Female Patients Require a Higher Propofol Infusion Rate for Sedation

Shigeru Maeda, DDS, PhD,* Yumiko Tomoyasu, DDS, PhD,† Hitoshi Higuchi, DDS, PhD,* Yuka Honda, DDS,* Minako Ishii-Maruhama, DDS, PhD,* and Takuya Miyawaki, DDS, PhD†

*Department of Dental Anesthesiology, Okayama University Hospital, Okayama, Japan, and †Department of Dental Anesthesiology and Special Care Dentistry, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Sedation may minimize physiologic and behavioral stress responses. In our facility, the infusion rate of propofol is adjusted according to the bispectral index (BIS) in all cases of implant-related surgery; multivariate analysis of retrospective data enabled us to extract independent factors that affect the dose of propofol in sedation that are considered useful indicators for achieving adequate sedation. The study population comprised all patients undergoing implant-related surgery under intravenous sedation in Okayama University Hospital from April 2009 to March 2013. The infusion rate of propofol was adjusted to maintain the BIS value at 70–80. The outcome was the average infusion rate of propofol, and potential predictor variables were age, sex, body weight, treatment time, and amount of midazolam. Independent variables that affected the average infusion rate of propofol were extracted with multiple regression analysis. One hundred twenty-five subjects were enrolled. In the multiple regression analysis, female sex was shown to be significantly associated with a higher average infusion rate of propofol. Females may require a higher infusion rate of propofol than males to achieve adequate sedation while undergoing implant-related surgery.

Key Words: Sedation; Propofol; Sex; Implant.

Sedation is useful for minor oral surgery because it helps prevent excessive increases in blood pressure and heart rate and reduces mental stress arising from the surgery.^{1–3} This is a significant benefit for both the patient and the operator. However, if the sedative level goes beyond moderate sedation, airway problems may arise, and deep sedation may also lead to a delay in recovery from sedation. In addition, implant surgery often takes longer than tooth extraction, and maintaining an adequate sedation level for longer procedures can be challenging. Thus, it is important to monitor the level of

sedation precisely during minor oral surgery if moderate sedation is the goal.

Sedation levels are usually subjectively evaluated using the reaction to a verbal command, observing the respiratory condition during surgery,^{4,5} and monitoring signs such as blood pressure, heart rate, and noninvasive arterial hemoglobin oxygen saturation. The bispectral index (BIS), an objective assessment tool for the prevention of intraoperative awareness during general anesthesia, has also recently been used to evaluate sedation levels.^{6–9} However, mainly because of the high cost of BIS, it is not standard equipment for sedation during dental treatment.

In our facility, sedation for implant-related surgery is performed with a continuous infusion of propofol, and the infusion rate is adjusted according to BIS in all cases. Thus, we hypothesized that a multivariate analysis of

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Address correspondence to Dr Shigeru Maeda, Department of Dental Anesthesiology, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8525, Japan; maedas@md.okayama-u.ac.jp.

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retrospective data would enable us to extract independent factors that affect the dose of propofol in sedation. The factors identified in this study are considered useful indicators of sedation for minor oral surgery even when BIS is not available.

METHODS

Study Design/Sample

This is a retrospective observational study in which the study population comprised all patients who underwent implant-related surgery under intravenous sedation in the Okayama University Hospital from April 2009 to March 2013.

Variables

The outcome variable was the average infusion rate of propofol. The potential predictor variables were age, sex, body weight, treatment time, and amount of midazolam.

Anesthetic Procedure and Data Collection Methods

Written informed consent was obtained before sedation. The patients were allowed no food for 6 hours and no water for 2 hours preoperatively. Intravenous sedation began with the insertion of an intravenous line. This was followed by injection of midazolam until the BIS value reached 70–80. This value was obtained when patients were at a score of 3–4 (score 3: responds only after name is called loudly and/or repeatedly; score 4: lethargic response to name spoken in a normal tone) on the Modified Observer's Assessment of Alertness/Sedation Scale (data not shown). Then, a continuous infusion of propofol was started, using a Terufusion Syringe Pump TE-371 (Terumo, Tokyo, Japan), in which Diprifusor target-controlled infusion software (Graseby, London, UK) is incorporated. During treatment, the target-controlled infusion value was adjusted to maintain a BIS value of 70–80.

Patients were continuously monitored via electrocardiograph, blood pressure, and arterial hemoglobin oxygen saturation levels. Oxygen was administered at 2 L/min through a nasal cannula. During treatment, a local anesthetic containing 2% lidocaine and 1:80,000 adrenalin was used as needed. After treatment, the infusion of propofol was terminated.

The sedation was managed by dental anesthesiologists certified by the Japanese Dental Society of Anesthesiology. The patients' information was anonymized and stored appropriately. This study was approved (No. 671) by the Ethics Committee at the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and conducted in accordance with the Helsinki Declaration.

Data Analysis

Data were analyzed using JMP 9.0.0 software (SAS Institute Inc, Cary, NC). Student's *t* test was used to compare the outcome variable (average infusion rate of propofol) and the sex difference, while linear regression was used to perform the bivariate regression analysis between the outcome variable and the continuous variables. To extract the variables that independently affected the primary outcome, potential predictors were selected using stepwise regression, for which the cutoff was a *P* value <.20, followed by multiple regression analysis. Confounding factors were examined using Fisher exact test.

RESULTS

One hundred twenty-five subjects (36 male, 89 female; mean age, 56.4 years) were enrolled in this study. All subjects were American Society of Anesthesiologists physical status 1 or 2. The average infusion rate of propofol was 51.0 ± 25.8 $\mu\text{g/kg/min}$ (mean $\pm$ standard deviation [SD]). Female sex was found to be significantly associated with a higher average infusion rate of propofol. The average infusion rate in male patients was 44.1 ± 16.0 $\mu\text{g/kg/min}$ (mean $\pm$ SD), whereas in female patients it was 54.7 ± 19.8 $\mu\text{g/kg/min}$ (mean $\pm$ SD; Figure 1).

Mean body weight, mean midazolam dose, and treatment time were 58.6 kg, 48.7 $\mu\text{g/kg}$, and 124.9 minutes, respectively. Among the 4 continuous variables analyzed in this study, only body weight was found to be significantly (negatively) correlated with the average infusion rate of propofol (Table 1).

Prior to standard least-squares multiple regression analysis, age and female sex were selected using stepwise regression. In the subsequent multiple regression analysis, female sex was shown to be significantly associated with the average infusion rate of propofol (Table 2).

In an examination of the relationship between body weight and sex, it was found that a significantly lower body weight was associated with female sex (Figure 2).

Figure 1. Differences in average infusion rate of propofol by sex. Data are mean $\pm$ SD; $n = 36$ and 89 for male and female, respectively. * $P < .01$.

DISCUSSION

In general anesthesia, females are reported to experience earlier emergence than males.^{10,11} In this sedation study, female sex was shown to be an independent factor affecting the average infusion rate of propofol. This result indicates that a higher dose of propofol per body weight is generally necessary in female patients to maintain the same level of sedation as in males. That is, a lower dose is likely to maintain adequate sedation in male patients. This finding, if supported by future prospective studies, should contribute to performing safer and more effective sedation.

There are conflicting reports that propofol plasma concentration is lower in female patients than in male patients when the infusion rate is set at a stable rate per kilogram of body weight,^{12,13} whereas there is no significant sex difference in measured propofol concentration for 50% loss of consciousness.¹⁴ Thus, the lower plasma concentration of propofol may promote earlier recovery in females. Although this difference in plasma concentration is suggested to result from a difference between males and females in the metabolism of propofol,¹⁵ the exact mechanism remains unclear. By contrast, Schnider et al^{16,17} established a model of the pharmacokinetics of propofol in which the difference

Table 2. Stepwise Logistic Regression Models for Average Infusion Rate of Propofol*

Variable	Estimate	SE	t Ratio	P Value (Prob> t)
Intercept	70.061	9.394	7.46	<.001†
Age	−0.320	0.166	−1.93	.056
Female sex	4.978	1.836	2.71	.008†

* $R^2 = .114$.

† Significant parameter.

between the plasma concentration of propofol in males and females is adjusted to some extent by using different formulae for lean body mass but not taking sex differences in the metabolism of propofol into account.

Although body weight was significantly and negatively correlated with the average infusion rate of propofol in this study, it was not shown to be an independent predictor, because lower body weight is a confounding factor of female sex. Age was significantly correlated with the primary outcome but was neither an independent predictor nor a confounding factor in regard to the sex of subjects. Because the elimination of propofol is slower in the geriatric population,^{18,19} the elimination rate of propofol is considered to decrease along with aging. However, because of a narrow age range, a small sample size, and an unequal sex ratio, significant modification by age might be masked in this study. In addition, midazolam was not shown to be an independent factor affecting the injection rate of propofol in this observational study, but it can be a factor if a high dose of midazolam is used. To assess the impact of midazolam, a prospective study in which only propofol is used should be performed on participants from a wide age range.

There were significantly more female than male subjects in this retrospective study. The reason for this may be related to an inconvenient opening hour of our hospital, which may have made it more difficult for full-time workers, in which men predominate in Japan, to attend surgery. Or a higher rate of female patients might desire sedation during implant surgery. In this study, we used the BIS value as a standard. However, since BIS values are known to be affected by head and neck surgery, especially under moderate sedation, some inaccuracies may have resulted.

Table 1. Continuous Variables and Their Relationship to Average Infusion Rate of Propofol

Variable	Average	SD	Correlation	Confidence Interval		P Value
				Lower 95%	Upper 95%	
Age, y	56.4	10.1	−.185	−0.350	−0.010	.039*
Body weight, kg	58.6	10.7	−.216	−0.378	−0.042	.015*
Midazolam, μg/kg	48.7	21.1	.131	−0.045	0.300	.145
Treatment time, min	124.9	34.7	−.162	−0.329	0.014	.014*

* $P < .05$.

Figure 2. Differences in body weight by sex. Data are mean $\pm$ SD; $n = 36$ and 89 for male and female, respectively. * $P < .01$.

In conclusion, a higher infusion rate of propofol is likely to be required in females than in males to achieve adequate moderate sedation.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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