Original Article

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Dose Response Curves of Plasma Concentration 50 of Propofol Target-Controlled Infusion for Supraglottic Airway Devices: A Randomized Controlled Trial

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Abstract:

Objective: We aimed to determine the plasma concentration 50 (CP_{50}) of propofol target controlled infusion (TCI) for successful insertion of four types of supraglottic airway devices (SGD).

Material and Methods: This prospective parallel randomized controlled, double blinded, superiority trial was conducted in June 2012 following approval by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand. Effect-site concentrations (Ce) of propofol TCI were determined by the modified Dixon's up-and-down method. After equilibration was established between the plasma and effect-site concentrations, a Supreme™, ProSeal™ (control groups), I-gel™ or Laryngeal Tube Suction II™ devices were inserted. The CP_{50} was determined by dose response logistic curves presented as means and 95% confidence intervals (CI). The General Estimating Equation was used to determine factors associated with hemodynamic changes.

Results: The Ces of TCI propofol requirements in the Supreme™, ProSeal™, I-gel™ and Laryngeal Tube Suction II™ groups were 5.8, 4.8, 5.6, and 5.8 μg/ml, respectively (effect size [95% CI]: 0.22 [0.06, 0.51], p-value 0.036). The CP_{50} [95% CIs] in the Supreme™, ProSeal™, I-gel™ and Laryngeal Tube Suction II™ groups were 5.8 [-0.01, 11.6], 4.9 [3.3, 6.5], 5.7 [5.0, 6.3] and 5.5 [4.7, 6.4] μg/ml, respectively. Heart rates and systolic blood pressure were significantly higher in the Laryngeal Tube Suction II™ group than in the ProSeal™ (p-value<0.01) and I-gel™ groups (p-value<0.01).

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Conclusion: The ProSeal™ and I-gel™ are preferred over the Supreme™ and Laryngeal Tube Suction II™ devices due to the lower CP_{50} and hemodynamic changes.

Keywords: effect-site concentration, target controlled infusion of propofol, ProSeal™, Laryngeal Tube Suction II™, I-gel™, Supreme™

Introduction

Many second-generation supraglottic airway devices (SGD) consisting of a double lumen or bite block as well as a gastric port have been developed[1]. Target-controlled infusion (TCI) is widely used for generating propofol with a pharmacokinetic microprocessor. TCI offers improved hemodynamic stability and requires lower propofol doses when compared with manually controlled infusion (MCI)[2]. The anesthesiologist can also set the target-plasma or effect-site concentration of TCI to achieve the desired clinical effect[3,4]. A previous study reported that the concentration of plasma 50% (CP_{50}) required for surgery using TCI to be 3.24 μg/ml for the Classic™ laryngeal mask airway (LMA) device[5]. Previous studies compared the CP_{50} between a second-generation SGD (Proseal LMA, Fastrach, the laryngeal tube) and the Classic™ LMA[6,7], but since the Proseal LMA and the laryngeal tube were compared using different protocols, previously reported CP_{50} among these SGD are questionable. The Supreme™ LMA was launched in Thailand in 2007 and since then has been commonly used in our institute. Eschertzhuber et al.[8] reported that ease of insertion and gastric tube placement were similar for the LMA ProSeal and LMA Supreme devices in paralysed, anaesthetised patients but oropharyngeal leak pressure and intracuff pressure were higher for the LMA ProSeal device. However, there had been no studies comparing the CP_{50} of propofol TCI between the Supreme™ and other second-generation SGDs at the time this study was done. Thus, we determined and compared the CP_{50} of propofol with the TCI system between the Supreme™ and other SGDs (the I-gel™, ProSeal™ and Laryngeal Tube Suction II™ devices) in combination with fentanyl preinduction, as well as examining hemodynamic changes during insertion of these devices, in patients undergoing elective surgery.

Material and Methods

This study was a parallel, randomized, controlled, double-blind, superiority trial, approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand (EC 552130812). All procedures were performed in accordance with the relevant guidelines and regulations. All patients gave their informed consent after receiving written information of the study objectives. The ClinicalTrials.gov (NCT04664595) was first registered in September 2014 but it was not yet completely released until December 2020. We enrolled patients having American Society of Anesthesiologists (ASA) physical status I-III, aged between 18 and 70 years and scheduled for general anesthesia for elective non-cardiac surgery with SGD between June 2012-June 2013. Those with a potentially difficult airway (cervical spine disease, Mallampati classification IV, or a mouth opening less than 2.5 cm), reactive airway disease, signs of respiratory infection or a plan to remain intubated were excluded. We also excluded patients who had a risk of gastric aspiration or morbid obesity (body mass index >35 kg/m^2). The DOI link by Protocols.io is dx.doi.org/10.17504/protocols.io.bvyun7ww.

Study protocol

The patients were randomized into 4 groups (Supreme™, ProSeal™, I-gel™, and Laryngeal Tube Suction II™ SGD) according to a computer-generated randomization list by block of 4, with equal allocation by a research assistant from the Anesthesiology Department. The patients were allocated consecutively using a concealed opaque envelope. The participants were enrolled by the investigator (NT) after they were admitted for at least one day before surgery. No oral premedication (opioid or sedative) was given at the ward before the surgeries. The post-anesthesia care unit nurse assigned participants to interventions and handed the envelope containing the allocated treatment to the anesthetist nurse in the operating room. During pre-anesthetic preparation, a 20G venous cannula was sited and the infusion port for propofol was connected as closely as possible to the intravenous catheter to minimize dead space. Once in the operating theater, standard monitoring was established, which included an electrocardiogram, non-invasive arterial blood pressure, pulse oximeter and end-tidal CO_2 concentration.

All patients were blinded to the study intervention and pre-oxygenated with 100% oxygen. After the administration of 2 μg/kg intravenous fentanyl for 5 minutes, anesthesia was induced with the Schnider pharmacokinetic TCI system. The treatment envelope was opened by the anesthetist nurse and then 1 of the 4 types of SGD was prepared. The first patient of each group received a propofol TCI effect-site concentration (Ce) of 4 μg/ml (Ce used by previous study)[6]. The Ce of propofol used for each patient was determined by the response of the previously tested patient using the modified Dixon's up-and-down sequential allocation technique[9]. One minute after achieving target concentration (initially with 4 μg/ml), if the patient did not move during ventilation, the assigned type of SGD was inserted by a staff anesthesiologist (NK) and a third-year resident (NT) who were unaware of the actual plasma concentration of propofol without the use of any neuromuscular blocking agents. NK and NT had at least two years of experience in SGD insertion. "No Response" was defined as an LMA Insertion Score of 0 and "Response" was defined as an LMA Insertion Score of at least 1[10]. If the patient moved during ventilation or SGD insertion after achieving target concentration, the Ce was increased by a step of 0.4 μg/ml and the patient was assessed every minute until there was no movement and then the first attempt or second attempt of the allocated SGD was made. The response of each patient determined the concentration of the next patient. After achieving the target concentration, if the systolic blood pressure (SBP) decreased by more than 30% from baseline, the Ce was decreased by a step of 0.4 μg/ml every minute until the SBP was decreased by not more than 20% from baseline with no movement during ventilation. The minimum Ce was the last target concentration (μg/ml) after successful SGD insertion with either an insertion score of 0 or at least 1. If the first attempt did not succeed (due to gagging, coughing, or movement), the Ce was increased by a step of 0.4 μg/ml and the patient was assessed every minute for each attempt. The Ce was adjusted as per protocol by the nurse investigators (MO/NP) who were unaware of the allocated treatment (they stayed behind a partition between the insertor and the TCI syringe pump).

When placing the device, the LMA insertion score was calculated immediately by the inserter (NK/NT). The LMA insertion score consisted of numerical evaluations of mouth opening, ease of insertion, swallowing, coughing, laryngospasm and movement. The insertion time was calculated based on the combination of each attempt starting from mouth opening to positioning the SGD. The insertion time, number of attempts and total duration from starting TCI to successful SGD placement were recorded by the anesthetist nurse in the operating room who stayed with the insertor in front of the partition. Complications/adverse events related with SGD insertion at the postanesthetic

care unit and at 24 hours after surgery were recorded by the nurse investigators (MO/NP).

Main exposure and other explanatory variables

Demographic data, ASA physical status and type of surgery were recorded. The main exposure variable was the type of second generation SGD. We considered the ProSeal™ LMA as the control group since it was commonly used in our clinical practice during the study period. Therefore, the Supreme™, I-gel™, and Laryngeal Tube Suction II™ devices were each compared to the ProSeal™ LMA. The selection of the device size in the I-gel™, Supreme™, and ProSeal™ groups depended on the patient's weight. A size-3 SGD was selected for patients who weighed 30-50 kg, size-4 was selected for patients weighing 50-70 kg and a size-5 was used for those weighing greater than 70 kg. A removable metal introducer was not used for the ProSeal™. For the Laryngeal Tube Suction II™ group, the selection of the size depended on the patient's height. A size-3 was used for those who were shorter than 155 cm, a size-4 was used for those whose heights were between 155-180 cm, and a size-5 was used for those who were taller than 180 cm.

Outcomes of the study

The primary outcome was the concentration of plasma required for 50% of patients to achieve successful SGD insertion (CP_{50}).

The secondary outcomes were the blood pressure and heart rate changes from baseline (Time 0) to the first 20 minutes (Time 20). These two outcomes were recorded every minute after SGD device insertion and were recorded by the anesthetist nurse in the operating room.

Sample size determination

The sample size for the primary outcome was estimated based on the study by Handa-Tsutsui et al.[11] who reported a difference in CP_{50} between the Fastrach and ProSeal LMA insertion of 0.9 μg/ml with a standard deviation of 0.5 μg/ml under a level of significance of 0.008 and 80% power to detect the difference. Therefore, the required sample size, which included a 10% dropout rate, was 10 patients/group. For the secondary outcomes, we hypothesized that the difference in post-insertion blood pressure between patients receiving the Supreme and ProSeal LMA devices would be 20% with a standard deviation of 10% under a level of significance of 0.008 and an 80% power to detect this difference. The required sample size, which included a 10% dropout rate, was 8 patients/group. Therefore, at least 40 patients were required.

Statistical analysis

The analysis followed the intention-to-treat principle. The R language and environment (R version 4.0.2, R Core Team, Vienna) was used for all analyses. Continuous data are expressed as median and range while categorical data are described using frequency. Differences in characteristics among the four groups were tested using Fisher's exact test for categorical data and the Kruskal-Wallis test for continuous variables. Effect sizes using Cohen's statistic are also presented. The dose response curves of CP_{50} of propofol TCI were determined by the probability of no movement relative to the minimum Ce and to obtain a propofol target concentration where 50% of the SGD attempts were successful in both groups. The maximum likelihood estimators of the model parameters using logistic regression curves are presented as means and 95% confidence intervals (CI)[12]. Multiple linear regression and general estimating equation models using the Geepack package in R[13] were used to determine factors associated with changes in systolic, diastolic, and mean arterial blood pressure and heart rate presenting as beta coefficient (β) and 95% CI. The types of SGD among hemodynamic outcomes were adjusted for age and time. A p-value of

<0.01 was considered to be statistically significant following the family-wise type-I error rate for multi-arm trials[14]. When the overall differences were significant, a posthoc analysis was performed for multiple comparisons between groups.

Ethics approval and consent to participate

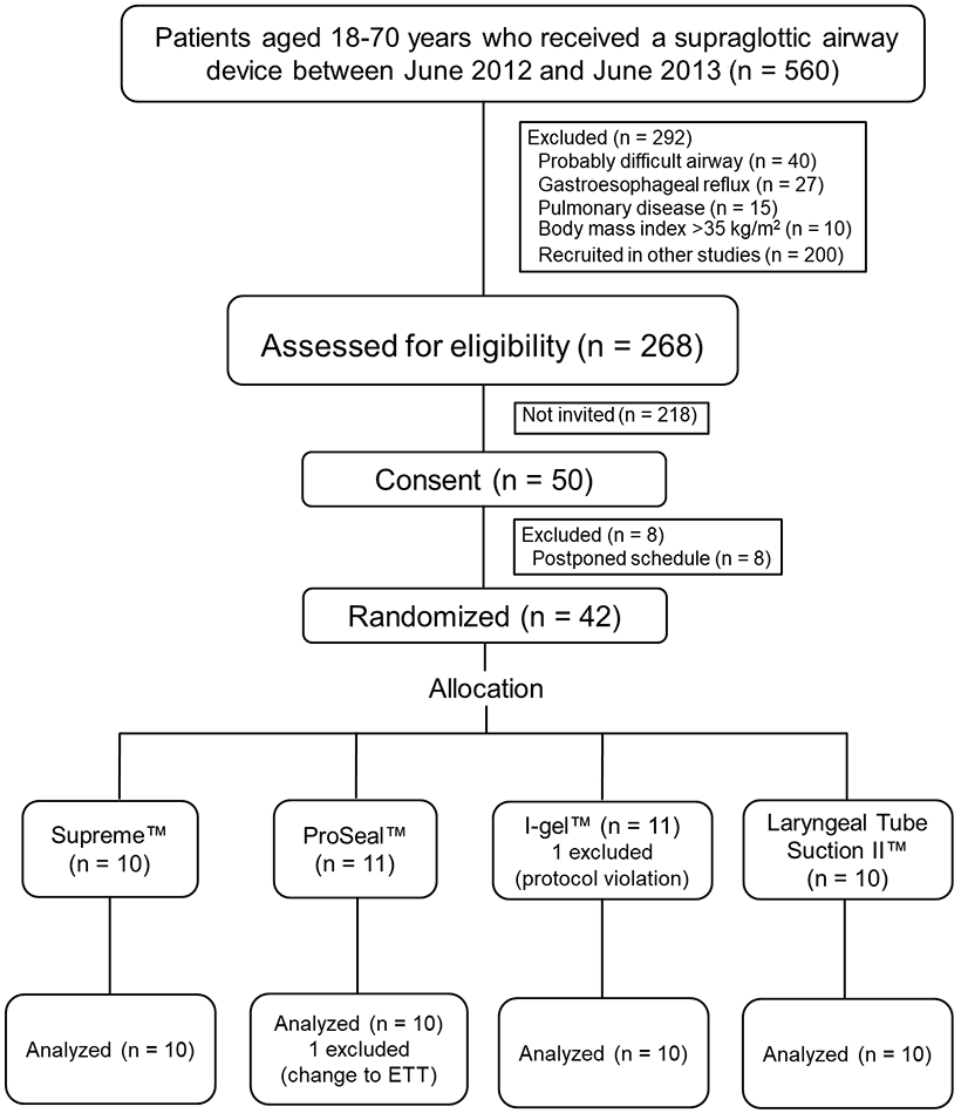
The study was approved by the Institutional Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand, Chairperson Assoc. Prof. Verapol Chandeying, EC. 552130812 on April 27, 2012. Written informed consent to participate was obtained from all study participants.

Results

Informed consent was obtained from 42 out of 560 eligible patients from June 2012 to June 2013 at Songklanagarind Hospital (Figure 1). One case in the I-gel™ group was excluded due to insertion failure since the device was changed to an endotracheal tube (protocol violation). There were no significant differences in gender, age, weight, height, ASA physical status or type of surgery between the 4 groups (Table 1).

Table 2 compares the outcomes between the four groups. The minimum Ce of propofol required to insert the SGD devices was significantly different among the four groups (effect size [95% CI: 0.22 [0.06, 0.51]) (Figure 2). The change in propofol target concentration (ug/ml) for each consecutive patient is shown in Supplemental File 1. The lowest Ce was 4.8 µg/ml, which occurred in the ProSeal™ group, and the highest was 5.8 µg/ml, which occurred in both the I-gel™ and Supreme™ groups (I-gel™ vs ProSeal™, p-value 0.028 and Supreme™ vs ProSeal™, p-value 0.008). When compared with the dose response curves, the CP_{50} [95% CI] of propofol required for the Supreme™, ProSeal™, I-gel™, and Laryngeal Tube Suction II™ devices were 5.79 [-0.01, 11.60] (p-value 0.050), 4.94 [3.34, 6.53] (p-value<0.001), 5.67 [5.05, 6.29] (p-value <0.001) and 5.52 [4.69, 6.35] (p-value<0.001), respectively (Figure 3). The insertion times for patients in the Supreme™, ProSeal™, I-gel™, and Laryngeal Tube Suction II™ groups were 23.5, 24.5, 27.0, 28.0 seconds, respectively (p-value 0.761). There were no significant differences in the success rates of SGD insertion in the first attempt among the four groups (p-value 0.08). There were no occurrences of desaturation or laryngospasm in any patients. The laryngeal mask insertion scores that evaluated the ease of insertion of the SGD were not significantly different between the four groups.

Table 3 shows the types of SGD associated with the changes in systolic, diastolic, and mean arterial blood pressure and heart rate by multiple linear regression models. After adjusting for time and age group, patients in the Supreme™ and Laryngeal Tube Suction II™ groups had significantly higher SBP than those in the ProSeal™ and I-gel™ groups whereas diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly higher in the Laryngeal Tube Suction II™ group only compared to those in the ProSeal™ and I-gel™ groups. The heart rates were significantly higher in the Laryngeal Tube Suction II™ group compared to those in the Supreme™, ProSeal™ and I-gel™ groups. The SBP, DBP, and MAP increased by age for patients aged 30 to 50 years compared to those aged ≤30 years. The blood pressure and heart rate decreased greatly during the first 5 minutes after induction as shown in Figure 4. Figures 4A and 4B show a consistently rapid drop in the SBP and heart rate in all groups in the first few minutes, reaching the lowest value at 5 minutes. Thereafter, the mean arterial pressure and heart rate slowly increased in all groups. No desaturation (SpO2 <95%) or life-threatening complications occurred in any patients. Perioperative adverse events among the groups are shown in Table 4. Direct questioning of the patients in the recovery room and on post-operative day 1 found that no patients had any awareness during their operation.



ETT=endotracheal tube

Figure 1 Consort flow diagram of the study

Table 1 Comparison of demographic characteristics among the 4 groups

Characteristic	Supreme™ (n=10)	ProSeal™ (n=10)	I-gel™ (n=10)	LTS II™ (n=10)	p-value
Male: female	1:9	4:6	4:6	4:6	0.372
Age (year)[+]	36.1±16.5	47.2+11.4	42.8+14.1	48.2+13.1	0.214
Weight (kg) [†]	65±12.2	62.6±13.5	63.8±8.4	56.6±12.4	0.409
Height (cm) [†]	153.5 (150.5, 159.8)	157.0 (155.2, 166)	159.0 (155.2, 168.8)	152.5 (150.0, 162.8)	0.382
Body mass index (kg/m^2)[+]	26.6±5.4	23.9±3.4	24.6±2.6	23.7±4.1	0.375
Mallampati grade					0.528
1	4 (40.0%)	5 (50.0%)	4 (40.0%)	2 (20.0%)	
2	4 (40.0%)	4 (40.0%)	5 (50.0%)	8 (80.0%)	
3	2 (20.0%)	1 (10.0%)	1 (10.0%)	0 (0.0)	
ASA classification					0.526
1	0 (0)	2 (20.0%)	1 (10.0%)	2 (20.0%)	
2	10 (100.0%)	7 (70.0%)	9 (90.0%)	8 (80.0%)	
3	0 (0)	1 (10.0%)	0 (0.0)	0 (0.0)	
Type of surgery					0.636
General	7 (70.0%)	5 (50.0%)	6 (60.0%)	7 (70.0%)	
Orthopedic	2 (20.0%)	2 (20.0%)	3 (30.0%)	0 (0.0)	
Plastic	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0%)	
Gynecology	1 (10.0%)	3 (30.0%)	1 (10.0%)	2 (20.0%)	

Values are presented as frequency (%) unless stated otherwise. [+]Mean±standard deviation, [†]Median (interquartile range).
ASA=American Society of Anesthesiologists, LTS=Laryngeal Tube Suction II™

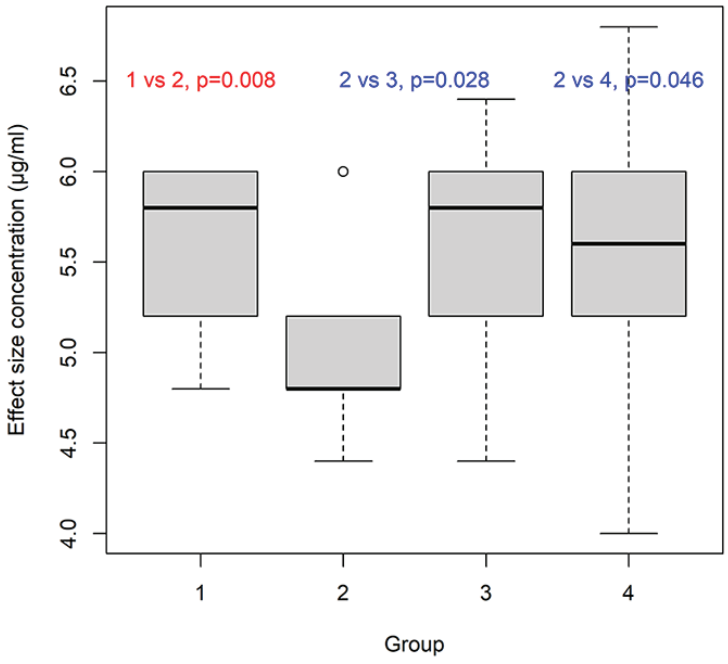


Figure 2 Minimum effect size concentration of propofol requirement among the four groups. group 1= Supreme™, group 2=ProSeal™, group 3=I-gel™, group 4=Laryngeal Tube Suction II™.

Table 2 Effect-site concentrations of propofol and insertion characteristics among the four groups (N=40).

Outcome	Type of supraglottic airway				p-value
	Supreme™ (n=10)	ProSeal™ (n=10)	I-gel™ (n=10)	LTS II™ (n=10)	
Effect-site concentration of propofol (μg/ml)+	5.8[b] (4.8-6.0)	4.8[a] (4.4-6.0)	5.8 [ab] (4.4-6.4)	5.6 [ab] (4.0-6.8)	0.036*
Insertion time (seconds)†	23.5 (20.2, 30.8)	24.5 (20.0, 30.0)	27.0 (17.5, 43.8)	28.0 (24.2, 36.2)	0.761
Number of attempts					0.078
1	5 (50.0%)	9 (90.0)	8 (80.0)	7 (70.0)	
2	5 (50.0%)	0 (0.0)	1 (10.0)	3 (30.0)	
3	0 (0.0)	1 (10.0)	1 (10.0)	0 (0.0)	
Time from TCI to SGD placement (minutes)†	7.6 (5.9, 9.0)	6.2 (5.3, 7.1)	6.5 (6.3, 7.5)	6.7 (6.2, 8.5)	0.555
Laryngeal mask insertion score					1.000
0	5 (50.0%)	5 (50.0%)	5 (50.0%)	5 (50.0%)	
≥1	5 (50.0%)	5 (50.0%)	5 (50.0%)	5 (50.0%)	
Complete mouth opening	9 (90.0%)	9 (90.0%)	7 (70.0%)	9 (90.0%)	0.805
Partial mouth opening	1 (10.0%)	1 (10.0%)	3 (30.0%)	1 (10.0%)	
Easy insertion	10 (100%)	9 (90.0%)	8 (80.0%)	10 (100%)	0.230
Difficult insertion	0 (0.0)	1 (10.0%)	2 (20.0%)	0 (0.0)	
No swallowing	5 (50.0%)	6 (60.0%)	8 (80.0%)	7 (70.0%)	0.417
Partial swallowing	5 (50.0%)	3 (30.0%)	1 (10.0%)	2 (20.0%)	
Complete swallowing	0 (0.0)	1 (10.0%)	1 (10.0%)	1 (10.0%)	
No coughing	10 (100%)	9 (90.0%)	10 (100%)	10 (100%)	0.231
Partial coughing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Complete coughing	0 (0.0)	1 (10.0%)	0 (0.0)	0 (0.0)	
No movement	9 (90.0%)	7 (70.0%)	5 (50.0%)	5 (50.0%)	0.246
Partial movement	1 (10.0%)	2 (20.0%)	5 (50.0%)	3 (30.0%)	
Complete movement	0 (0.0)	1 (10.0%)	0 (0.0)	2 (20.0%)	

Values presented are frequency (%) unless stated otherwise. +Median (range). †Median (interquartile range)
*Kruskal Wallis test (effect size [95% confidence interval: 0.22 [0.06, 0.51]). For multiple comparisons, groups having different superscripts ([ab]) were significantly different (p-value<0.01 by Wilcoxon rank sum test).
LTS Laryngeal Tube Suction II™, SGD supraglottic airway device, TCI target controlled infusion.

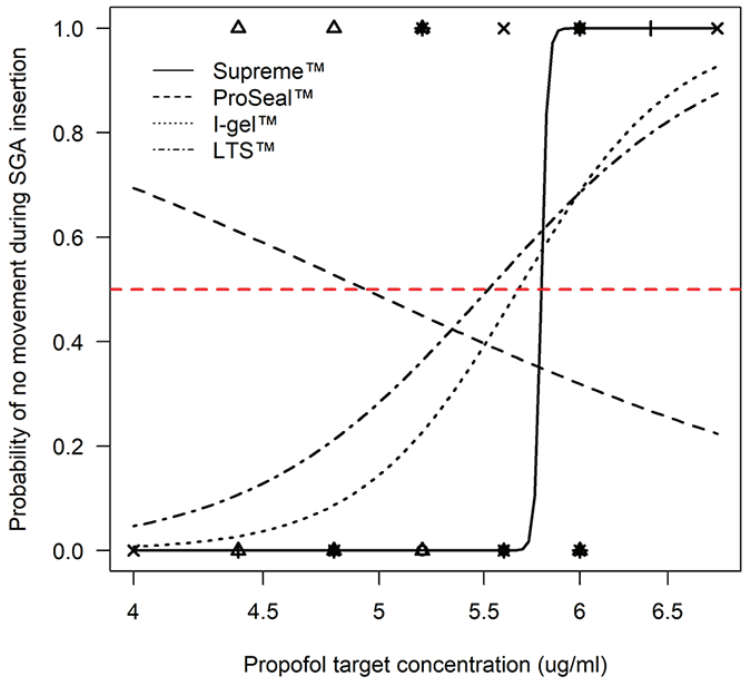


Figure 3 Dose response curves of 50% effective concentration of propofol requirement.

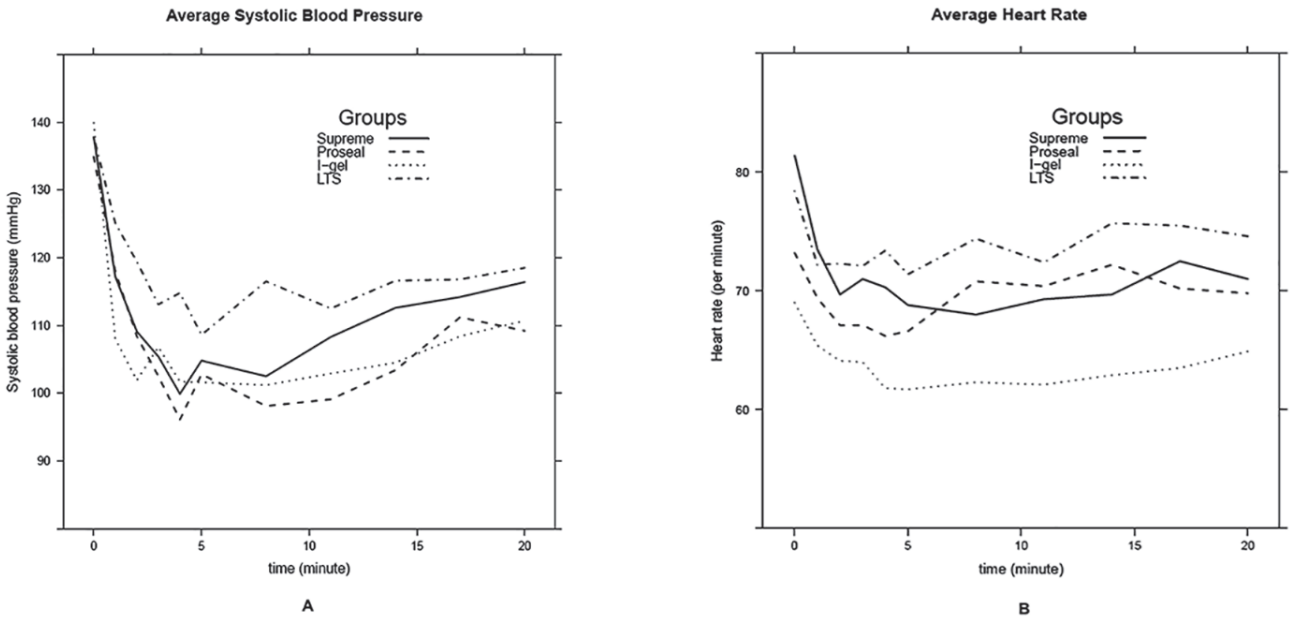


Figure 4 Systolic blood pressure (A) and heart rate (B) changes after supraglottic airway insertion. LTS, Laryngeal Tube Suction II™

Table 3 Effects of intervention groups, time after insertion, and age group on vital sign outcomes (N=440).

Variable	SBP (mmHg) β (95% CI)	DBP (mmHg) β (95% CI)	MAP (mmHg) β (95% CI)	Heart rate (/min) β (95% CI)
Group	p-value<0.001	p-value<0.001	p-value<0.001	p-value<0.001
ProSeal™	0 (ref)[a]	0 (ref)[d]	0 (ref)[g]	0 (ref)[j]
Supreme™	+11.8 (6.7, 17.0)[b]	+3.3 (-0.9, 7.6)[de]	+5.0 (0.7, 9.3)[gh]	+1.0 (-2.7, 4.6)[j]
I-gel™	+3.7 (-0.9, 8.3)[a]	-3.7 (-7.5, 0.1)[df]	-1.8 (-5.6, 2.0)[gi]	-5.7 (-9.0, -2.5)[k]
LTS™	+12.4 (7.8, 16.9)[b]	+4.9 (1.12, 8.7)[e]	+6.8 (3.0, 10.6)[h]	+5.1 (1.9, 8.3)[l]
Time (minutes)	p-value<0.001	p-value <0.001	p-value<0.001	p-value 0.161
0	0 (ref)[a]	0 (ref)[d]	0 (ref)[g]	0 (ref)[j]
4	-34.5 (-39.7, -29.3)[b]	-16.0 (-21.4, -10.5)[e]	-20.0 (-26.4, -15.5)[h]	-7.6 (-12.6, -2.5)[k]
5	-33.2 (-37.7, -28.6)[b]	-16.5 (-21.7, -11.2)[e]	-21.0 (-26.6, -15.7)[h]	-8.4 (-13.6, -3.2)[k]
8	-33.0 (-38.4, -27.7)[b]	-14.0 (-19.3, -8.6)[e]	-18.9 (-24.6, -13.3)[h]	-6.6 (-11.8, -1.4)[jk]
Age group (years)	p-value <0.001	p-value<0.001	p-value <0.001	p-value 0.283
18-30	0 (ref)[a]	0 (ref) [d]	0 (ref)[g]	0 (ref) [j]
31-40	+11.9 (7.6, 16.3)[b]	+9.9 (6.1, 13.7)[e]	+10.1 (6.2, 13.9)[h]	+2.0 (-1.0, 5.1)[jk]
41-50	+16.4 (11.2, 21.6)[c]	+19.5 (15.1, 23.9)[f]	+19.0 (14.7, 23.4)[i]	-3.2 (-6.8, 0.4)[jl]
>50	+11.1 (6.5, 15.6)[b]	+12.6 (9.3, 15.9)[e]	+11.6 (8.4, 14.9)[h]	-2.8 (-5.8, 0.2)[jl]

p-value by F-statistic, for multiple comparisons if p-value<0.01,

For SBP, groups having a different superscript ([ab, ac, bc]) were significantly different (p-value<0.01 by unpaired t-test). For DBP, groups having a different superscript ([de, df, ef]) were significantly different (p-value<0.01 by unpaired t-test). For MAP, groups having a different superscript ([gh, gi, hi]) were significantly different (p-value<0.01 by unpaired t-test). For HR, groups having a different superscript ([jk, jl, kl]) were significantly different (p-value<0.01 by unpaired t-test).

β=beta coefficient, CI=confidence interval, DBP=diastolic blood pressure, LTS=laryngeal Tube Suction II™, MAP=mean arterial pressure, Ref=reference, SBP=systolic blood pressure.

Table 4 Incidence of perioperative adverse events among groups (N=40)

Adverse event	Type of supraglottic airway				p-value
	Supreme™ (n=10)	ProSeal™ (n=10)	I-gel™ (n=10)	LTS II™ (n=10)	
Blood stain in supraglottic airway	3 (30.0%)	1 (10.0%)	1 (10.0%)	2 (20.0%)	0.592
Sore throat	3 (30.0%)	0 (0)	1 (10.0%)	3 (30.0%)	0.270
Hoarseness	2 (20.0%)	1 (10.0%)	2 (20.0%)	1 (10.0%	0.853

LTS=Laryngeal Tube Suction II™

Discussion

We determined the CP_{50} of all 4 types of second-generation supraglottic airway devices using CP_{50} dose response curves from a logistic regression model which has never been reported previously. We found that the CP_{50}s in the Supreme™, ProSeal™, I-gel™ and Laryngeal Tube Suction II™ groups were 5.8, 4.9, 5.7 and 5.5 μg/ml, respectively. Previous studies reported that the use of low dose fentanyl combined with propofol could markedly reduce the blood concentration of propofol necessary to suppress body movement during LMA insertion[15,16]. Therefore, we used intravenous fentanyl 2 μg/kg for 5 minutes before

induction with TCI propofol. As a result, the CP_{50}s of propofol we found may be lower than when compared with TCI propofol alone without fentanyl. The Association of Anaesthetists of Great Britain and Ireland recommends depth of anesthesia monitoring for patients anesthetized with total intravenous techniques and neuromuscular blocking drugs to reduce the risk of accidental awareness during general anesthesia[17]. Since neuromuscular blocking drugs were not used in our study, we performed ASA standard monitoring for anesthesia and recovery from anesthesia, instead of depth of anesthesia monitoring, as mentioned in the protocol, with no patient experiencing operative awareness in our study.

Most previous studies defined CP_{50} as the mean of crossover midpoints in each pair of movement (failure) to no movement (success)[5–7,18–19]. Some studies reported that CP_{50} using crossover midpoints by Dixon's up-and-down method and CP_{50} dose response curve by logistic regression model generated similar results[7,19]. We found that the CP_{50} of propofol requirement was lowest in the ProSeal™ group (CP_{50} [95% CI]: 4.94 [3.34, 6.53]) but was not significantly different compared to the others. Moreover, the dose response curve of the ProSeal™ group was reversed compared to the other groups; significantly more movement was seen for higher doses compared to the lower doses (p-value<0.001). Even though the CP_{50} of the ProSeal™ group was significantly different from zero, 10 subjects per group may not be adequate to make a firm conclusion. However, the minimum Ce for successful SGD insertion attempts in our study was significantly less for the ProSeal™ group compared to the Supreme™ group (p-value 0.008) and the median dose was similar to the CP_{50}. Handa-Tsutsui et al.[11] found that the CP_{50} of TCI propofol in their ProSeal™ device was 4.9 0.2 μg/ml, which was similar to our study. However, they compared the CP_{50} of TCI propofol in the ProSeal™ and Fastrach and classic LMA devices in which ProSeal™ had the highest CP_{50}. ProSeal™ is made of reusable silicone that is a soft material with a soft bite block. Therefore, the ProSeal™ device requires the lowest depth of anesthesia for insertion. In our study, we did not use a removable metal introducer with the ProSeal™ device making the insertion less invasive. However, there have been no studies comparing the CP_{50} of TCI propofol between LMA Proseal and other SGDs apart from the study by Handa-Tsutsui in 2005[11], as most recent studies compared the concentrations of end tidal sevoflurane between LMA Proseal and other SGDs[19,20]. Other studies have reported the end tidal sevoflurane concentration in the LMA Proseal group was higher than a classic LMA (3.15% vs 2.71%)[20] and LMA Supreme under TCI remifentanil infusion (1.20±0.41% vs 0.55±0.38%)[19]. Thus, we conclude that the ProSeal™ SGD may be less invasive than other supraglottic airway devices for TCI propofol.

We found that the Ce of TCI propofol was non-significantly higher in the Laryngeal Tube Suction II™ group compared to the ProSeal™ group (5.6 vs 4.8 μg/ml) and the CP_{50} of the Laryngeal Tube Suction II™ and the ProSeal™ showed similar results (mean [95% CI]:5.52 [4.69, 6.35] vs 4.94 [3.34, 6.53]). Although both devices contain reusable silicone, the Laryngeal Tube Suction II™ has two low pressure cuffs (proximal and distal) with two oval apertures between the two cuffs, which may produce greater stimulation compared to the ProSeal™ device. The CP_{50} of patients in the Laryngeal Tube Suction II™ group in our study was lower than reported in another study (6.3±0.3 μg/ml).[7] Since we administered fentanyl 2 μg/kg 5 minutes before SGD insertion (preinduction), the fentanyl could help suppress the normal airway reflex and reduce the CP_{50} of TCI propofol of the Laryngeal Tube Suction II™. Mihai et al.[21] in 2007 reported the usefulness of Laryngeal Tube Suction II in 100 healthy patients under effect site concentrations of propofol between 4–7 μg/ml with fentanyl 1 μg/kg but there was no comparison with other SGDs. They found a first attempt Laryngeal Tube Suction II insertion success

rate of 71% with 22% airway obstruction during surgery. We could not find any studies comparing the CP_{50} of TCI propofol among Laryngeal Tube Suction II and other SGDs, which may be due to the uncommon use of Laryngeal Tube Suction II recently.

The second highest CP_{50} value in our study occurred in the I-gel™ (mean [95% CI]: 5.67 [5.05, 6.29]) and this was higher than in the ProSeal™ group according to the logistic curve. Shukla et al.[22] reported a CP_{50} value of 4.5 μg/ml for the I-gel™ device, which was lower than in our study. Although the I-gel™ is made of a gel-like thermoplastic elastomer, a harder and bigger shaft for bite block compared to the ProSeal™ device can make the insertion more invasive and require higher doses of propofol. However, after the I gel™ device was inserted, we found that patients had lower heart rates and a similar mean arterial pressure compared to patients in the ProSeal™ group, which could have arisen from a lower stimulation due to lack of cuff pressure. Ashay et al.[23] reported the effective dose of propofol to prevent movement in 50% (ED_{50}) of propofol requirement by simple infusion was significantly lower when the I-gel™ device was used compared to a classic LMA (2.02±0.26 vs 2.70±0.28 mg/kg). Comparison with our study is difficult since our target was CP_{50} of TCI propofol without manual controlled infusion.

There are no studies comparing the CP_{50} of TCI propofol between the Supreme™ device and other second-generation SGDs. Monteserín-Matesanz et al.[19] compared end-tidal concentrations of sevoflurane between Supreme™ and ProSeal™ LMA under remifentanil TCI and found a lower sevoflurane concentration in the Supreme™ device (0.55±0.38%) compared to the ProSeal™ LMA (1.20± 0.41%). Zaballos et al.[24] reported the CP_{50} of propofol with saline required for LMA-Supreme™ was 6.32±0.67 μg/ml compared to propofol with remifentanil (2.50±0.80 μg/ml), which was consistent with our Ce and CP_{50} of the LMA-Supreme™ with fentanyl preinduction (5.8 and 5.8 ug/ml, respectively) even though the Cp50 of the LMA-Supreme™ from the logistic curve was not significantly different from zero (p-value 0.05). The Supreme™ device has a gastric drainage tube and provides a high seal pressure. This design has a rigid curved shaft that allows for easy insertion but it produces greater stimulation. We found that the use of the LMA-Supreme™ device resulted in a significantly higher SBP during induction compared to the ProSeal™ and I-gel™ devices (Table 3) which could be explained by the LMA-Supreme™ design. Thus, the required concentration of propofol for the Supreme™ device is greater than that for the ProSeal™ device.

The success rate for the first attempt in our study was non-significantly higher in the ProSeal™ group (90.0%) than those in the Supreme™ group (50.0%) (p-value <0.078). This was consistent with the study by Liew et al.[25] where the first success rate was not different between the ProSeal™ (72.0%) and the Supreme™ (82.0%) groups. The insertion times and time from TCI to SGD placement in our study were not different among the 4 groups, which was consistent with another study.[25] In both studies the insertions were managed and performed by experienced anesthesiologists.

What this study adds and implications of the study

This is the first study, to our knowledge, to report the Ce and CP_{50} of propofol among four types of second-generation supraglottic airway devices. The lowest to highest Ce and CP_{50} of propofol were found with the ProSeal™, Laryngeal Tube Suction II, I-gel™, and LMA-Supreme™ devices whereas the lowest to highest hemodynamic changes were found in the ProSeal™, I-gel™, LMA-Supreme™ and Laryngeal Tube Suction II devices. Since the Laryngeal Tube Suction II device had the most hemodynamic changes during insertion and is not commonly used worldwide, we recommend the ProSeal™ and I-gel™ for priority use rather than the LMA-Supreme™ based on their lower requirements of TCI propofol and more hemodynamic stability during insertion. In our practice, the

ProSeal™ and I-gel™ devices are considered as the first choices based on the several advantages as described in our results, and also in consideration of the fact that they can be reused after being sterilized in an autoclave for cost savings[26,27]. The LMA-Supreme™ is considered as the third choice since it required more TCI propofol and resulted in less hemodynamic stability, and also it is recommended for single use only with the price of 1,200 to 1,500 baht ($40-50 USD) per item.

Strengths and limitations

A strength of this study is that it was a randomized, double-blind trial where both the patients and nurse investigators were blinded to the allocation group. And although we could not blind the inserter, they were not aware of the main outcomes (Ce and CP_{50}). Second, all SGD insertions were performed by two experienced investigators (NK, NT) to reduce the possibility of technical performance error. Third, we used a critical p-value of 0.01 to control the chance of a family-wise type-I error to minimize false positive outcomes across this multi-armed trial. However, our study had a number of limitations. First, the study was conducted on healthy patients (98.0% of ASA I-II). Thus, our results may not apply to unhealthy patients. Second, based on the dose response curves of CP_{50}, which had a very wide 95% CI, the sample size might not have been adequate to determine the CP_{50} of LMA-Supreme™ when using a logistic regression model. Third, the depth of anesthesia as assessed by bispectral index was not performed in our study due to its unavailability during the study period. The generalizability of our results is also limited since the trial was conducted in a single hospital.

Conclusion

The ProSeal™ and I-gel™ are preferred over the Supreme™ and Laryngeal Tube Suction II™ devices according to the lower CP_{50} and fewer hemodynamic changes Further studies based on dose response curves for CP_{50} of the LMA-Supreme™ airway device should be performed.

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Conflict of interest

The authors have no conflicts of interest to declare.

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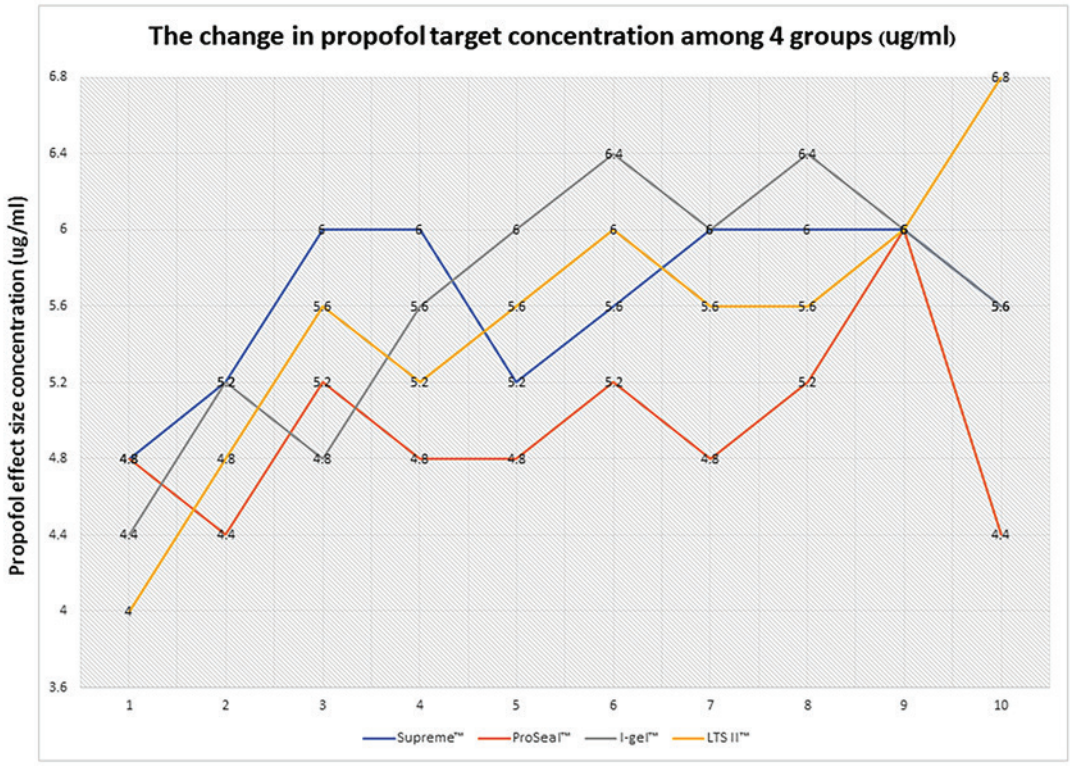

Supplemental File 1 Changes in propofol target concentrations (ug/ml) for each consecutive patient (N=40).