의학석사 학위논문

2 세 미만의 소아에서 프로포폴의 목표농도조절주입을 위한 약동학-약력학 모형의 외적 타당도 평가

External Validation of a Pharmacokinetic-Pharmacodynamic Model of Propofol for Target-Controlled Infusion in Children Under Two Years of Age

2018 년 2 월

서울대학교 대학원

의학과 마취통증의학 전공

지 상 환

Abstract

External Validation of a Pharmacokinetic-Pharmacodynamic Model of Propofol for Target-Controlled Infusion in Children Under Two Years of Age

Sang-Hwan Ji

Department of Medicine

Anesthesiology and Pain Medicine Major

The Graduate School

Seoul National University

Background: Previously, a linked pharmacokinetic-pharmacodynamic model (Kim model) of propofol was developed for children aged 2 to 12 years, allowing target-controlled infusion. Despite an increasing need for intravenous anesthesia using propofol during surgery in children younger than two years of age, no pharmacokinetic-pharmacodynamic model of propofol has been developed for this population. Therefore, in this study, we performed an external validation of Kim's propofol model for children aged less than two years.

Methods: Twenty-four children below the age of two years undergoing neurosurgery were enrolled. Anesthetic induction was commenced using a target-controlled infusion of 2% propofol based on Kim model and continuous infusion of remifentanil under bispectral index (BIS) monitoring. The target effect-site concentration of propofol was set to 2, 3, 4, and 5 μg/ml, each followed by arterial blood sampling after 10 min of equilibrium. Population estimates of pooled bias, inaccuracy, divergence, and wobble were calculated to evaluate the performance of the Kim model.

Results: A total of 95 plasma concentrations and 91 BIS values were used for evaluation of the Kim model. For plasma concentration of propofol, the bias was -0.96% and inaccuracy was 21.0%. For BIS, the bias was -7.7% and inaccuracy was 20.6%.

Conclusions: The pooled bias and inaccuracies from the pharmacokinetic-pharmacodynamic predictions were within clinically acceptable range. Therefore,

the Kim model may be applicable for propofol target-controlled infusion in children under two years of age.

Key words : intravenous anesthesia; propofol; pharmacokinetics; pharmacodynamics; children

Student number : 2016-21957

CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

Introduction

Total intravenous anesthesia is a popular method of general anesthesia. One of the techniques for employing total intravenous anesthesia is target-controlled infusion of propofol. For adults, the pharmacokinetic and pharmacodynamic models that are commonly used for propofol target-controlled infusion are the Marsh [1] and the Schnider models [2, 3], which are both 3-compartment models.

However, these models are not well-suited for pediatric patients because of the difference in pharmacokinetic-pharmacodynamic parameters; pediatric patients have a larger volume of distribution, higher systemic clearance [4] than adults have, and propofol has lower potency for them than for adults [5].

Although previous models, such as the Kataria model [6], the pediatric Marsh model [1], and the Schüttler model [7], have attempted to establish pharmacokinetic guidelines for propofol use in pediatric patients, they have been unable to outperform the Schnider model [8 9]. More recently, a model was developed for propofol target-controlled infusion in children between 2 and 12 years of age (the Kim model) [10], and it is currently being used in a few centers. Pharmacokinetic-pharmacodynamic parameters for Kim's model are shown in Table 1. However, there is no pharmacokinetic-pharmacodynamic model of propofol for children less than 2 years of age, which has made it difficult to perform clinical trials in this population.

In this study, we performed an external validation of the Kim model in children under 2 years of age to determine whether the Kim model is also suitable

for this population.

Methods

Ethics approval

The study was approved by the Institutional Review Board (H-1509-131-708) and the Ministry of Drug and Food Safety (20150228285), and written informed consent was obtained from the parents and legal guardians. It was registered prior to patient enrolment at http://cris.nih.go.kr (KCT0001752, principal investigator : Hee-Soo Kim, approved : 18/12/2015).

Study population

Pediatric patients less than 2 years of age who were scheduled to undergo elective neurosurgery were enrolled. Exclusion criteria were as follows: history of a drug allergy or hypersensitivity to propofol; underlying cardiovascular disease, bradycardia, or hypotension; significant pulmonary, renal, or hepatic disease; haemodialysis treatment; body mass index greater than 35 kg/m^2; or other conditions inappropriate for the study.

We enrolled a total of 24 children in the study. Of the population, age (years, mean ± SD) was 0.91 ± 0.53, height (cm) was 71.7 ± 8.9, weight (kg) was 9.1 ± 2.0. Thirteen of them were boys, eleven were girls. This manuscript adheres to the applicable CONSORT guidelines (Figure 1).

Study protocol

On the day of surgery, the patients arrived in the operating room after appropriate fasting and without premedication. Monitoring of three-lead electrocardiogram (ECG), non-invasive blood pressure, peripheral pulse oximetry (S_pO_2), and end-tidal carbon dioxide (E_tCO_2) was done using a Solar 8000 (GE Medical, Milwaukee, WI, USA). Anesthesia was induced with 2% propofol (Fresofol MCT 2% 50ml Inj., Fresenius Kabi Austria GmBH, Graz, Austria) and remifentanil (Ultiva^{TM} 1 mg, GlaxoSmithKline, Parma, Italy). Propofol was loaded in a 50 ml Kovax-Syringe (Korea vaccine, Gyeonggi-do, Korea), and infusion was performed using a syringe pump (Pilot Anesthesia 2, Fresenius vial, France) that was controlled using target-controlled infusion software (Asan pump, ver. 2.1.3; Bionet Co., Ltd., Seoul, Korea) according to the Kim model. The initial target effect site concentration of propofol was set at 4.0 μg/ml, and the initial infusion rate of remifentanil was 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After loss of consciousness, 0.6 mg/kg of rocuronium was administered to facilitate tracheal intubation. Arterial cannulation was done to start invasive blood pressure monitoring, and to enable intermittent blood sampling. Bispectral Index (BIS ; Covidien, Minneapolis, MN, USA) was also monitored to maintain adequate anesthetic depth, and to evaluate the pharmacodynamic performance of the Kim model. We maintained the patients' BIS value between 40 and 60, and their blood pressure and heart rate between 80% and 120% of baseline, by adjusting the target effect-site concentration of propofol and the infusion rate of remifentanil.

During surgery, the target effect-site concentration of propofol was set to 2, 3, 4, and 5 μg/ml, which was followed by arterial blood sampling after 10 min of equilibrium. The total elapsed time, predicted plasma concentration of propofol, and predicted BIS for each point were automatically recorded on a computer using the target-controlled infusion software. The actual plasma concentrations of propofol were analyzed, and the actual BIS values at each point were manually recorded. During the study period, the patients' blood pressure and heart rate were recorded and compared to the predicted propofol plasma concentration by repeated-measures analysis of variance (RMANOVA) using SPSS software (ver. 22.0; SPSS Inc., Chicago, IL, USA).

Measurement of plasma concentration of propofol

Each of the blood samples collected in this study were put into an Eppendorf tube® (Eppendorf, Hamburg, Germany) within 30 min, centrifuged at 3,000 rpm for 10 min, and the supernatants were stored at -70°C. Plasma concentrations of propofol were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) after liquid-liquid extraction with methyl *tert*-butyl ether (MTBE). Briefly, 200 μL of human plasma was mixed with 50 μL of an internal standard (IS; 100 ng/mL, propofol-d^{17}), and then extracted with 1 mL of MTBE. Plasma samples were mixed by vortexing, centrifuged, and then the organic phase was dried at 40°C under a stream of nitrogen. The residue was reconstituted in 100 μL of 90% aqueous methanol and injected into the LC-MS/MS system. The analyte and IS were

separated on a UHP ASB C18 column (100 x 2.1 mm, 1.9 μm, Agela Technologies, USA) under a gradient. The mobile phase consisted of 0.1% ammonium hydroxide in 10 mM ammonium acetate and 0.1% ammonium hydroxide in acetonitrile. Negative electrospray ionization in multiple reaction monitoring (MRM) mode was employed. The MRM was based on m/z transition of 177.1>177.1 for propofol and 194.2>194.2 for IS. The calibration curve was linear over the range of 10–2,000 ng/mL, with a correlation coefficient (r) greater than 0.99 for all instances. The lower limit of quantification of propofol was 10 ng/mL. The precision and accuracy of quality control samples (30, 150, and 1,500 ng/mL) were all within 15%.

Calculation of predicted BIS

The predicted BIS value, according to effect-site concentration of propofol, was calculated using the sigmoid E_{max} model: $\text{Effect} = E_0 + (E_{max} - E_0) \times \frac{{C_e}^{\gamma}}{{C_{e50}}^{\gamma} + {C_e}^{\gamma}}$, where Effect is the predicted BIS value, E_0 is the baseline BIS value, E_{max} is the maximum possible drug effect on the BIS, and γ is the steepness of the effect-site concentration versus BIS relationship. Values for E_0, E_{max}, C_{e50}, and γ from the Kim model are shown in Table 1.

External validation

We employed the concept of performance error (PE) using the following equation, as previously mentioned [10, 11]:

$$PE_{ij} = \frac{measured_{ij} - predicted_{ij}}{predicted_{ij}}$$

where $predicted_{ij}$ is the j[th] prediction of plasma propofol concentration or BIS value of the i[th] patient, and $measured_{ij}$ is the j[th] actual measurement of plasma propofol concentration or actual BIS value of the i[th] patient.

We took the following four parameters into account: inaccuracy, divergence, bias and wobble. Inaccuracy was measured by obtaining the median absolute performance error (MDAPE). For i[th] individual, MDAPE is defined as :

$$MDAPE_i = median\{|PE_{ij}|, j = 1, \dots N_i\}$$

where N_i is the number of PEs in the i[th] individual. MDAPE is an absolute value that represents the size of the errors. Divergence is calculated for the i[th] individual as the slope obtained from linear regression of that individual's $|PE_{ij}|$s against time :

$$Divergence_i\ (\%/h) = 60 \times \frac{\sum_{j=1}^{N_i}|PE_{ij}| \times t_{ij} - (\sum_{j=1}^{N_i}|PE_{ij}|) \times (\sum_{j=1}^{N_i} t_{ij})/N_i}{\sum_{j=1}^{N_i}(t_{ij})^2 - \left(\sum_{j=1}^{N_i} t_{ij}\right)^2/N_i}$$

where t_{ij} is the time (min) that the corresponding PE_{ij} was determined. Divergence provides time-related trends of errors. Bias is determined as median performance error (MDPE). MDPE for the i[th] individual is :

$$MDPE_i = median\{PE_{ij}, j = 1, \dots N_i\}.$$

Since MDPE is a signed value, it represents the direction of errors. Wobble is simply a measure of the variability of the PE_{ij} in the i[th] individual:

$Wobble_i$ = median absolute deviation of $\{PE_{ij}, j = 1, \ldots N_i\}$ from $MDPE_i$

After calculating all the parameters for each individual, we subsequently calculated the population estimate. The pooled data approach was used according to a previous study [11]. Calculations of the parameters were done using the fit4NM package (Ver. 4.5.2., Eun-Kyeong Lee and Gyu-Jeong Noh, http://www.fit4nm.org, accessed at 15/03/2017). Box plots of the measurements for each estimation point were drawn using MedCalc® (Ver. 17.2., MedCalc software bvba, Ostend, Belgium).

Results

The study was designed so that blood samples and BIS values would be collected at each of the propofol target effect-site concentrations (2, 3, 4, and 5 μg/ml) for each child, which would provide us with 96 blood samples and BIS values out of 24 candidates. However, 1 blood sample and 1 BIS value were unobtainable due to insufficient time during surgery to reach equilibrium, and an additional 4 BIS values were unavailable due to disturbances during surgery. In total, 95 blood samples and 91 BIS values were obtained from the subjects.

The population estimates (95% CI) were as follows ; for plasma propofol concentration, bias of -0.96% (-8.45% to 6.54%), inaccuracy of 21.0% (15.0% to 27.0%), divergence of -17.4%/h (-25.3%/h to -9.50%/h), and wobble of 12.8% (7.29% to 18.2%). For BIS value, bias of -7.72% (-11.7% to -3.74%), inaccuracy of 20.6% (17.4% to 23.9%), divergence of -4.59%/h (-8.71%/h to -0.47%/h), and wobble of 9.07% (6.69% to 11.5%). The inaccuracies were less than 25% for both pharmacokinetics and pharmacodynamics. Analysis of the negative bias suggested that the plasma concentration of propofol was slightly overestimated but appropriate. Moreover, the BIS value was slightly lower than expected, which indicated that the propofol effect was slightly stronger than we predicted. Nonetheless, the calculated bias for the model was deemed acceptable considering the performance of previous models [1, 12].

In addition, external validation of the Kim model showed that 70.5% of the measured propofol plasma concentrations and 65.9% of the actual BIS values were

within 70% and 130% of the predicted value. This is depicted in Figure 2, which shows a scatter plot of the predicted versus the measured propofol plasma concentrations, as well as the predicted and measured BIS values. The performance errors of propofol plasma concentration and BIS for each individual with respect to elapsed time are shown in Figure 3.

Our results indicated that there was a statistically significant decrease in the heart rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure as the predicted plasma concentration of propofol increased ($P = 0.006$, 0.030, 0.001, and 0.005, respectively) (Table 2). In addition, in the majority of the patients, the heart rate and mean blood pressure remained between 80% and 120% of baseline (73.7% and 64.2%, respectively).

Discussions

The results from this study showed that the Kim model is a clinically acceptable model for propofol use in children under 2 years of age considering of the model's inaccuracy and bias. Previous studies have considered an inaccuracy of less than 30% to be acceptable [13]. In support, other established models have been shown to have inaccuracies within this range [1, 12].

Performances of several pediatric pharmacokinetic-pharmacodynamic models were evaluated in previous studies, and the results together with this study are shown in Table 3 [1, 3, 6-8, 10]. The Marsh model and the Schnider model [1, 3] did not include pharmacodynamic data by means of BIS value, and evaluation of pharmacodynamic performance was done by Rigouzzo and colleagues. [8]. The Kataria model [6] only provides the median absolute weighted residual (29.6%). Although Rigouzzo and co-workers [8] provided pharmacokinetic performance data for the Schnider and Kataria models, the values of bias and inaccuracy implied poor performance for these models. The Schüttler model [7] exhibited a slightly better performance than the Kim model for children aged 2–12 years, but it performed similarly for children under 2 years of age. Importantly, with regard to bias and inaccuracy, the performance of the Kim model for young children is comparable to those of previous models. The biggest difference between previous models and the current study is the age of the population. We only included children under two years of age, whereas previous studies did not include children less than six years of age. In addition, the newly developed model was the only pharmacokinetic-

pharmacodynamic linked model to be performed simultaneously on the same subjects. It is important to note that propofol infusion guided by the Kim model did not bring about hemodynamic instability, as heart rate and blood pressure were well maintained throughout the operation.

The results from this study indicated that the performance of the Kim model was better for propofol plasma concentration and similar for BIS value in patients under two years of age than in patients 2 to 12 years of age. Interestingly, since the bias for the BIS value was a negative number (-7.7%), we can infer that the actual BIS value was lower than predicted, which implies that the propofol efficacy was greater in younger children. One possible reason for the enhanced propofol efficacy in young children may be immaturation of the hepatic enzyme *CYP2B6*, since its expression level is only 10% in a 10-month-old baby, and only 50% in a 1.3-year-old baby, relative to its expression in an adult [14, 15]. However, inter-individual variability in the response to propofol is also prevalent, especially in neonates, so it remains unclear what precisely affects the propofol efficacy [16]. Regardless, the divergence and wobble remained similar between the two groups for both pharmacokinetics and pharmacodynamics, suggesting that the time-affected variability and intra-individual variability did not differ.

Since this two-compartment model employs a fixed V_1 of 1.69L, there was a concern that while this V_1 is suitable for children 2 to 12 years of age, it might be relatively large for children less than 2 years of age. However, our results exhibited less inaccuracy in predicting the plasma concentration for younger

children. In addition, the bias for the plasma concentration in older children was -20%. Taken together, our data indicated that the V_1 for the Kim model is underestimated and is more appropriate for children under 2 years of age.

Our study has some limitations. First, we were unable to build a new model for this population, because more frequent blood sampling is required to obtain a hysteresis graph, which may not be feasible for small children under two years of age. Consequently, we conducted an external validation of the Kim model as an alternative to reduce the need for frequent blood sampling. Second, we used an intermediate version of Kim model in this study that does not consider remifentanil dose. However, the final version of Kim model exists that include the mean infusion rate of remifentanil as a covariate for pharmacodynamic model [10]. It was found to be too technically difficult to reflect the changes in remifentanil infusion rate as a covariate in the program, so we selected the intermediate model for predicting BIS. Finally, when predicting the BIS value, surgical stimuli should also be taken into account for a more accurate estimation. However, the Kim model, as well as previous models, did not take surgical stimuli into consideration. Fortunately, we were able to achieve a satisfactory level of prediction for the BIS value even without incorporating surgical stimuli, but it will be important for surgical stimuli to be included as a variable in future prediction models.

In conclusion, as the biases and inaccuracies in pharmacokinetic and pharmacodynamic predictions are clinically acceptable, Kim model for propofol target-controlled infusion is applicable to children under two years of age.

References

1. Marsh B, White M, Morton N, Kenny GN: Pharmacokinetic model driven infusion of propofol in children. *British journal of anaesthesia* 1991; 67: 41-8

2. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; 88: 1170-82

3. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; 90: 1502-16

4. Murat I, Billard V, Vernois J, Zaouter M, Marsol P, Souron R, Farinotti R: Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns. Comparison of three data analysis approaches. *Anesthesiology* 1996; 84: 526-32

5. Rigouzzo A, Girault L, Louvet N, Servin F, De-Smet T, Piat V, Seeman R, Murat I, Constant I: The relationship between bispectral index and propofol during target-controlled infusion anesthesia: a comparative study between children and young adults. *Anesthesia and analgesia* 2008; 106: 1109-16, table of contents

6. Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL: The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; 80: 104-22

7. Schuttler J, Ihmsen H: Population pharmacokinetics of propofol: a multicenter study. *Anesthesiology* 2000; 92: 727-38

8. Rigouzzo A, Servin F, Constant I: Pharmacokinetic-pharmacodynamic modeling of propofol in children. *Anesthesiology* 2010; 113: 343-52

9. Constant I, Rigouzzo A: Which model for propofol TCI in children. *Paediatric anaesthesia* 2010; 20: 233-9

10. Choi BM, Lee HG, Byon HJ, Lee SH, Lee EK, Kim HS, Noh GJ: Population pharmacokinetic and pharmacodynamic model of propofol externally validated in children. *Journal of pharmacokinetics and pharmacodynamics* 2015; 42: 163-77

11. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. *Journal of pharmacokinetics and biopharmaceutics* 1992; 20: 63-94

12. Glen JB, Servin F: Evaluation of the predictive performance of four pharmacokinetic models for propofol. *British journal of anaesthesia* 2009; 102: 626-32

13. Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL: Miller's Anesthesia. 8th edition. Philadelphia, Elsevier Saunders, 2015, p 948

14. Chidambaran V, Costandi A, D'Mello A: Propofol: a review of its role in pediatric anesthesia and sedation. *CNS drugs* 2015; 29: 543-63

15. Tateishi T, Nakura H, Asoh M, Watanabe M, Tanaka M, Kumai T, Takashima S, Imaoka S, Funae Y, Yabusaki Y, Kamataki T, Kobayashi S: A comparison of hepatic cytochrome P450 protein expression between infancy and postinfancy. *Life Sci* 1997; 61: 2567-74

16. Allegaert K, Peeters MY, Verbesselt R, Tibboel D, Naulaers G, de Hoon JN,

Knibbe CA: Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *British journal of anaesthesia* 2007; 99: 864-70

Table 1. Pharmacokinetic – pharmacodynamic parameters for Kim model

	Parameter	Estimate
PK	V_1 (L)	1.69
	V_2 (L)	27.2 + 0.93×(weight–25)
	k_{10} (/min)	$0.89\times (\text{weight}/23.6)^{0.97}/1.69$
	k_{12} (/min)	0.7692
	k_{21} (/min)	1.3/(27.2+0.93×(weight–25))
	Cl (L/min)	$0.89\times (\text{weight}/23.6)^{0.97}$
	Q (L/min)	1.3
PD (Intermediate)	E_0	76.9
	E_{max}	35.4
	$C_{e\,50}$(μg/mL)	3.78 – 0.183×age
	γ	3.02
	k_{e0} (/min)	0.557
PD (Final)	E_0	79.9
	E_{max}	30.6
	$C_{e\,50}$(μg/mL)	3.65 – 0.102×age – 1.72×REMI
	γ	2.11
	k_{e0} (/min)	0.372

PK : Pharmacokinetic, PD : Pharmacodynamic, V_1 : Central volune of distribution, V_2 : Peripheral volume of distribution, k_{10} : Elimination constant, k_{12} : Distribution

constant, k_{21}: Redistribution constant, Cl : Metabolic clearance, Q : Inter-compartmental clearance, E_0 : Baseline Bispectral Index value before propofol administration, E_{max}: Minimum possible Bispectral Index value, $C_{e_{50}}$: C_e at 50% of the maximal propofol effect on Bispectral Index, γ : Steepness of the C_e versus Bispectral Index relationship, k_{e0} : Blood-brain equilibration rate constant

Table 2. Comparison of heart rate and blood pressure for each predicted plasma concentration of propofol

	2000 ng/ml	3000 ng/ml	4000 ng/ml	5000 ng/ml	*P*-value
HR (beats/min)	123.4±18.6	116.2±10.8	109.8±10.2	109.2±11.6	0.006*
SBP (mmHg)	97.0±16.5	97.5±19.8	90.3±15.4	88.7±18.0	0.030*
DBP (mmHg)	54.5±11.9	52.2±12.7	46.3±7.7	46.4±8.9	0.001*
MBP (mmHg)	72.3±15.3	69.1±17.5	60.6±16.6	61.3±11.3	0.005*

HR; Heart rate, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, MBP; Mean blood pressure. Values are mean ± SD. * $P < 0.05$

Table 3. Comparison of pharmacokinetic-pharmacodynamic performance of propofol infusion models for children

	Kim*	Kim	Kataria	Marsh	Schüttler	Schnider
Range of age (Yrs)	0-2	0.2-12	3-11	2-10	2-88	25-81
Bias_PK (%)	-0.96	-20.2	52.5	0.9	-3.4	44.3
Inaccuracy_PK (%)	21.0	30.3	52.5	20.1	24.9	44.3
Bias_PD (%)	-7.72	1.46	1.91	-1.57	0.00	-1.73
Inaccuracy_PD (%)	20.6	18.9	19.1	21.8	22.0	21.0

Bias_PK : Bias for plasma propofol concentration, Inaccuracy_PK : Inaccuracy for plasma propofol concentration, Bias_PD : Bias for Bispectral Index value, Inaccuracy_PD : Inaccuracy for Bispectral Index value

* This study for children under two years of age

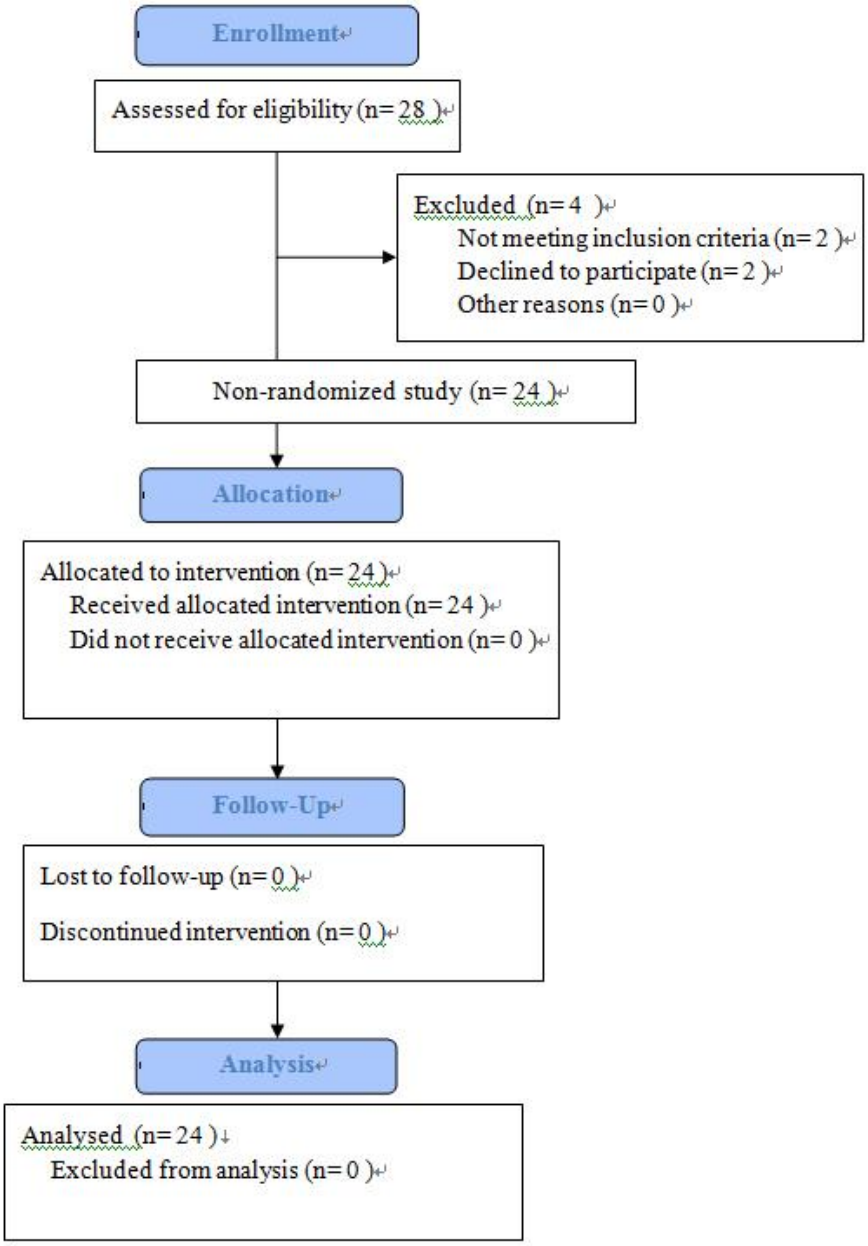
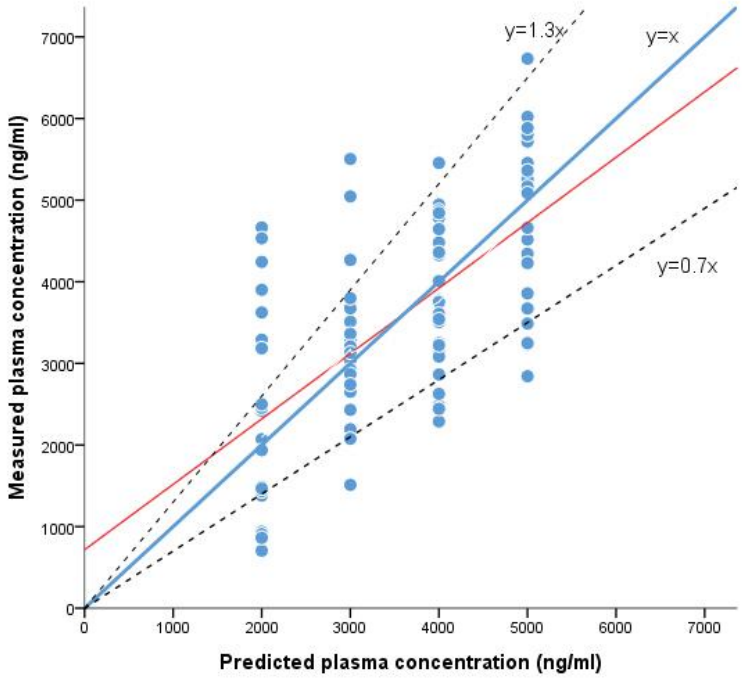


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram


y=1.3x
y=x
y=0.7x
Measured plasma concentration (ng/ml)
Predicted plasma concentration (ng/ml)
0
1000
2000
3000
4000
5000
6000
7000

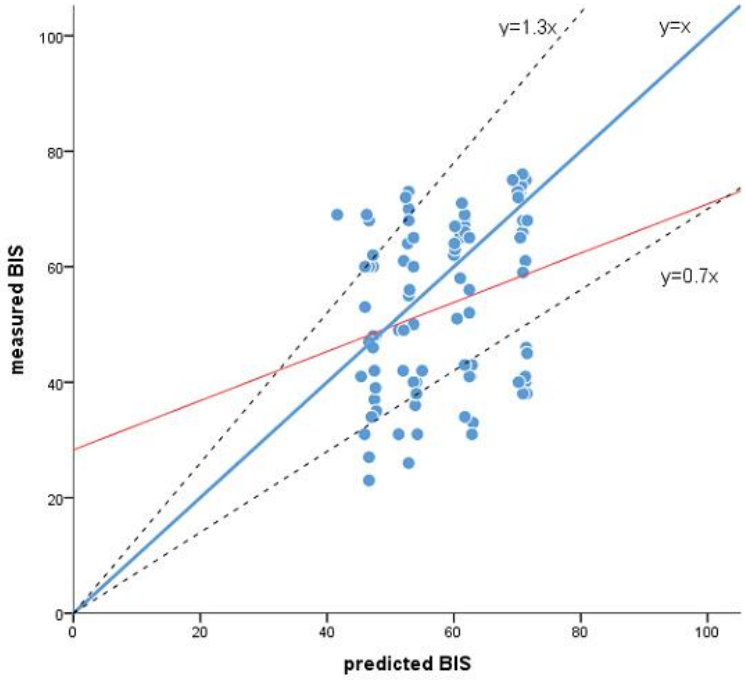

y=1.3x
y=x
y=0.7x
measured BIS
predicted BIS
0
20
40
60
80
100

Figure 2. Scatter plot of predicted plasma concentration (C_p) – measured plasma concentration (C_m) of propofol, and predicted BIS (BIS_p) – measured BIS (BIS_m). The red solid line depicts the regression line. $C_m = 0.801 \times C_p + 716.7, R^2 = 0.431; BIS_m = 0.426 \times BIS_p + 28.293, R^2 = 0.072$, BIS : Bispectral Index.

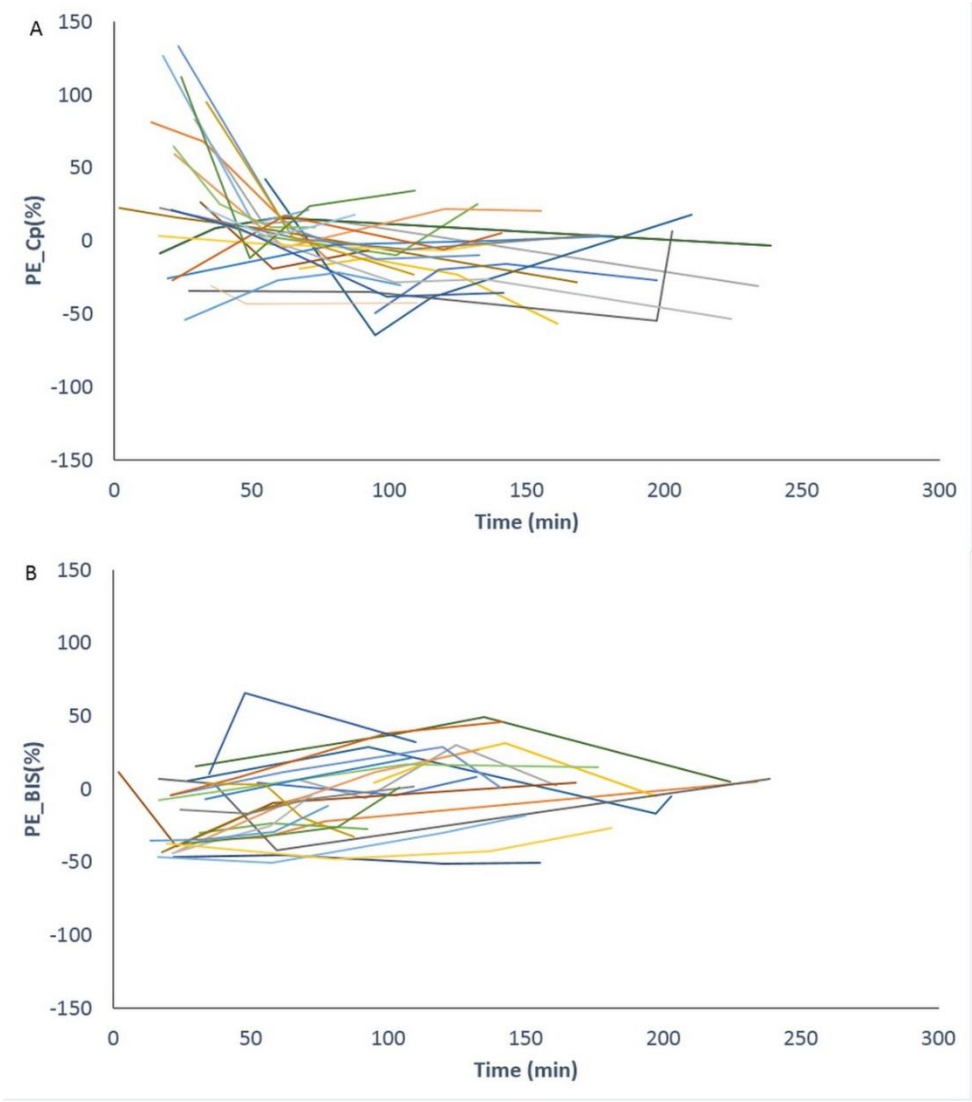


Figure 3. Performance error of plasma concentration of propofol (A), and BIS value (B) for each individual along elapsed time. BIS: Bispectral Index

요약(국문초록)

배경 : 2 세에서 12 세 사이의 소아들을 대상으로 한 프로포폴의 약동-약력학 모형 (Kim 모형)이 개발되어 목표농도조절주입법을 가능하게 하고 있다. 2 세 미만의 소아들을 대상으로 한 수술에서도 전정맥마취의 필요성이 증가하고 있으나, 그들을 대상으로 한 약동-약력학 모형은 현재까지 개발된 바가 없다. 우리는 본 연구에서 2 세 미만의 소아들을 대상으로 Kim 모형의 외적 타당도를 평가해 보았다.

방법 : 신경외과수술을 받는 2 세 미만의 소아 24 명을 연구에 포함시켰다. 통상적인 방법으로 마취유도를 한 후, Kim 모형이 탑재된 목표농도조절주입 프로그램을 사용하여 이중분광지수(BIS™) 감시 하에 2% 프로포폴과 레미펜타닐을 지속정주하였다. 프로포폴의 목표효과처농도를 2, 3, 4, 5 μg/ml 로 각각 설정하고 10 분간의 평형을 유지한 다음, 동맥혈채혈을 시행하여 혈장농도를 분석하였다. 네 가지의 인구집단 추정치 (pooled bias, inaccuracy, divergence, wobble) 를 사용하여 Kim 모형의 정확도를 평가하였다.

결과 : 95 개의 혈장 프로포폴 농도와 91 개의 이중분광지수 값이 얻어졌다. 프로포폴의 혈장농도에 대해서는 bias 가 −0.96%,

inaccuracy 가 21.0% 였고, 이중분광지수에 대해서는 bias 가 −7.7%, inaccuracy 가 20.6% 였다.

결론 : 약동−약력학적 예측에 대한 Bias 와 inaccuracy 는 임상적으로 허용 가능한 수치였다. 따라서, Kim 모형은 2 세 미만의 소아에서 프로포폴의 목표농도조절주입에 사용되어도 타당하다.

주요어 : 정맥마취, 프로포폴, 약동학, 약력학, 소아

학번 : 2016−21957