Predicted EC_{50} of Propofol Using Target Controlled Infusion with and without Fentanyl for Colonoscopy

Russana Thaharavanich MD*, Krairerk Sintavanuruk MD*,
Surajak Laosuwan MD*, Sukanya Pongruekdee MD*

** Department of Anesthesiology, Charoenkrung Pracharak Hospital, Bangkok, Thailand*

Objective: *To determine the propofol effect site target concentration at which 50% of patients did not respond to stimulation for colonoscopy ($EC_{50colonoscopy}$) using a target controlled infusion (Schnider model) and to investigate whether fentanyl reduces these required concentrations.*

Material and Method: *Subsequent to an approval from the institute medical ethics committee, 40 unpremedicated patients, ASA physical status 1-2, aged 18-70 years, BMI less than 30 kg/m^2 and scheduled for elective colonoscopy were randomly assigned to a saline-propofol group (control group) or a 1 mcg/kg fentanyl-propofol group (fentanyl group). Propofol was initiated using a target controlled infusion. Initial effect site target concentration (EC) administered to the first patient in each group were 2.5 mcg/ml. For each subsequent patient, EC was determined by the response of the previous patient by the Dixon's up-and-down method (with 0.5 mcg/ml as a step size). Individual patient response to colonoscopy was described as 'no movement' or 'movement'. $EC_{50colonoscopy}$ values were obtained by calculating the mean of 20 patients in each group.*

Results: *The patient demographic data were not significantly different between the two groups. Total propofol dose in the control group was also significantly higher than that in the fentanyl group. The values for $EC_{50colonoscopy}$ were 3.25 $\pm$ 0.47 mcg/ml in the control group and 2.65 $\pm$ 0.40 mcg/ml in the fentanyl group (p = 0.00).*

Conclusion: *The propofol EC_{50} for colonoscopy was decreased by supplemental 1 mcg/kg fentanyl with no significant difference in hemodynamic values between the two groups.*

Keywords: *Anesthesia, Target controlled infusion, Effect site target concentration, Propofol, Colonoscopy*

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Colonoscopy has become a common procedure performed in patients requiring evaluation of a variety of large bowel disorders. Early detection and routine screening for colorectal cancer with colonoscopy is essential. Today there is an increasing demand for colonoscopy. The procedure is frequently performed in ambulatory regimen and often, requires the cooperation of the patient. Providing anesthesia during colonoscopy may improve outcomes by allowing an efficient examination, ensuring patient comfort and reducing complications. Propofol is accepted as a suitable drug for ambulatory anesthesia because it provides good induction quality, smooth rapid, pleasant, full relief from discomfort, clear-headed and rapid recovery to alertness without residual sedative effects. Propofol does not possess analgesic properties thus if it is administered as the sole agent, deep sedation may be required to keep the patient comfortable. Combination with fentanyl is considered safe in the gastroenterogical literature because of the smaller propofol doses and reduction of accidental oversedation[1]. Some reports show that fentanyl reduced median effective concentration of propofol used for various noxious stimuli[2,3].

Target controlled infusion (TCI) is a technique for the administration of intravenous agents based on real time pharmacokinetic and pharmacodynamic simulations. Its aim is to control and maintain a steady therapeutic level of drugs in plasma or at the effective site by automatic adjusting of the infusion rate, according to its computer software calculation[4-6]. There have been no reports that calculated the 50% effect site concentration (EC_{50}) of propofol required for colonoscopy. Therefore, the present study sought to determine the propofol effect site target concentration at which 50% of patients did not respond to stimulation

Correspondence to:
Thaharavanich R, Department of Anesthesiology, Charoenkrung Pracharak Hospital, 8 Charoenkrung Rd, Bang Kolaem, Bangkok 10120, Thailand.
Phone: 0-2289-7265, 0-2289-7068
E-mail: russana2000@hotmail.com

for colonoscopy ($EC_{50colonoscopy}$) using a target controlled infusion (Schnider model) and to investigate whether supplement 1 mcg/kg fentanyl influenced these required concentrations.

Material and Method

After an approval of Ethics Committee for Researches Involving Human Subjects, the Bangkok Metropolitan Administration and written informed consent, 40 patients underwent elective colonoscopy, ASA physical status of 1 or 2, aged 18-70 years, were enrolled in the present prospective, randomized double blinded control study. Patients were excluded from the present study if they met one of the following criteria; took analgesic medication, had a body mass index (BMI) more than 30 kg/m^2, were considered at risk of aspiration, had the history of propofol or fentanyl allergy and hemodynamic instability from excessive fluid loss after bowel preparations.

Included patients were randomly allocated into two groups, 20 patients in each, received saline and propofol (control group) or received fentanyl 1 mcg/kg and propofol (fentanyl group). Every patient was unpremedicated and received Ringer acetate for hydration 10 ml/kg within one hour before induction of anesthesia. When the patient arrived in the operating room, 100% oxygen via face mask and monitors (ECG, noninvasive blood pressure, pulse oximetry and bispectral index) were applied. After saline or fentanyl intravenous injection with a blinded syringe for more than 3 min 36 s (the time at which peak effect site concentration occurs)[7], propofol administration was initiated by using the TCI with Schnider pharmacokinetic model software [Injectomat TIVA Agilia™ Syringe pump (software version 4.0, Fresenious Kabi AG, Homburg, Germany)]. Time to loss of eyelash reflex was recorded as induction time. Colonoscopy was performed after propofol reached target concentration. Mean arterial pressure (MAP), heart rate, SpO_2 and BIS were recorded every 1 min for the first 5 min, then every 5 min.

The response of the patient to the procedure was classified as either 'movement' or 'no movement'. Movement was defined as a presence of gross purposeful muscular movement or eye opening. For their comfort and safety, patients experiencing movement had their propofol TCI effect site concentration immediately increased 1 mcg/ml every minute until no movement was experienced.

Test concentration of propofol was predetermined by a Dixon's up-and-down method[8]. Initial effect site target concentration administered to the first patient in each group was 2.5 mcg/ml. If the patient reacted with movement, effect site target concentration of the subsequent patient was increased by 0.5 mcg/ml. If there was no movement, it was decreased by 0.5 mcg/ml. A single measurement of movement or no movement was obtained from each patient. $EC_{50colonoscopy}$ values were obtained by calculating the mean of 20 patients in each group. The authors also compared the BIS measurements, hemodynamic data and total propofol dose between the two groups. Propofol administration was ceased approximately 5 min before the conclusion of colonoscopy. Time to eye opening (time from discontinued propofol until eye opened when gently calling the patient's name) was recorded as a recovery time. At the post anesthesia care unit (PACU), the total time in PACU and complications such as nausea, vomiting, or dizziness that occurred in PACU were recorded. Patients were discharged by the PACU staff when they met the discharge criteria.

Statistical analysis

Patient characteristic data, hemodynamic data, BIS measurements, and propofol dose were analyzed by using as mean $\pm$ SD. A p-value of less than 0.05 was considered an unpaired Student's t-test and presented statistically significant.

Results

Dose response data for each patient obtained using the up-and-down method in control and fentanyl group are illustrated in Fig. 1. The $EC_{50colonoscopy}$ in the control group was 3.25 $\pm$ 0.47 mcg/ml and that in the fentanyl group was 2.65 $\pm$ 0.40 mcg/ml.

Patient demographic data for age, weight, height and BMI between groups are shown in Table 1;

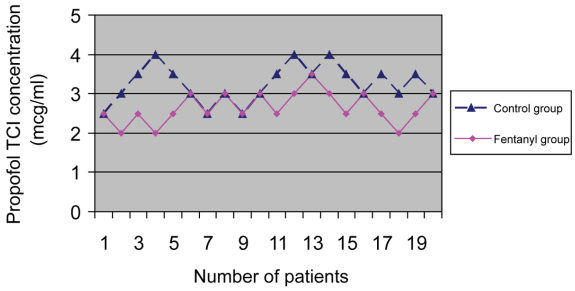

Fig. 1 Dose response data for each patient obtained using the up-and-down method in Control (n = 20) and Fentanyl group (n = 20)

there were no significant differences between the two groups. There were no significant differences in baseline values of MAP, HR, SpO_2 and BIS between the two groups. There were also no significant differences in all intraoperative and postoperative hemodynamic values between the two groups. Duration of procedure and the time to loss of eyelash reflex did not differ significantly between the two groups. Comparison of the time to eye opening in the control group showed significantly longer than in the fentanyl group (p = 0.04). The total propofol dose in the control group was also significantly higher than that in the fentanyl group (p = 0.03). The $EC_{50colonoscopy}$ in the fentanyl group was significantly lower than that in the control group (p = 0.00). No incidence of respiratory complications (apnea, choking, laryngospasm), desaturation (SpO_2 less than 96%) and hypotension (BP decreased more than 20% from the baseline) were observed in all patients.

Duration in PACU did not differ significantly between the two groups as shown in Table 2. There were no significant differences in PACU complications between the two groups. No incidence of postoperative nausea/vomiting occurred in both groups. Only one

Table 1. Demographic data, hemodynamic data, BIS, time to loss of eyelash reflex, duration of surgery, time to eye opening, total propofol and $EC_{50colonoscopy}$ in the two study groups presented as mean ± SD

Variables	Control (n = 20)	Fentanyl (n = 20)	p-value
Age (years)	56.00 ± 8.43	55.35 ± 9.13	0.89
Weight (kg)	59.70 ± 11.92	59.15 ± 9.59	0.92
Height (cm)	159.15 ± 7.30	157.05 ± 7.49	0.34
Mean arterial pressure (mmHg)			
Preoperative	88.95 ± 13.85	94.55 ± 13.36	0.17
Intraoperative	77.50 ± 14.83	83.40 ± 17.23	0.28
Postoperative	73.25 ± 13.93	73.80 ± 9.15	0.79
Heart rate (bpm)			
Preoperative	77.05 ± 15.65	78.00 ± 15.71	0.63
Intraoperative	70.90 ± 14.95	70.45 ± 13.02	0.98
Postoperative	71.70 ± 14.39	69.55 ± 11.56	0.79
BIS			
Preoperative	96.45 ± 2.67	95.45 ± 3.35	0.41
Intraoperative	70.05 ± 12.06	73.40 ± 12.89	0.32
Postoperative	75.15 ± 10.57	72.10 ± 10.20	0.40
Time to loss of eyelash reflex (min)	1.75 ± 0.79	1.70 ± 0.80	0.79
Duration of surgery (min)	16.75 ± 10.67	17.75 ± 10.32	0.45
Time to eye opening (min)	6.35 ± 2.83	5.10 ± 2.51	0.04*
Total propofol (mg)	227.55 ± 99.04	171.95 ± 61.24	0.03*
$EC_{50colonoscopy}$ (mcg/ml)	3.25 ± 0.47	2.65 ± 0.40	0.00*

* Significant different between group; p-value less than 0.05

Table 2. Duration in PACU between the two study groups presented as mean ± SD and PACU complications in the two study groups presented as cases

Variables	Control (n = 20)	Fentanyl (n = 20)	p-value
Duration in PACU (min)	94.25 ± 20.15	94.75 ± 23.08	0.87
PACU complications (cases)			
Nausea/vomiting	0	0	
Drowsiness	0	0	
Dizziness	1	1	
Recall	0	0	

PACU = post anesthesia care unit

patient in each group felt dizziness and fulfilled discharge criteria within the time limit. All patients were interviewed after finishing the procedure in PACU. No patient recalled any events during the procedure.

Discussion

Earlier studies evaluating different administration techniques during general anesthesia have demonstrated TCI superiority over both intermittent bolus injections and manually controlled delivery[9,10]. TCI offers several advantages compared to manual infusion. These advantages are better control of anesthetic depth, quicker recovery and less hemodynamic instability[11]. TCI pumps use pharmacokinetic models to deliver predetermined target concentrations of drugs in plasma or brain. It is now possible to display the predicted effect site target concentration using the distribution coefficient between plasma and brain based on electro-encephalographic (EEG) studies[12]. When targeting the effect site, the preset level will relate to the calculated propofol concentration in the brain rather than in the blood. This will allow the blood levels of propofol to exceed the preset target levels thus allowing the blood-brain equilibrium to be developed faster. This means shorter induction time and better control of anesthesia. Despite an approximate 30% inaccuracy of calculated-target concentration compared to blood-drug measurements (due to interindividual variability and/or model performance), TCI allows more precise titration to a given clinical effect and makes it easier to achieve steady-state drug-plasma concentration[4-6]. By contrast, manual adjustment of the drug continuous-infusion rates result in more unstable drug concentrations[6]. Pharmacokinetic models for propofol TCI are varied and many studies have described the target controlled infusion of propofol in anesthetic doses[5,13], but publications about propofol doses for colonoscopy used by effect site target controlled techniques are limited. The authors have used the TCI with Schnider pharmacokinetic model software [Injectomat TIVA Agilia™ Syringe pump (software version 4.0, Fresenious Kabi AG, Homburg, Germany)] for the present study because this model is available in the institute of the authors and is used daily in clinical practice. The Schnider pharmacokinetic model has been used because of a more rapid plasma and effect site target concentration equilibration than the Marsh model[14].

The present study of 40 patients who underwent colonoscopy has determined the predicted EC_{50} of propofol required for the procedure ($EC_{50colonoscopy}$) and secondly, provided clinical evidence that preadministered 1 mcg/kg fentanyl would reduces $EC_{50colonoscopy}$ of propofol. The authors used the predicted effect site target concentration and adapted up-and-down method to determine $EC_{50colonoscopy}$ of propofol. Although the effect site target concentrations of propofol in the present study all had predicted_value, Marsh et al demonstrated that the correlation between measured and predicted value is adequate for clinical use[15]. The up-and-down method is designed to detect the 50% effective dose with fewer samples[8]. A previous study by Leslie et al, investigating the blood concentration of propofol for colonoscopy, they reported that it was range 1.7-3.6 mcg/ml[16]. Thus, the authors set the initial effect site target concentration of the first patient in each group at 2.5 mcg/ml. The authors chose a relatively large step size of 0.5 mcg/ml, which provides a relatively rough measurement scale because there have been no previous reports of $EC_{50colonoscopy}$ of propofol.

The results from the present study showed that $EC_{50colonoscopy}$ of propofol and supplemental 1 mcg/kg fentanyl were 3.25 ± 0.47 mcg/ml and 2.65 ± 0.40 mcg/ml respectively. The total dose of propofol in the control group was significantly higher than that in the fentanyl group. The time to eye opening also was significantly longer in the control group than that in the fentanyl group. Preadministered 1 mcg/kg fentanyl is inferred to be a sufficient dose to decrease $EC_{50colonoscopy}$ of propofol with no significant differences in all hemodynamic values, BIS and time to loss of eyelash reflex. There is a synergistic interaction between propofol and fentanyl[17]. Propofol has sedative and hypnotic effects, whereas fentanyl acts mainly as an analgesic agent, producing poor sedation, even at high concentration[1]. Consequently, combination of fentanyl and propofol would supplement one another and provide satisfactory anesthetic conditions to various noxious stimuli[2,3]. Supplemental fentanyl does not significantly increase either the complications or the total time in PACU when compared to the other.

Because of wide pharmacokinetic variation between patients for propofol and fentanyl, these data may not be applicable to all patients. For instance, children, elderly patients, pregnancy, high-risk groups (ASA 3-4) and obese patients.

Conclusion

In the present study, using the up-and-down method, propofol was administered via the TCI

(Schnider model, Fresenius), $EC_{50colonoscopy}$ of propofol and supplemental fentanyl were 3.25 ± 0.47 mcg/ml and 2.65 ± 0.40 mcg/ml respectively. The $EC_{50colonoscopy}$ in the fentanyl group was significantly lower than that in the control group. The propofol $EC_{50colonoscopy}$ was decreased by supplemental 1mcg/kg fentanyl with no significant differences in all hemodynamic values, BIS, and complications.

Potential conflicts of interest

None.

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การเปรียบเทียบค่า EC_{50} ของยา propofol ในการระงับความรู้สึกทางหลอดเลือดดำแบบ target controlled infusion สำหรับการส่องกล้องลำไส้ใหญ่ระหว่างกลุ่มที่ใช้และไม่ใช้ fentanyl

รุศนา ทหราวานิช, ไกรฤกษ์ สินธวานุรักษ์, สุรจักร เหล่าสุวรรณ, สุกัญญา พงศ์ฤกษ์ดี

วัตถุประสงค์: *เพื่อหาค่า effect site target concentration ของ propofol ในการให้การระงับความรู้สึกที่ผู้ป่วยร้อยละ 50 ไม่เคลื่อนไหวสำหรับการส่องกล้องตรวจลำไส้ใหญ่ ($EC_{50colonoscopy}$) และศึกษาถึงผลของการใช้ fentanyl ร่วมกับ propofol ว่าจะมีผลทำให้ค่า $EC_{50colonoscopy}$ ของ propofol ลดลงหรือไม่*

วัสดุและวิธีการ: *การศึกษานี้ได้ผ่านการพิจารณาจากคณะกรรมการพิจารณา และควบคุมการวิจัยในคนของกรุงเทพมหานคร ผู้ป่วยที่เข้าร่วมในการศึกษาเป็นผู้ป่วย ASA physical status 1-2 อายุ 18-70 ปี มี BMI น้อยกว่า 30 kg/m^2 และเป็นผู้ป่วยที่อยู่ในตารางนัดผ่าตัดล่วงหน้า สุ่มแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มละ 20 คน ผู้ป่วยกลุ่มควบคุมจะได้รับยา propofol ร่วมกับน้ำเกลือ ผู้ป่วยอีกกลุ่มจะได้รับยา propofol ร่วมกับ fentanyl ขนาด 1 mcg/kg ทั้งสองกลุ่มจะได้รับยา propofol ผ่านเครื่องให้สารละลายทางหลอดเลือดดำชนิดกระบอกยาแบบ target controlled infusion (TCI) โดยกำหนดค่าเป้าหมายระดับยาเป็น effect site target concentration (EC) เมื่อเริ่มการศึกษาจะกำหนดค่า EC เริ่มต้นของการให้การระงับความรู้สึกของผู้ป่วยรายแรกของทั้งสองกลุ่มอยู่ที่ 2.5 mcg/ml ใช้วิธี Dixon's up-and-down method โดยทำการบันทึกว่าขณะทำหัตถการผู้ป่วยเคลื่อนไหวหรือไม่เคลื่อนไหว เพื่อนำมากำหนดค่า EC เริ่มต้นของผู้ป่วยรายถัดไปในกลุ่มเดียวกัน หากผู้ป่วยเคลื่อนไหวจะเพิ่มค่า EC เริ่มต้นของผู้ป่วยรายถัดไปในกลุ่มเดียวกันขึ้นอีก 0.5 mcg/ml แต่หากผู้ป่วยไม่เคลื่อนไหวก็จะลดค่า EC เริ่มต้นของผู้ป่วยรายถัดไปในกลุ่มเดียวกันลงอีก 0.5 mcg/ml บันทึกค่า EC เริ่มต้นของผู้ป่วยแต่ละราย และนำค่า EC เริ่มต้นที่ได้ของผู้ป่วยในแต่ละกลุ่ม กลุ่มละ 20 ราย มาคำนวณหาค่าเฉลี่ยเป็นค่า $EC_{50colonoscopy}$ ของผู้ป่วยแต่ละกลุ่ม*

ผลการศึกษา: *ข้อมูลทั่วไปของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ปริมาณ propofol ที่ใช้ในกลุ่มควบคุมสูงกว่ากลุ่ม fentanyl อย่างมีนัยสำคัญ ค่า $EC_{50colonoscopy}$ ในกลุ่ม control เท่ากับ 3.25 $\pm$ 0.47 mcg/ml และในกลุ่ม fentanyl เท่ากับ 2.65 $\pm$ 0.40 mcg/ml*

สรุป: *ค่า $EC_{50colonoscopy}$ ของ propofol มีค่าลดลงเมื่อให้ fentanyl 1 mcg/kg ร่วมในการระงับความรู้สึกสำหรับการส่องกล้องตรวจลำไส้ใหญ่ โดยค่าสัญญาณชีพของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ*