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Influence of body fatness on propofol requirements for loss of consciousness in target-controlled infusion

A STROBE-compliant study

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Abstract

This prospective observational study evaluated the effects of body fat on the pharmacologic effect of propofol. Hundred patients aged 18 to 75 years who were scheduled to undergo orthopedic surgery under regional block were enrolled. All participants underwent bioelectrical impedance analysis and were allocated into 2 groups: the high and normal adiposity group, according to percent body fat. Following successful regional block, propofol was incrementally infused until loss of consciousness (LOC) with a target-controlled infusion pump. The effect-site concentration of propofol at LOC and the total infused dose of propofol per total body weight until LOC were recorded. At the end of the surgery, the infusion of propofol was stopped. The elapsed time to recovery of consciousness (ROC) and the effect-site concentration at ROC were recorded. These pharmacologic data were compared between 2 groups. The effect-site concentration of propofol at LOC (μg/mL) was significantly lower in the high adiposity group than in the normal group in both sexes (3.5 ± 0.4 vs 3.9 ± 0.6; P = .020 in males, and 3.4 [interquartile range: 2.9–3.5] vs 3.8 [interquartile range: 3.3–3.9]; P = .006 in females). Total dose per total body weight until LOC (mg/kg) were also significantly lower in the high adiposity group than in the normal group. There was no significant difference in the data related to ROC. The pharmacologic effects of propofol may be affected by the composition of body components. The concentration of propofol using a target-controlled infusion system may be diminished in patients with a high proportion of body fat.

Abbreviations: BIA = bioelectrical impedance analysis, BIS = bispectral index, BIS_{LOC} = BIS value at LOC, BIS_{ROC} = BIS value at ROC, Ce_{LOC} = the effect-site concentration of propofol at LOC, Ce_{ROC} = the effect-site concentration of propofol at ROC, GABA = γ-aminobutyric acid, LOC = loss of consciousness, ROC = recovery of consciousness, TBW = total body weight, TCI = target-controlled infusion, T_{ROC} = the elapsed time to ROC.

Keywords: body composition, fat, obesity, pharmacology, propofol

1. Introduction

Propofol, an alkylphenol derivative, is highly lipid-soluble, and is emulsified with 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phospholipid.[1] The enhancement of the action of γ-aminobutyric acid (GABA) through $GABA_A$ receptor has been considered to be a major mechanism of the pharmacologic effect of propofol.[1] Lipophilicity is the major physiochemical properties of drugs affecting the pharmacokinetics including absorption, distribution, metabolism, and excretion. The drugs with high lipid-solubility, low plasma protein binding, and low ionization have a higher volume of distribution. These drugs readily pass through the lipid bilayer and are consequently distributed to the lipophilic body region, such as adipose tissue, leaving the bloodstream. The rapid termination of the hypnotic effect following a single bolus administration results from the fast redistribution of propofol from the effect-site (brain) into inactive peripheral tissues such as the muscle and adipose tissue.

The pharmacokinetics of propofol follows a 3-compartment model, which is composed of central (blood, brain, and liver), rapid equilibrating (muscle and viscera), and slowly equilibrating compartments (adipose tissue).[2] The amount of adipose tissue might affect the volume of distribution and alter the pharmacology of propofol. It is well known that total body weight (TBW)-based dosing of propofol is prone to error in achieving an appropriate pharmacologic effect, especially in women or obese individuals because of the relatively higher proportion of body fat.[3]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The high volume of distribution also affects the elimination of the drug, especially after prolonged continuous infusion. The accumulation of drugs in the peripheral compartment prolongs the action of the drug because relatively large peripheral compartments steadily release the drug into the central compartment (plasma) despite the elimination of the drug by the liver or kidney. The drug with the higher volume of distribution generally has the longer elimination half-life.[4] Because the peripheral volume of distribution of propofol is much larger than the central volume of distribution, the changes in body composition may affect the elimination of propofol, particularly after prolonged continuous infusion.[3,5,6]

This prospective study aimed to investigate the effects of body composition such as body fat on the pharmacologic effects of propofol. We hypothesized that body fatness affect the pharmacologic effect of propofol. The pharmacologic profiles of propofol, loss of consciousness (LOC), or recovery of consciousness (ROC) were evaluated during continuous infusion using a target-controlled infusion (TCI) system.

2. Methods

This prospective observational study was approved by the Institutional Review Board of Jeonbuk National University Hospital (number: CUH 2018-11-038), and registered with the WHO International Clinical Trials Registry Platform (KCT0004196). This study was conducted in the orthopedic operating room setting of the single university hospital from October 2019 to September 2020. Informed consent was obtained from all participants.

One hundred patients aged 18 to 75 years of American Society of Anesthesiologists physical status 1 or 2, who were scheduled to undergo upper or lower extremity orthopedic surgery under regional block, were enrolled in this prospective study.

The exclusion criteria were as follows. Participants who had an egg or soy allergy, severe hepatorenal impairment, and difficulty in communication, such as hearing problems, were excluded from the study. Participants with metal implants, including cardiac pacemakers and implantable cardioverter defibrillators were also excluded because bioelectrical impedance analysis (BIA) measurement was contraindicated in such patients.

All subjects enrolled in the study received body composition measurements using BIA method, on the day before surgery. Inbody S10® (Biospace, Seoul, Korea) analyses body composition using a 4-compartment model, which divides body composition into 4 components: total body water, protein, mineral, and body fat.[7] BIA, which has been validated in several studies,[8–10] is a cost-effective, easily bed-side applicable, and radiation-free body composition measurement method. Body composition measures including body fat mass (kg), percent body fat (%), skeletal muscle mass (kg), fat-free mass (kg), and the amount of extracellular and total body water (L) were obtained from BIA for all participants.

The participants were allocated into 2 groups; the high and normal adiposity group, according to the predetermined cut-off of percent body fat by Kim et al[11] defining excessive body fat for each sex. They defined overweight as ≥17% in men and ≥32% in women of percent body fat in Asian population. In the current study, the high adiposity group has percent body fat above the cut-off value, and the normal adiposity group has below the cut-off value.

2.1. Anesthesia regimens

Anesthesia regimens were standardized for all participants. On arrival at the operating room, the anesthesia monitors, including noninvasive blood pressure, electrocardiogram, pulse oximetry, and bispectral index (BIS), were applied to the patients. All participants did not receive any premedication. Ultrasound-guided brachial plexus block or sciatic and femoral nerve block were performed according to the surgical site. A total of 30 mL of 1.5% lidocaine with epinephrine 5 μg/mL was injected into the neural sheath. After successful sensory and motor blockage was achieved, propofol was infused for sedation.

At least 5 minutes prior to the initiation of propofol infusion, 2 mL of 2% lidocaine was injected to prevent propofol injection pain. Propofol (Fresofol® 2% injection 50 mL, Fresenius Kabi, Austria) was infused with a TCI pump (Orchestra® Base Primea, Fresenius Vial, France), which the modified Marsh pharmacokinetic model was preprogrammed, in plasma targeting mode. The initial target plasma propofol concentration was 1.5 μg/mL and was increased stepwise by 0.5 μg/mL at 4-minute intervals to reach LOC while providing 100% oxygen via a simple face mask. LOC was defined as no response to the verbal command "open your eyes." The effect-site concentration of propofol at LOC (Ce_{LOC}) was recorded. In addition, the total infused dose of propofol per TBW (mg/kg) until LOC and the BIS value at LOC (BIS_{LOC}) were also recorded, and subsequently, the operation was started. During the operation, the target effect-site concentration of propofol that had induced LOC was maintained. At the end of the surgery, the infusion of propofol was stopped. The elapsed time to ROC (T_{ROC}), the effect-site concentration of propofol at ROC (Ce_{ROC}), and BIS value at ROC (BIS_{ROC}) were recorded. ROC was defined as obedience to the verbal command "open your eyes." Hemodynamic parameters, including noninvasive blood pressure and heart rate, were continually recorded until the end of anesthesia. All interventions were performed by an anesthesiologist who was blinded to the study group.

The patients' characteristics, including body composition measures, and the pharmacologic data of propofol such as Ce_{LOC}, BIS_{LOC}, T_{ROC}, Ce_{ROC}, and BIS_{ROC} were compared between 2 groups. The relationship between the percent body fat and the pharmacologic data of propofol was evaluated.

2.2. Sample size calculation and statistical analysis

In the current study, the sample size was predetermined by *t* test sample size calculation using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY) based on the assumption that the minimum detectable difference of Ce_{LOC} was 0.5 μg/mL between the 2 groups. A total of 84 patients were required with a significance level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). Considering possible dropout, the total sample size was enlarged to 105 by 25% increment.

All statistical analysis was performed using IBM SPSS Statistics for Windows, version 26. Two-tailed independent-samples *t* test or Mann–Whitney rank-sum *U* test was used to analyze continuous variables after performing Shapiro–Wilk test. Linear regression analysis was performed to verify the relationships between percent body fat and the pharmacologic data of propofol. BIS values and hemodynamic parameters, including blood pressure and heart rate, were analyzed by 2-way repeated measures analysis of variance. All descriptive data are expressed as the number of patients, mean ± standard deviations, and median (interquartile range). A *P* value of <.05 was considered statistically significant.

3. Results

Among the 100 participants enrolled, 96 subjects (44 men and 52 women) were analyzed. Four patients who failed regional block, had propofol-induced paradoxical excitation, and complained of a severe propofol injection pain were dropped from the study. The subject flow diagram is presented in Figure 1.

Patient characteristics including body composition measures were compared between the high and normal adiposity groups (Table 1). Body mass index was significantly higher in the high

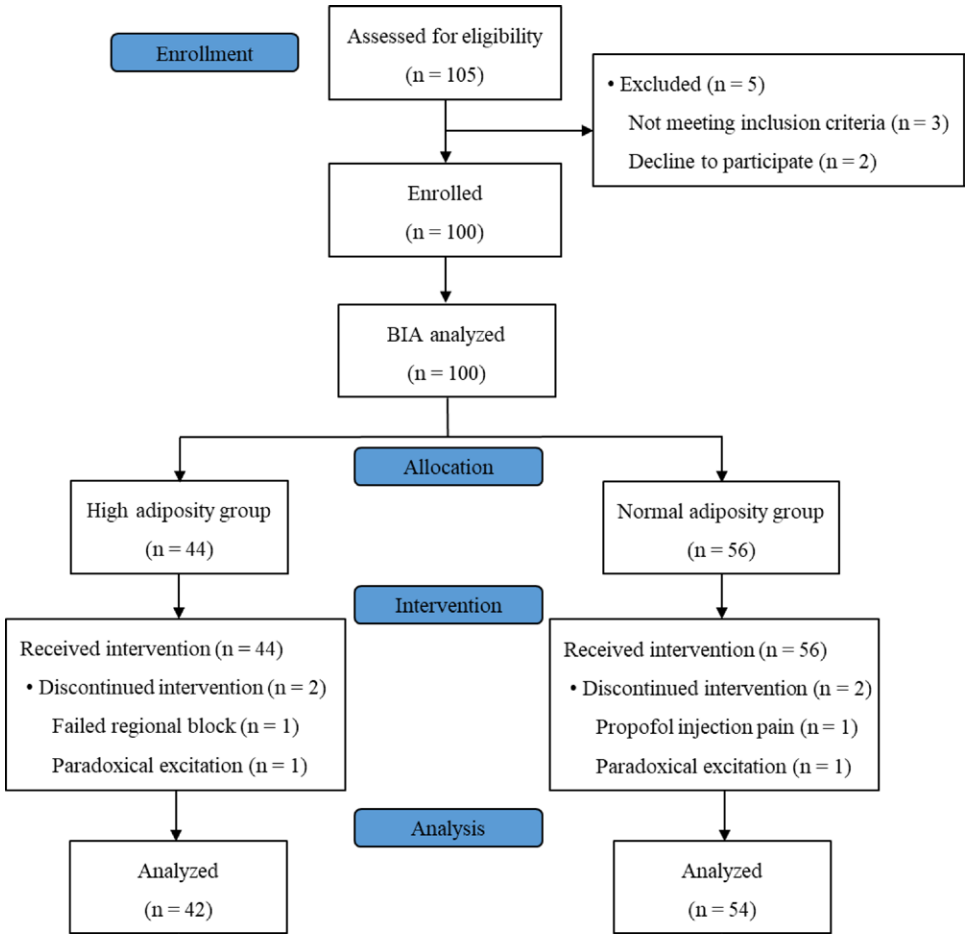

Figure 1. Subject flow diagram. BIA = bioelectrical impedance analysis.

adiposity group than in the normal adiposity group for each sex. The body fat mass and percent body fat were also significantly higher in the high adiposity group than in the normal group. The skeletal muscle mass and fat-free mass were not significantly different between the 2 groups.

The pharmacologic effects of propofol in the 2 groups are presented in Table 2. Ce_{LOC} (μg/mL) was significantly lower in the high adiposity group than in the normal group for each sex. The total infused doses of propofol per TBW until LOC (mg/kg) were also significantly lower in the high adiposity group than in the normal group in both sexes. However, there were no significant differences in BIS_{LOC} between the 2 groups. The data related to the recovery from unconsciousness, including T_{ROC}, Ce_{ROC}, and BIS_{ROC}, were not statistically different between the 2 groups.

In the linear regression analysis, there was a linear relationship between the percent body fat and Ce_{LOC} (r = –0.583, P < .001 in males, and r = –0.296, P = .033 in females; Fig. 2). The percent body fat and total infused doses of propofol per TBW until LOC was also linearly correlated (r = –0.567, P < .001 in males, and r = –0.491, P < .001 in females; Fig. 3).

There were no significant differences in BIS values between the 2 groups at each time point (Fig. 4). Mean arterial pressures and heart rates were not statistically different between the 2 groups at each time point (Figs. 5 and 6).

4. Discussion

Propofol is the most frequently used hypnotic agent for sedation as well as for induction and maintenance of general anesthesia. It is a preferred anesthetic drug due to its rapid onset and offset, and relatively short context-sensitivity half-life.[12] Propofol can be used safely even in patients with an underlying medical conditions such as hepatorenal dysfunction or bronchial asthma.[13] Furthermore, it prevents postoperative nausea and vomiting, and presents a sense of well-being followed by awakening.[14] When administered, it rapidly crosses the blood-brain barrier and manifests its pharmacological effect by potentiating GABA, an inhibitory neurotransmitter, at the $GABA_A$ receptor.[2,15] However, propofol has an unpredictable pharmacologic interindividual variation, and has narrow therapeutic index which makes difficult to optimize the dose. The currently available adult pharmacokinetic models of propofol are Schnider and Marsh models. Those are preprogrammed in the TCI system that allow a continuous infusion of propofol at a constant plasma or effect-site concentration. However, the concentrations achieving the desired level of hypnosis are variable due to its interindividual pharmacologic difference.

In the current study, the average Ce_{LOC} of propofol were 3.5 and 3.4 μg/mL in male and female, respectively, in high adiposity group. The average Ce_{LOC} of propofol were 3.9 and 3.8 μg/mL in male and female in normal (body composition) group. In previous studies, 90% effective concentration (Ce90; plasma concentration associated with 90% probability of LOC) of propofol was 4.34 μg/mL, and Ce95 was 5.4 μg/mL.[16] The results are quite lower than the previous studies.[16,17] The discrepancy may come from methodological difference. The previous studies directly measured plasma concentration of propofol, but the current study calculated effect-site concentration from preprogrammed TCI system.

The current study showed that body composition characteristics might affect the pharmacology of propofol. The required

Table 1

Patient characteristics including body composition measures in the high and normal adiposity groups.

	High adiposity group (n = 42)	Normal adiposity group (n = 54)	*P*
Number of patients			
Male	20	24	
Female	22	30	
Age (yr)			
Male	45.5 (29.0–60.8)	39.5 (23.8–52.5)	.316
Female	51.5 (44.0–56.5)	53.5 (43.0–61.8)	.373
Body weight (kg)			
Male	74.7 (68.0–87.9)	68.0 (63.3–73.8)	.016*
Female	69.1 (58.6–80.8)	54.8 (52.0–57.9)	<.001*
BMI (kg/m^2)			
Male	26.1 (24.7–28.9)	22.8 (21.7–24.8)	<.001*
Female	28.9 (25.1–32.3)	22.2 (21.2–23.5)	<.001*
Body fat mass (kg)			
Male	16.1 (12.8–20.7)	7.3 (4.8–10.4)	<.001*
Female	23.9 (20.8–32.6)	14.6 (11.5–17.2)	<.001*
Percent body fat (%)			
Male	22.1 ± 4.1	10.7 ± 4.1	<.001†
Female	36.5 (34.5–39.8)	26.3 (22.5–29.7)	<.001*
Skeletal muscle mass (kg)			
Male	33.7 (30.9–37.1)	34.5 (32.0–37.4)	.823
Female	24.1 ± 4.8	22.7 ± 3.2	.216
Fat-free mass (kg)			
Male	59.0 ± 11.8	61.5 ± 7.3	.391
Female	45.0 (38.2–50.2)	40.0 (38.4–44.5)	.251
Extracellular water (L)			
Male	16.1 (14.7–18.3)	16.6 (14.8–17.6)	.814
Female	12.5 (10.8–13.6)	11.2 (10.7–11.7)	.105
Total body water (L)			
Male	75.6 ± 13.4	76.5 ± 9.9	.808
Female	57.5 (49.4–63.8)	50.9 (49.2–56.5)	.208

Data are presented as numbers, median (interquartile range) or mean ± standard deviations.

BMI = body mass index.

*P < .05 by Mann–Whitney rank-sum test.

†P < .05 by 2-tailed t test.

Table 2

Pharmacologic effect of propofol in the high and normal adiposity groups.

	High adiposity group (n = 42)	Normal adiposity group (n = 54)	*P*
Effect-site concentration at LOC (μg/mL)			
Male	3.5 ± 0.4	3.9 ± 0.6	.020*
Female	3.4 (2.9–3.5)	3.8 (3.3–3.9)	.006†
Total infused dose per TBW until LOC (mg/kg)			
Male	2.2 ± 0.5	2.7 ± 0.7	.023*
Female	1.9 (1.6–2.2)	2.5 (2.0–3.0)	.006†
BIS value at LOC			
Male	70.0 (61.8–77.8)	71.5 (58.5–80.0)	.897
Female	68.1 ± 9.8	69.5 ± 9.5	.605
The elapsed time to ROC (min)			
Male	12.5 (8.0–17.8)	13.5 (8.3–18.0)	.841
Female	7.0 (4.8–12.3)	7.0 (4.8–11.0)	.703
Effect-site concentration at ROC (μg/mL)			
Male	1.4 (1.3–1.5)	1.4 (1.0–1.6)	.924
Female	1.8 (1.4–1.9)	1.9 (1.4–2.2)	.316
BIS value at ROC			
Male	73.3 ± 11.0	67.0 ± 12.7	.091
Female	68.7 ± 7.3	71.0 ± 8.1	.309

Data are presented as means ± SD and median (interquartile range).

BIS = bispectral index, LOC = loss of consciousness, ROC = recovery of consciousness, SD = standard deviation, TBW = total body weight.

*P < .05 by 2-tailed t test.

†P < .05 by Mann–Whitney rank-sum test.

dose of propofol for LOC was significantly lower in the high adiposity group than in the normal group. The reason why LOC achieved with a lower dose of propofol in the population with excessive body fat can be explained is in relation to the decreased central volume of distribution. In the obese population, the proportion of lean body mass (fat-free mass) per TBW may decrease, because the increased extent of fat tissue is greater.[18] The central volume of distribution includes plasma and highly perfused organs such as brain, liver, and kidney. Because central volume of distribution is embraced by lean

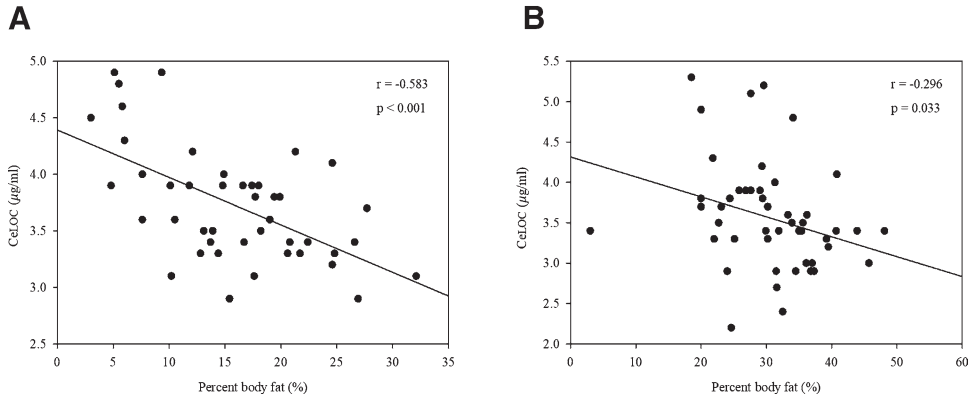

Figure 2. Relationship between percent body fat and effect-site concentration of propofol at loss of consciousness. (A) Male. (B) Female. Ce_{LOC} = effect-site concentration of propofol at loss of consciousness.

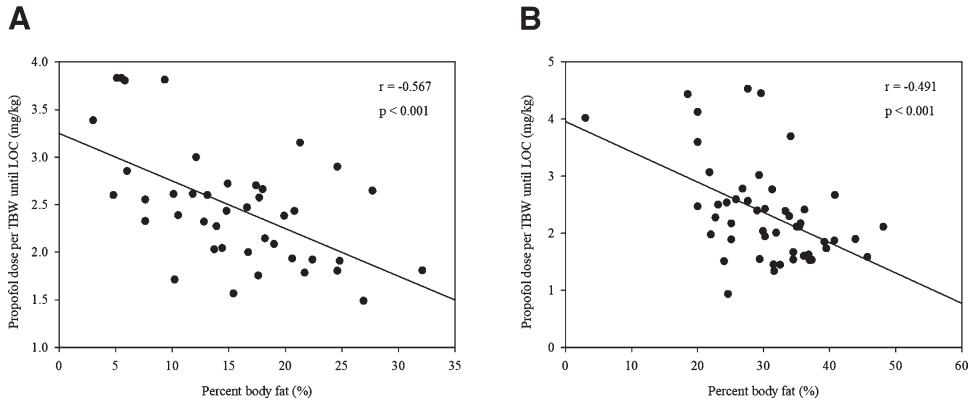

Figure 3. Relationship between percent body fat and required dose of propofol per total body weight for loss of consciousness. (A) Male. (B) Female. LOC = loss of consciousness, TBW = total body weight.

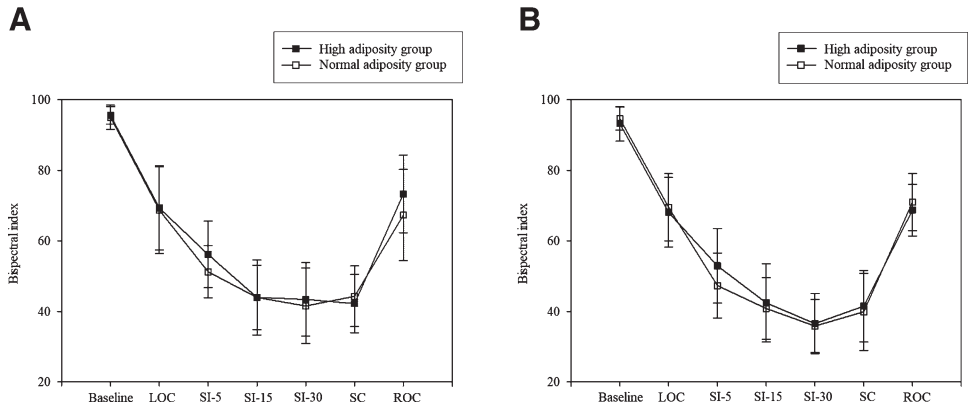

Figure 4. The changes of bispectral index. (A) Male. (B) Female. LOC = loss of consciousness, ROC = recovery of consciousness, SC = skin closure, SI-5 = 5 minutes after skin incision, SI-15 = 15 minutes after skin incision, SI-30 = 30 minutes after skin incision.

body weight, the volume in proportion of TBW is relatively less in obese population. There were several studies that presented body fatness affect the pharmacology of propofol. Ingrande et al[19] and Subramani et al[20] suggested that lean body weight is more appropriate dosing scalar for propofol in morbidly obese patients. The other studies reported propofol requirement for LOC is better correlated with lean body weight than TBW[21] and percent body fat is an important factor for predicting awakening from unconsciousness.[22] However, the previous studies calculated lean body weight by formula or measured percent body fat using thickness of skinfolds. The current study showed negative linear relationships between percent body fat and the required target concentration or dose of propofol for LOC, respectively. It is noteworthy that this investigation first demonstrated these relationships by analyzing body composition quantitatively using BIA methods.

The author hypothesized that recovery from unconsciousness may be slower in the high adiposity group following continuous infusion of propofol, because a large amount of body fat can act as a reservoir for propofol. However, there was no difference in the recovery profile of propofol between the high and normal adiposity groups. Although the continuous release of the drug from slow equilibrating compartment include adipose tissue into plasma, the rapid metabolism of propofol by the liver

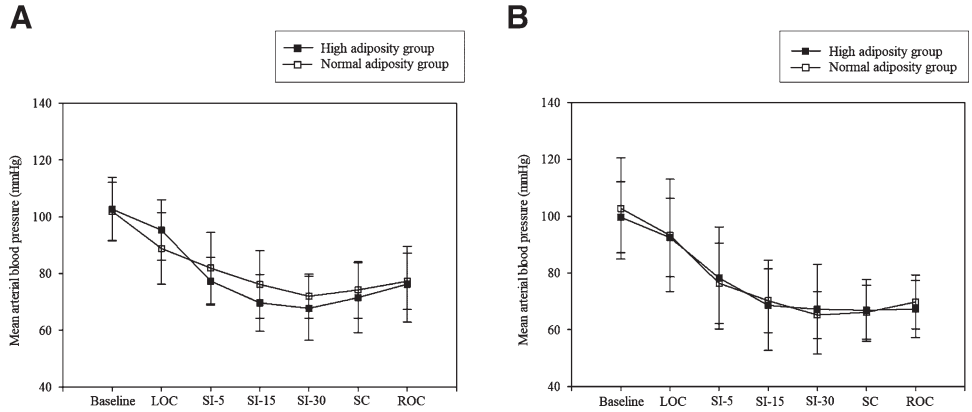

Figure 5. Mean arterial pressures. (A) Male. (B) Female. LOC = loss of consciousness, ROC = recovery of consciousness, SC = skin closure, SI-5 = 5 minutes after skin incision, SI-15 = 15 minutes after skin incision, SI-30 = 30 minutes after skin incision.

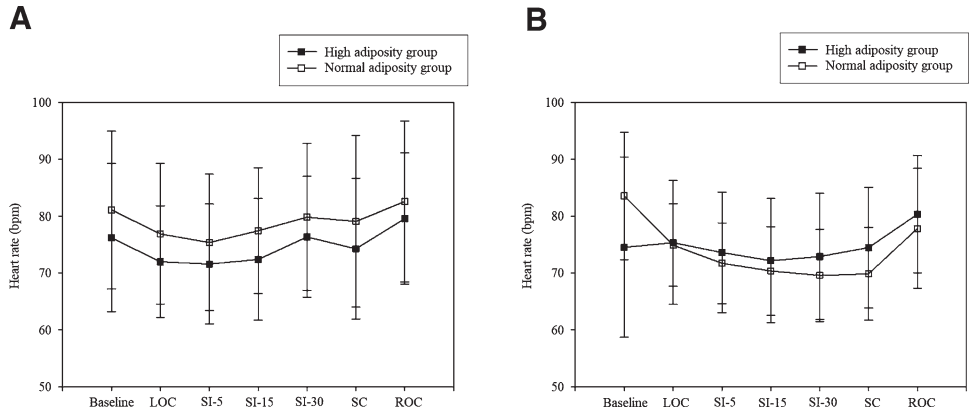

Figure 6. Heart rates. (A) Male. (B) Female. LOC = loss of consciousness, ROC = recovery of consciousness, SC = skin closure, SI-5 = 5 minutes after skin incision, SI-15 = 15 minutes after skin incision, SI-30 = 30 minutes after skin incision.

can decline plasma concentration to the arousal level in several minutes in clinical anesthesia practice.[15] Therefore, the recovery from unconsciousness would not be affected by the amount of fat tissue in the current study.

The Marsh pharmacokinetic model, used in the current study, is based on the experiments of average population, and the model uses TBW as a size descriptor.[23] This model uses the assumptions that the volume of distribution and clearance of propofol are directly proportional to TBW. Although this most widely used pharmacokinetic model for propofol provides a clinically acceptable predictive performance of the drug concentration during anesthesia, uncertainty still exists due to the TBW-based dosing algorithm.[24] However, the possibility of higher concentration than the predicted value by TCI system in the high adiposity group cannot be ruled out. Several previous studies showed Marsh pharmacokinetic model is prone to error in dosing propofol, especially in obese population.[25–29] In the current study, consistent with previous studies, the required effect-site concentration of propofol to achieve LOC was lower in the high adiposity group. It is thought that the relatively small volume of distribution in the obese population is not applied in the Marsh model. In the present study, alternative pharmacokinetic models such as integrating body fatness, allometric, or lean body mass scaling have been developed.[28,30,31] In the future, new pharmacokinetic models applying body composition would be required.

This study has a limitation. The effect-site (brain) concentration displayed in the TCI system is not an actual measurement of the drug concentration, but a calculated value through the pharmacokinetic model preprogrammed in the TCI device. Therefore, it may not accurately reflect the actual drug concentration in the brain.

In conclusion, the pharmacologic effects of propofol may be affected by body fatness. The concentration of propofol using a TCI system may be diminished in patients with a high proportion of body fat.

Author contributions

Conceptualization: Seonghoon Ko.
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Investigation: A Ram Doo, Min Jong Ki, Seong Ok Park.
Supervision: Seonghoon Ko.
Writing – original draft: A Ram Doo.
Writing – review & editing: A Ram Doo, Jun Ho Lee, Seonghoon Ko.

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