the Thaiclinicaltrials.org (TCTR20220829004).

The inclusion criteria were patients aged at least 18 years with the American Society of Anesthesiologists (ASA) physical statuses I-III scheduled for an elective EGD under moderate-to-deep sedation at Srinagarind Hospital. Patients who had a body mass index greater than 30 kg/m², were hypersensitive to propofol, eggs, or soybeans, or had a history of coronary vascular, respiratory, or cerebrovascular disease were excluded. Written, informed consent was obtained from each patient.

The patients were divided into two groups based on age with Group A being aged 18 to 64, and Group B being aged 65 years and above. After taking nothing by mouth for at least eight hours, an intravenous catheter (22 G) was cannulated for propofol infusion. Oxygen at 3 to 5 LPM was administered via a nasal cannula. Continuous standard monitoring was conducted with non-invasive blood pressure, pulse rate, electrocardiography, pulse oximetry, and respiratory rate analysis, based on thoracic bioimpedance. A bispectral index (BIS) monitor was used for all patients. Before commencing the EGD, the patients were administered a topical anesthesia with 10% lidocaine spray at five intraoral points, which were right and left tonsils, right and left base of the tongue, and the uvula, three times, with intervals of five minutes. The procedures were performed by an endoscopist who had more than one year's EGD experience, and the same-size endoscopy scope was used for all cases. After the patients had turned to the left lateral decubitus position, propofol (Propofol-Lipuro 1% 10 mg/mL, B. Braun, Melsungen, Germany) was administered by a TCI system (Perfusor Space, B. Braun, Melsungen, Germany) using Schnider model for propofol[12].

The patients in Group A were premedicated with fentanyl 1 mcg/kg with the doses rounded to the higher nearest 5 or 10 mcg, intravenously five minutes before the procedure. For the first patient, the propofol Cet started at 3.0 mcg/mL. As to the patients in Group B, they were premedicated with fentanyl 0.5 mcg/kg with the doses rounded to the higher nearest 5 or 10 mcg, intravenously five minutes before the procedure. The propofol Cet started at 2.0 mcg/mL for the first patient.

The effect site concentration (Ce) was maintained at the set level for at least five minutes before endoscope insertion. During insertion of the EGD scope, the presence or absence of a somatic response to the insertion of the scope, or of a gag reflex, were recorded.

Patient responses were observed by a nurse anesthetist or an anesthesiologist, both of whom were blinded to the TCI pump and Cet. A smooth insertion of the endoscopic scope was defined as no, or minimal, somatic response or gag response during its insertion. A somatic response was defined as a patient refusal or a purposeful patient movement of the head and extremities upon insertion of the endoscopy scope. Those responses were rated as 1) none with no movement, 2) mild with face grimacing, or a small movement in the extremities requiring no restraint by other assistants, 3) moderate with movement requiring slight restraint with the assistance of the nurse, without the need to discontinue the procedure, and 4) severe with movement requiring strong restraint with the assistance of the nurse, and discontinuation of the procedure. The presence of a gag response was defined as retching, coughing, or gagging. A moderate-to-severe somatic response or gag response signified an ineffective Cet of propofol.

Once the somatic response was positive, the Cet was increased by 0.3 mcg/mL until the endoscope was successfully inserted. The target Cet was to be decreased by 0.3 mcg/mL if hypotension, desaturation, or bradycardia occurred.

The Cet of propofol was individually adjusted, based on the presence or absence of a response in the previous patient. The Cet for the next patient was increased by steps of 0.3 mcg/mL if a somatic response was present, indicating an insufficient Cet

of propofol. Alternatively, the Cet was decreased by steps of 0.3 mcg/mL if there was no response, indicating an effective Cet.

The adverse anesthesia events recorded were desaturation from oxygen saturation decreased to less than 90% for more than three minutes, hypotension from systolic arterial pressure less than 90 mmHg, and bradycardia from heart rate of less than 45 bpm. Correction of the adverse anesthesia events were manual assistance of an obstructed airway or insertion of a nasopharyngeal airway for desaturation. Fluid administration or a vasopressor was given for hypotension, while atropine at 0.3 to 0.6 mg was administered intravenously for bradycardia. The propofol Cet was decreased by 0.3 mcg/mL until hemodynamic stability was achieved.

Data collection

The demographic data collected were age, gender, weight, height, ASA physical status, and underlying disease. Vital signs and BIS levels were recorded at baseline as well as before, during, and five minutes after endoscope insertion. Also recorded were the starting Cet, the Cet upon successful scope insertion, the degree of response to the endoscope insertion, details of adverse anesthesia events, total propofol usage, duration of anesthesia, and duration of endoscopy.

Statistical analysis

Categorical data were expressed as number (n) and percent (%). Numerical data were expressed as mean ± standard deviation (SD). The Cet of propofol was analyzed by calculating the midpoint concentration of all independent pairs of six crossover points from non-smooth insertion to smooth insertion. The Cet was defined as the mean of the median crossover concentration. The effective concentration 50% (EC50) of propofol in each group was defined by a modification of Dixon's up-and-down method. The effective concentration 95% (EC95) of propofol in each group was defined as percentile 95 in each group. The analysis was performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Forty eligible patients were enrolled, with 21 patients in Group A, and 19 patients in Group B. All patients were able to complete the entire study, and their data were included in the final analysis.

Table 1. Demographic data and anesthesia management

	Group A (n=21)	Group B (n=19)
Age (years); mean±SD	51.5±10.8	72.3±5.6
Sex: male; n (%)	10 (47.6)	7 (36.8)
BMI (kg/m^2); mean±SD	21.5±3.2	22.8±3.5
ASA classification; n (%)		
I	7 (33.3)	0 (0.0)
II	14 (66.6)	16 (84.2)
III	0 (0.0)	3 (15.7)
Underlying disease; n (%)		
None	16 (76.2)	9 (47.4)
Diabetes mellitus	2 (9.5)	2 (10.5)
Hypertension	3 (14.3)	8 (4.2)
Dyslipidemia	1 (4.8)	0 (0.0)
Others	1 (4.8)	9 (47.4)
Total propofol (mg); mean±SD	270.1±86.5	204.5±78.9
Duration of anesthesia (minute); mean±SD	33.5±21.0	33.8±20.6

ASA=American Society of Anesthesiologists; BMI=body mass index; SD=standard deviation

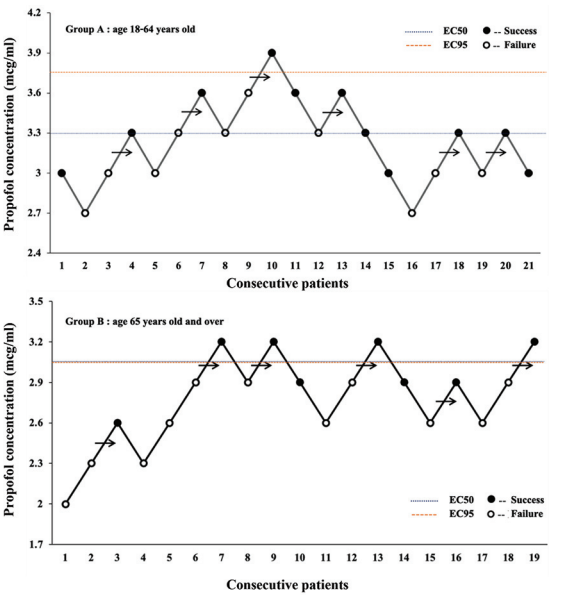

Figure 1. Responses of consecutive patients to EGD scope insertion and starting Cet of propofol.

The majority of the patients were female, and the most common ASA classification was ASA II. The most frequent associated medical problem was hypertension. The demographic data of the patients are listed in Table 1.

The propofol Cet for EGD under sedation using TCI for consecutive patients in each group are shown in Figure 1.

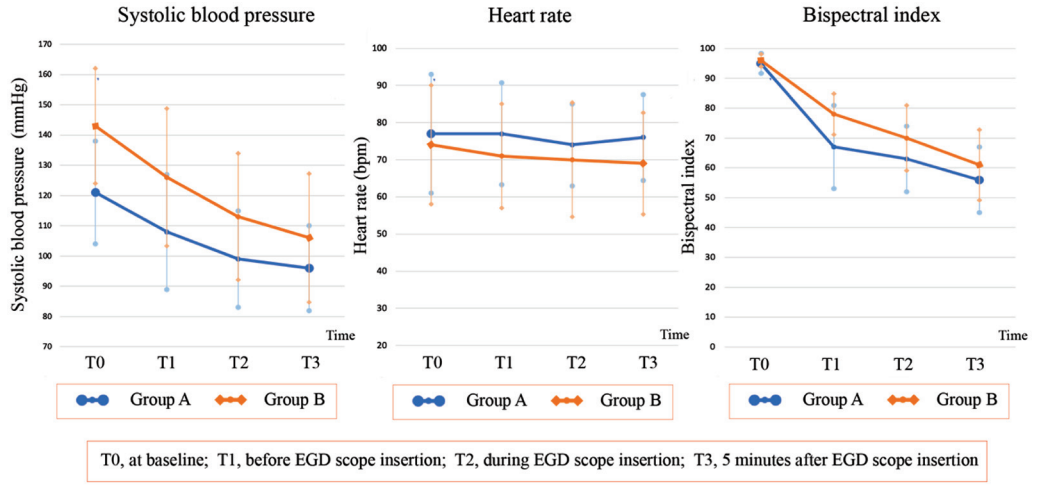

Figure 2. Systolic blood pressure, heart rate, and bispectral index value during baseline, before EGD scope insertion, during EGD scope insertion and 5 minutes after EGD scope insertion.

Table 2. Adverse anesthesia events

	Group A (n=21); n (%)	Group B (n=19); n (%)
Adverse events	11 (52.3)	7 (36.8)
Hypotension	11 (52.3)	6 (31.5)
Bradycardia	0 (0.0)	0 (0.0)
Desaturation	0 (0.0)	1 (5.2)

In Group A, the EC50 of propofol was 3.30 mcg/mL (95% CI 3.05 to 3.55), while the EC95 was 3.75 mcg/mL (95% CI 3.34 to 4.16). As to Group B, the EC50 was 3.05 mcg/mL (95% CI 2.75 to 3.35) and the EC95 was 3.05 mcg/mL (95% CI 2.92 to 3.18).

The average propofol consumptions were 270.1±86.5 mg and 204.5±78.9 mg for Group A and B, respectively. The average anesthesia duration was 33.5±21.0 minutes in Group A, and 33.8±20.6 minutes in Group B.

The vital signs and BIS levels at baseline (T0), before EGD scope insertion (T1), during EGD scope insertion (T2), and five minutes after EGD scope insertion (T3) are illustrated in Figure 2. Mean BIS during EGD scope insertion (T2) were 63.8±11.69 in group A and 70.7±10.91 in group B.

Adverse anesthesia events occurred in eleven Group A patients or 52.3% and seven Group B patients or 36.8% (Table 2). The most common complication was hypotension. Only one patient in group B had transient desaturation. No bradycardia was found in the present study.

Discussion

Anesthesia for EGD is increasingly being required. Many anesthesia techniques and equipment have been utilized to provide safe and effective anesthesia. Moderate-to-deep sedation with propofol continue to be widely used for EGD procedure. It has increased both patient and endoscopist satisfaction with the procedure[13]. With TCI, propofol is able to be more precisely administered for each patient and in accordance with the patient's age, gender, and body weight. In the current prospective descriptive study, Dixon's up-and-down sequential allocation method was used to identify the appropriate Cet of propofol for sedation with TCI for the EDG procedure.

For patients aged 18 to less than 65 years, this investigation established that the EC50 of propofol for the EGDs was 3.30 mcg/mL (95% CI 3.05 to 3.55), and the EC95 was 3.75 mcg/mL (95% CI 3.34 to 4.16). By comparison, the EC50 for patients aged at least 65 years was 3.05 mcg/mL (95% CI 2.75 to 3.35), and the EC95 was 3.05 mcg/mL (95% CI 2.92 to 3.18).

Research by Smith on the effects of fentanyl on the plasma concentration (CP50) of propofol ranged from a loss of consciousness to skin incisions[14]. With propofol alone, the CP50 for loss of consciousness was 3.3 mcg/mL, while for skin incisions, it was 15.2 mcg/mL. However, fentanyl was able to reduce the CP50 of propofol by approximately 40%, depending on the fentanyl dose. This indicates that other concomitant medications such as opioids, benzodiazepine, and local anesthetics might also affect propofol requirements. With the concomitant use of narcotics, the determined Cet may not reflect

the actual propofol requirement in the sedation for EGDs. However, with the current practice, sedation for EGD procedure usually administer narcotics, mainly fentanyl, as an analgesic drug in the majority of the patients.

Kazama et al explored the plasma concentration of propofol TCI for EGD in three age groups, 17 to 49 years, 50 to 69 years, and 70 to 89 years[6]. The ED50 for EGD were 2.98, 2.35, and 1.77 for each group, respectively. These values are lower than the results of the present study. Though the differences in race and ethnicity can also cause different responses to medications[15], in the work by Kazama et al, the EGD scope insertion time after plasma equilibrium was 15 minutes, which is longer than that found by the current investigation, which was five minutes. The longer time period could provide adequate time for the propofol to distribute homogeneously and completely throughout the plasma and the target site. However, a long-time interval might not suit hospitals that have high numbers of patients to service. In addition, the level of sedation required and the experience of endoscopists at each institute can affect medication requirements. The present study showed a decreasing requirement for propofol in the older age group since plasma concentration (CP50) decreased by approximately 20% for each 10-year increasing in age[14].

The BIS levels before, during, and after the EGD scope insertion were within the moderate-to-deep sedation range or 60 to 90[16]. This is appropriate for the procedure. However, in some patient BIS level was in the general anesthesia level after scope insertion since the level of sedation was deeper with an increase in procedure time. Thus, a longer maintenance time after the propofol concentration has reached the set target level could deepen patient sedation without the need to increase the dose of propofol. Alternatively, the propofol dose could be decreased with a longer maintenance time. Decreases in the mean arterial blood pressure were found to be related to the BIS level. As the respiratory function was maintained or declined slightly with moderate-to-deep sedation, the incidence of desaturation was low.

The incidences of adverse events in the present study were 52.3% in Group A and 36.8% in Group B. The vast majority of the events was hypotension with 100% in Group A and 85.7% in Group B. Propofol can cause vasodilatation that leads to hypotension. The higher dose requirement of the younger group could cause a greater incidence of hypotension. The BIS values of Group B were slightly higher than those of Group A, which could be related to the higher incidence of hypotension in Group A. The fentanyl dose of the older patients was lower than that of the younger ones. This would have also contributed to the incidence of adverse events in the younger patients. Additionally, the majority of the patients who had hypotension were those with a successful EGD scope insertion without a dose adjustment. This might reflect a higher than appropriate dose for those patients. This emphasizes the importance of having a titratable and precisely administered propofol dose to lessen the incidence of adverse events. Still, the adverse events were able to be treated with fluid administration and an intermittent bolus of vasopressor. Ensuring optimum fluid hydration and minimizing the period for nothing by mouth prior to the EGD procedure might decrease the risk of hypotension from propofol administration.

There are limitations to the present study. After the Ce of propofol reached the Cet set, the concentration was maintained for a short period, which was five minutes, before EGD scope insertion. This might not have ensured that equilibration between plasma and the effect-site compartment had been achieved. However, to maximize utilization of the endoscopy unit, having a long maintenance period might not be practicable in public hospitals that have high numbers of patients. The presented study focused on the time point of EDG scope insertion that had the highest stimulation of the entire procedure, so the result might not apply to the entire EGD procedure with less stimulation after EGD scope insertion. Furthermore, the presented study did not used BIS to control depth of sedation, therefore, level of sedation might not be strictly controlled. Data indicated that during EGD scope insertion, sedation level was in the deep sedation to even general anesthesia in some patient and deeper after scope was successfully inserted. However, the present study directly determined response to EGD scope insertion and level of Cet somehow suggests that deep level of sedation or deeper is required for smooth EGD scope insertion and Cet should decrease after the EGD scope has been successfully inserted. Further studies regarding these topics may be required. The experience level of endoscopists could also affect the propofol requirement as the less experienced endoscopists could cause stronger stimuli than the skilled endoscopists. As Srinagarind Hospital is a training center, some endoscopists have less experience. Nonetheless, the present study only included patients who were performed by an

endoscopist who had more than one year experience in EGD prior to the present study. Finally, as the somatic responses and gag reflexes were evaluated by anesthesiologists and nurse anesthetists, the results could vary due to the use of subjective criteria. However, the clear category definitions and the use of trained personnel could lessen subjective bias.

Conclusion

The appropriate target concentration of propofol for sedation during EGD using TCI (ED95) is 3.75 mcg/mL in patients aged 18 to 65 years, and 3.05 mcg/mL in patients aged over 65 years. The most common adverse event of moderate-to-deep sedation with propofol using TCI is hypotension.

What is already known on this topic?

Moderate-to-deep sedation with propofol continue to be widely used for EGD procedure. Target controlled infusion systems provide particularly good control of intravenous anesthetic infusion. Appropriated level of sedation with appropriate concentration at effect site of propofol could facilitates smoothness of procedure.

What this study adds?

Appropriated Cet of propofol for EGD procedure with TCI was determined. Appropriate Cet of propofol for patients aged 18 to 64 years is 3.75 mcg/mL (95% CI 3.34 to 4.16). Appropriate Cet of propofol for patients aged 65 years and over is 3.05 mcg/mL (95% CI 2.92 to 3.18).

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Authors' contributions

NR designed, planned, and conducted the study. NM, CB, and NP assisted in data collection, analysis, and interpretation of data. NR performed the statistical analysis and produced the figures and tables. All authors contributed to data interpretation and writing of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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