Comparison between Intermittent Propofol Bolus Techniques and Target-Controlled Infusion in Patients Underwent Gastrointestinal Endoscopy

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ABSTRACT

***Background*:** *Nowadays, the use of propofol for sedation during gastrointestinal endoscopic procedure has become more popular, either by intermittent-bolus (IB) technique or target-controlled infusion (TCI). The aim of this study was to compare the outcomes of both techniques including the total consumption of propofol, consumption per minute, total cost, side effects and its recovery time.*

***Method*:** *This study was a single-blinded randomized clinical trial conducted at Digestive Endoscopy Center, Cipto Mangunkusumo Hospital, Jakarta between October and November 2013. There were fifty patients with pre-operative American Society of Anesthesiologist (ASA) Physical Status Classification I-III, aged 18-65 years, body mass index 18-30 kg/m² who were randomized to obtain sedation with IB propofol or TCI after having a premedication with 1 µg/kgBW fentanyl. The outcomes including the duration of sedation, total dose, propofol consumption per minute, the total cost, the incidence of hypotension, the incidence of desaturation, and recovery time were then evaluated using SPSS version 21.0.*

***Results*:** *Duration of procedure between two groups was not significantly different (p = 0.718). Total dose of propofol, its consumption per minute and total cost were higher in TCI group (p = 0.010; p = 0.004; p = 0.001). The incidence of hypotension, desaturation and recovery time were not significantly different (p = 0.248; p = 0.609; p = 0.33) in both groups.*

***Conclusion*:** *IB technique is more efficient in terms of total propofol dose, consumption per minute and total cost compared to the TCI technique. The incidences of hypotension, desaturation and recovery time profiles were comparable between the two groups.*

Keywords: *gastrointestinal endoscopy, intermittent bolus, propofol, sedation, TCI*

ABSTRAK

Latar belakang: *Akhir-akhir ini penggunaan propofol untuk sedasi pada endoskopi saluran cerna semakin populer, baik dengan teknik bolus berkala maupun dengan menggunakan teknik target-controlled infusion (TCI). Penelitian ini bertujuan untuk membandingkan luaran kedua teknik tersebut dalam cakupan dosis total propofol, konsumsi permenit, biaya total, efek samping dan waktu pulih.*

Metode: *Penelitian ini merupakan uji klinis acak tersamar tunggal yang dilakukan di Pusat Endoskopi Saluran Cerna, Rumah Sakit Cipto Mangunkusumo, Jakarta. yang dilakukan pada bulan Oktober sampai November 2013. Sejumlah lima puluh pasien pre-operatif berdasarkan American Society of Anesthesiologist (ASA) Physical Status Classification I-III, usia 18-65 tahun, indeks massa tubuh 18-30 kg/m² yang dirandomisasi untuk mendapatkan sedasi dengan pemberian propofol bolus berkala atau TCI setelah dipremedikasi fentanil 1 µg/kgBB. Selanjutnya dilakukan evaluasi luaran untuk durasi sedasi, dosis total, konsumsi propofol permenit, biaya total, angka kejadian hipotensi, angka kejadian desaturasi, dan waktu pulih menggunakan program SPSS versi 21.0*

Hasil: *Durasi tindakan pada kedua kelompok tidak berbeda bermakna (p = 0,718). Dosis total propofol, konsumsi permenit dan biaya total lebih besar pada kelompok TCI (p = 0,010; p = 0,004; p = 0,001). Pada kedua kelompok hipotensi, desaturasi dan waktu pulih tidak berbeda bermakna (p = 0,248; p = 0,609; p = 0,33).*

Simpulan: *Pemberian propofol teknik bolus berkala lebih efisien dilihat dari dosis total, konsumsi permenit dan biaya total dibandingkan TCI. Angka kejadian hipotensi dan desaturasi serta waktu pulih sebanding pada kedua kelompok.*

Kata kunci*: endoskopi saluran cerna, bolus berkala, propofol, sedasi, TCI*

INTRODUCTION

Upper gastrointestinal endoscopy is one of routine procedures performed at various hospitals in Indonesia. The number of patients who have undergone esophagogastroduodenoscopy (EGD) in Cipto Mangunkusumo Hospital between January 2007 and December 2009 is 2311 patients.[1] Although sedation and analgesia have been associated with several cardiac and pulmonary side effects, but they may increase patient tolerance during endoscopic procedure by reducing anxiety and pain.[2,3]

Some drugs have been frequently used for gastrointestinal endoscopic procedures such as propofol, opioid, benzodiazepine, and ketamine.[4] Propofol can be administered through several techniques e.g. intermittent bolus (IB), manually controlled infusion (MCI) and target-controlled infusion (TCI). All of these techniques have their advantages and their drawbacks.[5,6] Although the technique of TCI propofol administration in Cipto Mangunkusumo Hospital has only been known in the recent years, but it has been frequently utilized, especially for procedures exceeding 30 minutes.[7] In TCI instrumentation, the dose of intravenous drug given to the patients is adjusted according to the target concentration of the anesthetics at the site of drug effect (effect-site concentration).

TCI device will determine the administered dose according to the programmed formula. An anesthesiologist will use the device and provide data for input, including age, body weight, body height and the desired effect-site concentration dose. The advantage of using TCI are there is no peak and through concentration as has been found in bolus administration or extremely slow drug onset as has been noticed in the plain continuous infusion.[8] The addition of short-acting opioid such as remifentanil for propofol TCI technique may create a more adequate condition for esophageal endoscopy procedure and may reduce the needs of propofol with equally rapid return to responsiveness compared to the technique using propofol alone.[9]

Dal et al conducted a study using a combination of remifentanil (0.05 mcg/kg/minute) and intermittent propofol boluses. The study suggested that the use of remifentanil combined with intermittent propofol boluses during colonoscopy may cause increased mean arterial pressure (MAP), which was much higher than remifentanil combined with TCI-technique propofol. The study also demonstrated that there was no difference in terms of total propofol consumption and recovery time.[10] The opioid agent frequently utilized as a combination with propofol in Cipto Mangunkusumo is fentanyl.[4] A study conducted by Yuliana about effect-site concentration, an application of Schnider's formula in Malay race using TCI technique propofol and 2 mcg/kgBW fentanyl, indicated that the loss of consciousness (LOC) occurred at Ce 3.8 ± 0.5.[11]

The administration of propofol for sedation at Cipto Mangunkusumo Hospital is mostly done by using intermittent bolus technique and TCI. Up to now, no study has been conducted at Cipto Mangunkusumo Hospital on the comparison of propofol total dose and consumption between those administered by IB technique and TCI technique with an adjuvant of fentanyl in patients who undergo gastrointestinal endoscopic procedure.[4] Furthermore, no study has also been conducted about the comparison of propofol total cost, medical equipment, side effects and recovery time between both techniques. Therefore, the aim of this study was to evaluate whether there is any difference of each outcomes between propofol intermittent bolus technique and TCI technique including the mean value of propofol total dose, consumption per minute, total cost, cost for medical equipment, side effects and its recovery time based on the fast-track criteria. The primary hypothesis of our study was that there was no outcome difference of propofol administration between bolus and TCI techniques for sedation.

METHOD

This study was an experimental study and was a single-blinded randomized clinical trial. It was conducted at Digestive Endoscopy Center, Cipto Mangunkusumo Hospital, Jakarta between October and

November 2013. The calculation of minimum sample size was performed using the formula of numerical analysis against two populations of two independent (unpaired) groups. As a result, in this study we found that the minimum sample size was 25 patients for each group.

The target population was patients who underwent gastrointestinal endoscopic procedure with sedation. The accessible population was adult patients who underwent gastrointestinal endoscopic procedure with sedation. The inclusion criteria were patients aged 18-65 years, those who had BMI of 18-30 kg/m^2, ASA I-III, agreed to participate in the study and had signed the informed consent form for medical procedures. The exclusion criteria were patients with a history of allergy to propofol, allergy to fentanyl, patients with neurological deficits, severe cardiac disorder and patients who were hemodynamically unstable.

Subjects who fulfilled the inclusion criteria were enrolled in the study. Study samples were obtained by non probability sampling using consecutive sampling technique. Samples were randomized into two groups using block randomization and concealment was done by sealed opaque envelope method in sequence according to the randomization order. The envelopes were then taken by the anesthesiology resident who performed the sedation.

Sedation was performed by giving propofol through IB or TCI technique after the patient had received premedication of 1 µg/kgBW fentanyl according to the randomization order. In the IB group, propofol was administered with an initial dose of 1 mg/kgBW, which was subsequently titrated into 0.3 mg/kgBW for every 1 minute until the index of consciousness (IOC) score of 45 – 60 was reached. If the IOC score was < 45, the propofol administration was stopped; if the IOC score > 60, the propofol bolus was continued at the dose of 0.3 mg/kgBW for every 1 minute.

In TCI group, the patients received propofol through TCI device. The rate and dose of propofol in the TCI device given to the patients were based on the Schneider's formula in order to achieve the propofol initial target effect-site concentration of 3 g/mL. If the IOC score during the procedure (intraprocedural) was < 45, target Ce was reduced 0.5 µg/mL. If the IOC score > 60, the target of effect-site concentration was increased as much as 0.5µg/mL. The results of evaluated outcomes were duration of sedation, total dose, propofol consumption per minute, total cost, incidence of hypotension, incidence of desaturation and recovery time and those were recorded by other anesthesiology residents.

The data, which had been included in the research form, was processed by SPSS program version 21.0. To evaluate differences of two numerical variables in a group and mean difference of two groups, T-test was used. If the distribution was not normal, the Mann-Whitney test was performed. The inferred significance level was 5% indicating that if $p < 0.05$, then the difference was statistically significant and likewise.

The study was commenced after having an ethical approval by the Ethical Committee at Faculty of Medicine University of Indonesia. All candidates for the study subjects had the right to refuse to participate in the study without penalty of altered medical treatment provided by the doctor.All subjects who were willing to participate in the study were asked to sign a written informed consent form. Subjects had the right to obtain information from the investigator at any time convenient and they had the right to withdraw from the study whenever they liked.

RESULTS

The patients were categorized into 2 treatment groups, i.e. 25 patients for each group. No patient was excluded from the study. Normal distribution of numerical data was presented in mean value ± SD; while abnormal distribution of numerical data was shown in median value (minimum – maximum); moreover, categorical data was presented in n (%).

Table 1. Demographic characteristic of the patients

Variable	Bolus group n (%)	TCI group n (%)
Age (years)	52 (20-65)	50 (18-65)
Sex		
Male	14 (56%)	13 (52%)
Female	11 (44%)	12 (48%)
Weight (kg)	58 (41 - 90)	53 (42 - 82)
Height (cm)	162.28 ± 6.38	160.64 ± 8.36
BMI (kg/m^2)	22. 2 (18 - 30)	21.8 (18 - 30)
ASA physical status classification		
I	7 (28%)	4 (16%)
II	15 (60%)	15 (60%)
III	3 (12%)	6 (24%)
Initial blood pressure (mmHg)		
Systolic	129 ± 14.65	136.12 ± 19,84
Diastolic	74 (60 - 96)	74 (61 - 120)
Hypertension		
Yes	8 (32%)	10 (40%)
No	17 (68%)	15 (60%)
Procedure		
EGD	19 (76%)	12 (48%)
Colonoscopy	4 (14%)	7 (28%)
EUS	1 (4%)	5 (20%)
EGD + colonoscopy	1 (4%)	1 (4%)
IOC initial	92.52 ± 2.25	92.12 ± 1.94

BMI: body mass index; ASA: American Society of Anesthesiologist; EGD: esophagogastroduodenoscopy; EUS: endoscopic ultrasound; IOC: index of consciousness; TCI: target-controlled infusion

Table 2. Correlation between the duration of sedation, total dose, propofol consumption per minute and total cost

Variable	Bolus group (n = 25)	TCI group (n = 25)	p	Mean difference	95% CI	
					min	max
Duration of sedation (minutes)	20 (5-40)	20 (6-40)	0.718#			
Total dosis (mg)	185.00 ± 83.66	251.88 ± 91 22	0.010*	66.88	17.10	116.65
Consumption per minutes (mcg/kgBB/ minutes)	150 (85-250)	191 (126-343)	0.004#			
Total cost (IDR)	IDR 276,877 ± IDR 97,394	IDR 404,482 ± IDR 71,813	< 0.001*	IDR 127,965	IDR 79,304	IDR 176,735

*unpaired T-test; #Mann-Whitney test; The power for a variable of total dose in this study was 77.09% and the power for this variable was 91.7%; TCI: target-controlled infusion

The results of the study, i.e. duration of sedation, total dose, propofol consumption per minute and total cost can be seen in Table 2.

Data in the table show the total cost in mean value ± SD and they were statistically tested by unpaired T-test; the results indicated that there was a significant difference ($p < 0.05$) in both groups.

The incidence of hypotension was calculated based on documentation as a single 1 point despite that a patient might experience several times of incidence for hypotension. The incidence of hypotension in both groups can be seen in Table 3.

Table 3. Correlation between propofol administration technique and hypotension

Group	Hypotension		p	RR	95% CI	
	Yes n (%)	No n (%)			min	maks
TCI	12(48%)	13 (52%)	0.248†	1.5	0.820	0.322
Bolus	8 (32%)	17(68%)				

†Chi-square test; the power of this variable was 20.3%; RR: relative risk; TCI: target-controlled infusion

The other side effect that had been measured in this study was desaturation. The value was calculated when there was a score of < 92% without limitation of desaturation duration.

Table 4. Correlation between propofol administration technique and desaturation

Group	Desaturation		p
	Yes n (%)	No n (%)	
TCI	1 (4%)	24 (96%)	0.609 (2-sided)††
Bolus	3 (12%)	22 (88%)	

†† Fisher test; The power of this variable was 7%; TCI: target-controlled infusion

Data in Table 5 show that there was a difference of median value for recovery time between the bolus and TCI groups. However, the Mann-Whitney test for mean value did not show significant results.

Table 5. Correlation between propofol administration technique and recovery time

Variable	Bolus (n = 25)	TCI (n = 25)	p
Recovery time (minutes)	5 (5-15)	10 (5-15)	0.33#

#Mann-Whitney test; TCI: target-controlled infusion

DISCUSSION

This study is the first study that compared the outcomes of propofol administration techniques at Cipto Mangunkusumo Hospital, i.e. between the technique of intermittent bolus and TCI techniques of the Schnider Ce model. There was no significant difference on demographical characteristics of patients between the bolus and TCI groups; therefore, both groups were comparable.

The median value for propofol consumption per minute in the bolus group was 150 (85-250) mcg/kgBW/minute; while in the TCI group was 191 (126-343) mcg/kgBW/minute. Based on the results of statistic test, the difference of propofol consumption per minute between both groups was significant ($p = 0.004$).

The result is similar with the study conducted by Leslie et al who compared propofol administration techniques for sedation between intermittent bolus, manually-controled infusion (MCI) and TCI in local breast biopsy procedure.[8] The mean value of propofol consumption using TCI administration technique was greater compared to the intermittent bolus technique (83 mcg/kg/minute vs. 59 mcg/kg/minute). The difference may occur because the mechanism of TCI device at early phase is giving a large bolus in order to achieve target concentration in target organ as swift as possible, without exceeding the target dose. The infusion was then stopped so that the plasma concentration reduced and the concentration in the target organ increased achieving the target concentration simultaneously. The dose given to the patient at early sedation becomes very large, particularly for a procedure with short duration. Sedation procedure with duration ≤ 15 minutes in the TCI group was found in 8 subjects and in the bolus group it was found in 10 subjects.

The mean value of consumption per minute in TCI group with duration ≤ 15 minutes was 229 mcg/kgBW/minute compared to those with duration > 15 minutes which was 200 mcg/kgBW/minute. The mean value of consumption per minute in the bolus group with duration ≤ 15 minutes was 179 mcg/kgBW/minute

compared to those with duration > 15 minutes, which was 140 mcg/kgBW/minute. In this period, the TCI machine is still in the phase or has just completed the administration of propofol bolus. This is different with the administration using intermittent bolus technique, which is a titration performed according to body weight and IOC target.

Clinically, the significant mean difference of propofol consumption per minute was 50 mcg/kgBW/minute; while the result of our study showed a mean difference of 48.72 mcg/kgBW/minute.

It can be concluded statistically that there was a significant difference of propofol consumption per minute; however, it was clinically not significant. The power of this variable was 91.7%, which indicates that the mean value of propofol consumption per minute should be taken into consideration for sedation in endoscopic procedure.

The duration of sedation in both groups was similar, i.e. 20 (5-40) minutes in the bolus group and 20 (6-40) minutes in TCI group and statistically there was no significant difference ($p = 0.718$). Based on those results, it can be concluded that the difference of total dose may occur due to the number of propofol consumption per minute. The large number of propofol consumption per minute in the TCI group would cause a greater total dose. This was observed based on the mean value of total dose in TCI group, which was 251.88 ± 91.22 mg and 185.00 ± 83.66 mg in the TCI group; therefore, statistically, there was a significant difference ($p < 0.05$).The results were determined as clinically significant based on a reference that the value is 200 mg and the mean difference between both groups was 66.88 mg. It can be concluded statistically that there was a significant difference, but clinically there was no significant difference between the TCI group and the bolus group. The power of this variable in the study was 77.09%. It is similar to the determined value, i.e. 80%. A greater sample size is necessary so that the total dose can be considered to evaluate the efficiency of drug use between both techniques. The minimum sample size needed is 30 subjects for each group. The total cost spent in TCI group was greater compared to the bolus group. It occurred since greater number of propofol ampules was needed in TCI group and there was greater cost of medical equipment in TCI group including the cost for extension tube, 20 cc syringes, three-way catheter and the rent cost of TCI device which was calculated of its single use. The mean total cost in the bolus group was IDR 276,877.00 ± 97,394.00; while in TCI group it was IDR 404,482.00 ± 71,813.00. The statistic test showed significant results ($p < 0.05$) with mean difference of IDR 127,965.00. The mean difference was clinically not significant since before the study was started the value, which was considered as significant, was determined at IDR 177,280.00. It was the result of adding the price of an ampule of propofol (IDR 127,280.00) and rental cost of TCI device (IDR 50,000.00). Therefore, it can be concluded that statistically there was a significant difference, but clinically there was no difference in terms of total cost between both groups.

The incidence of side effects, i.e. hypotension and desaturation showed no difference between both groups. This result is different from the results of Chan et al study in Taiwan, which compared the cardiovascular and respiratory parameters in TCI technique in comparison with intermittent bolus for gastrointestinal endoscopic procedure. Chan et al study demonstrated that the TCI group has lesser incidence of hypotension and hypoxia. The sample size of the group was relatively large, i.e. 220 subjects including those in esophagoduodenoscopy group (n = 100) and colonoscopy group (n = 120).[12]

The incidence of hypotension in TCI group was about 12 (48%) subjects and in the bolus group was 8 (32%) subjects. Proportionally, the incidence of hypotension in the TCI group was larger than the other group, but it was statistically not significant ($p > 0.05$). The incidence was correlated to the dose of medicine given for the patients and the initial condition of their blood pressure. Based on the preliminary data, we found that the total dose in TCI group was statistically and significantly larger than those in the bolus group. The number of patients with hypertension in both groups was comparable, but the initial mean systolic blood pressure in the TCI group was higher, i.e. 136.12 ± 19.84 mmHg compared to 129 ± 14.65 mmHg in the bolus group. Most patients in bolus group who had hypotension were at ≥ 60 years of age; while most patients in TCI group who experienced hypotension aged more than 45 years with BMI ≥ 23.5 and they had a history of previous hypertension. Considering that the significant clinical difference is 20%, then it can be said that the proportional difference of 16% was clinically not significant. The variable power was relatively low, i.e. 20.3%; therefore, a larger sample size is required with an estimation of 50-100 subjects for each group.

The incidence of desaturation was proportionally larger in bolus group, which included 3 subjects (12%) compared to those in TCI group, which was 1 subject

(4%); however, it was statistically not significant ($p > 0.05$). The three desaturation value in the bolus group occurred for those aged 55-60 years with BMI of 24 – 30 and it happened in the first 10 minutes. The desaturation took place after the administration of initial bolus dose of 1 mg/kgBW and a titration of 0.3 mg/kgBW. The desaturation possibly occurred because the administered dose was too large and it was given over a very short time period; therefore, there was a concentration surge in plasma and target organs resulting in respiratory depression. In contrast, the TCI devices provided a bolus without exceeding the target dose and it would stop automatically. The infusion was then continued with appropriate rate to maintain the steady target concentration in the blood and target organ.[7] Considering the significant clinical difference is 20%, then it can be said that there was no difference in terms of desaturation value between both groups, either statistically or clinically. The variable power was very low, i.e. 7% and it does not represent the actual condition in the community. Therefore, a larger sample size is required with an estimation of 100 subjects for each group.

The recovery time between both techniques seemed to be different, but it was statistically not significant ($p = 0.33$). Different mean value was also found because the mean total dose of propofol with TCI technique was larger than the bolus technique. However, the difference was not significant since the elimination of propofol in both groups was comparable, which was known based on the ASA criteria and the concomitant disease. Based on the calculation of statistic results, we found that the difference of mean recovery time between both groups was 0.7 minutes. Clinically, the determined value for recovery time difference between 2 groups was 5 minutes; therefore, it can be said that there was no difference of recovery time between both groups, either statistically or clinically. This result is similar to the results of Dal et al study, which compared intermittent bolus propofol starting from 0.5 mg/kgBW dose and the propofol given with TCI technique with effect-site concentration dose of 2 µg/mL for 66 subjects. The study indicated that the recovery time and patients who started opening their eyes were comparable in both groups.[10] The results of our obviously contradicts the initial hypothesis, which declared that there was no outcome difference of propofol administration between bolus and TCI techniques. This study showed that there is outcome difference between both techniques for propofol administration. The outcomes of total dose, mean propofol consumption and total cost of TCI technique were significantly and statistically greater than the bolus technique. In addition, the outcomes of hypotension, desaturation and recovery time were not different between both groups.

CONCLUSION

For endoscopic procedure, propofol administration using bolus technique is more efficient in terms of total dose and propofol consumption compared to the TCI technique. The side effect of hypotension, desaturation and recovery time are comparable between both groups. In gastrointestinal endoscopic procedure propofol bolus administration can be considered as an alternative to propofol administration using TCI technique.

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