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Research Article

Induction Dose of Thiopental Sodium for Pediatric Sedation during Radiologic Examination

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- Sedation; Thiopental; Children; Pediatric; Radiological examination

Abstract

Objective: The dose of thiopental sodium for pediatric sedation has been determined mainly based on the patient's weight. However, children's demographic characteristics other than the weight can affect the sedative effect of thiopental sodium. The purpose of this study was to determine the demographic characteristics that affect the induction dose of thiopental sodium for pediatric sedation.

Methods: We performed a retrospective chart review of children (<18 years of age) who underwent computed tomography/magnetic resonance imaging between January 2011 and August 2016 at a single tertiary medical center. We collected data on the demographics and the thiopental dose in children in whom sedation was successfully induced, without complications related to thiopental sodium. Regression analysis was performed to evaluate the relationship between the dose of thiopental sodium and the demographics.

Results: A total of 819 children who underwent successful sedation were included in the regression analysis. Weight, height, body surface area (BSA), and age were significantly correlated with the induction dose of thiopental sodium. Based on the multiple regression analysis, the equation for determining the induction dose of thiopental sodium for pediatric sedation was derived as follows: -8.153 + 0.799 × age (month) + 153.844 × BSA.

Conclusions: Not only weight but also age, height, and BSA should be considered for determining the induction dose of thiopental sodium for pediatric sedation by using the proposed regression equation. However, further clinical research should be performed to validate the equation.

ABBREVIATIONS

CT: Computed Tomography; MRI: Magnetic Resonance Imaging; ECG: Electrocardiography; ASA: American Society of Anesthesiologists; NIBP: Non-Invasive Blood Pressure; BSA: Basal Surface Area

INTRODUCTION

Children cannot always be expected to cooperate when undergoing diagnostic tests or procedures. Thus, sedation may be necessary to calm the patients and relieve their anxiety [1,2].

Physicians have found it challenging to determine the appropriate dose for pediatric sedation. If the dose is insufficient to achieve sedation, the diagnostic test or procedure may be unsuccessful. The failure of sedation may result in delayed testing, incorrect findings, and failure of the procedure. Furthermore, unexpected movement of the child may affect safety and cause accidents. Conversely, an excessive dose of sedatives may cause severe side effects, such as airway obstruction, apnea, hypotension, and cardiac arrest [3]. Therefore, it is crucial to address the lack of a fully established method for determining the appropriate dose for pediatric sedation [4].

Currently, the sedatives used in pediatric sedation include propofol, thiopental sodium, ketamine, and midazolam. Among these sedatives, thiopental sodium is useful for children undergoing short procedures because it is a rapid-onset, short-acting barbiturate [5]. Furthermore, thiopental sodium provides effective sedation during magnetic resonance imaging (MRI) and is a cost-effective alternative to other commonly used agents. Nevertheless, the recommended dose of thiopental sodium used for pediatric sedation has a broad range (2-5 mg/kg) and is based only on the weight of the patient [6]. However, pharmacokinetic parameters of thiopental sodium, such as its volume of distribution and clearance, have been reported to change as children grow. Therefore, the dose of thiopental for pediatric sedation should be determined based not only on weight, but also on other demographics of children, such as height and age. The aim of this study was to investigate the demographic characteristics that affect the dose of thiopental sodium for pediatric sedation.

MATERIALS AND METHODS

This was a retrospective study that analyzed the medical records of children (aged 0 ~ 18 years) with an American

Society of Anesthesiologists (ASA) classification of 1 or 2 and who had undergone successful sedation with thiopental sodium for computed tomography (CT) or magnetic resonance imaging (MRI) examination in a single tertiary hospital with institutional review board approval from June 1, 2011 to August 31, 2016. Patients were excluded from the analysis if they received any sedatives other than thiopental sodium before or during the examination, or if respiratory infection or uncorrected heart disease were evident.

Protocol of pediatric sedation

Each patient underwent the following protocol during sedation for radiologic examinations. After the patient and their parents entered the CT or MRI room, a pulse oximeter, electrocardiograph machine, non-invasive blood pressure cuff, and end-tidal CO_2 monitor were attached to the patient and corresponding parameters were monitored every 5min during the examination. After 0.004mg/kg of glycopyrrolate was intravenously administered, the patient received an intravenous bolus injection of 2 mg/kg of thiopental sodium.

The loss of consciousness was confirmed based on 1) the lack of eyelash reflex or 2) the fitting of a facial mask without resistance. The sedation level was evaluated using a modified Ramsay Sedation Scale and maintained at 4–6 points during the radiologic examination. If the loss of consciousness was not achieved, an additional bolus injection of 2mg/kg of thiopental sodium was administered at 1-min intervals until the patient lost consciousness. If the patient recovered consciousness or movement occurred during the examination, an additional dose (1 mg/kg) of thiopental sodium was injected and the patient was excluded from the study.

After the radiologic examination, the patient was moved and during recovery from sedation, oxygen and hemodynamic monitoring was performed in a pediatric sedation center. Patient discharge was decided upon when the hemodynamic value could be maintained within 20% of the value before sedation, when the modified Aldrete recovery score was > 9, when consciousness of the patient was fully recovered, and when water could be consumed without nausea or vomiting.

Data collection

Data were collected from electronic medical records, including demographic information (sex, age, weight, height, and body surface area [BSA]), the diagnosed disease, the type of radiologic examination, the duration of the examination, the initial and any additional doses of thiopental sodium, and the administration time of thiopental sodium. The incidence of any complications was also recorded, such as respiratory depression, airway obstruction, hypotension, bradycardia, or aspiration. In the present study, BSA was defined using the following formula:

$$\sqrt{\text{Weight}(\text{kg}) \times \text{Height}(\text{cm}) / 3600}.$$

The induction dose of thiopental sodium was defined as the total dose administered until the patient lost consciousness. Respiratory depression was defined as the presence of desaturation (SpO_2 < 90%), hypercapnia (E_TCO_2 > 50 mmHg), and apnea. Hypotension or bradycardias were measured against the normal values for blood pressure and pulse rate, respectively, for the patient's age. Successful sedation was defined as unconsciousness achieved with the administration of thiopental sodium, without interruption of the examination because of recovery of consciousness or substantial movement, and without complications during the examination. Only the data from cases of successful sedation were included in the regression analysis.

Data analyses

The relationship between sex, age, weight, height, BSA, and the induction dose of thiopental sodium was evaluated using simple linear regression. A regression equation was then proposed based on the results of multiple regression analysis. Prior to the multiple linear regressions, the variance inflation factor (VIF) between sex, age, weight, height, and BSA was estimated to detect multiple collinearity; a VIF > 10 indicated multiple collinearity. Sex, age, weight, height, or BSA exhibiting multiple collinearity could not be analyzed simultaneously in a single model; therefore, variables without multiple collinearity were analyzed using different models. The model was visually inspected for linearity, heteroscedasticity, and normality of residuals. Additionally, studentized residual analysis was performed to verify normal distribution and iso-dispersion of residuals. A probability–probability plot (P-P plot) was drawn to evaluate the skewness of distribution. Statistical analyses were performed using Statistical Analysis Software (version 9.4, SAS Inc., Cary, NC, USA).

RESULTS

After review of the medical records of cases of pediatric sedation with thiopental sodium, a total of 819 cases were defined

Table 1: Characteristics of children of the 819 children included in present study.

Demograhics	n = 819
Gender	
Male	435 (53.1%)
Female	384 (46.9%)
Median age, month	19.9 (9.25 – 36.3)
Median weight, kg	10.4 (8-14)
Median height, cm	80.4 (68-94)
Median BSA , m^2	0.51 (0.4-0.63)
ASA class	
I-II	744 (90.8%)
III	75 (9.2%)
Examination	
CT	682 (83.3%)
MRI	137 (16.7%)
CT+MRI	0 (0.0 %)
Imaging site	
Brain	476 (58.1%)
Head & Neck	142 (17.3%)
Spine	182 (22.2%)
Others	23 (2.4%)

Values are median (IQR) or number (%)
Abbreviations: ASA: American Society of Anesthesiologists; BSA; Basal Surface Area; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

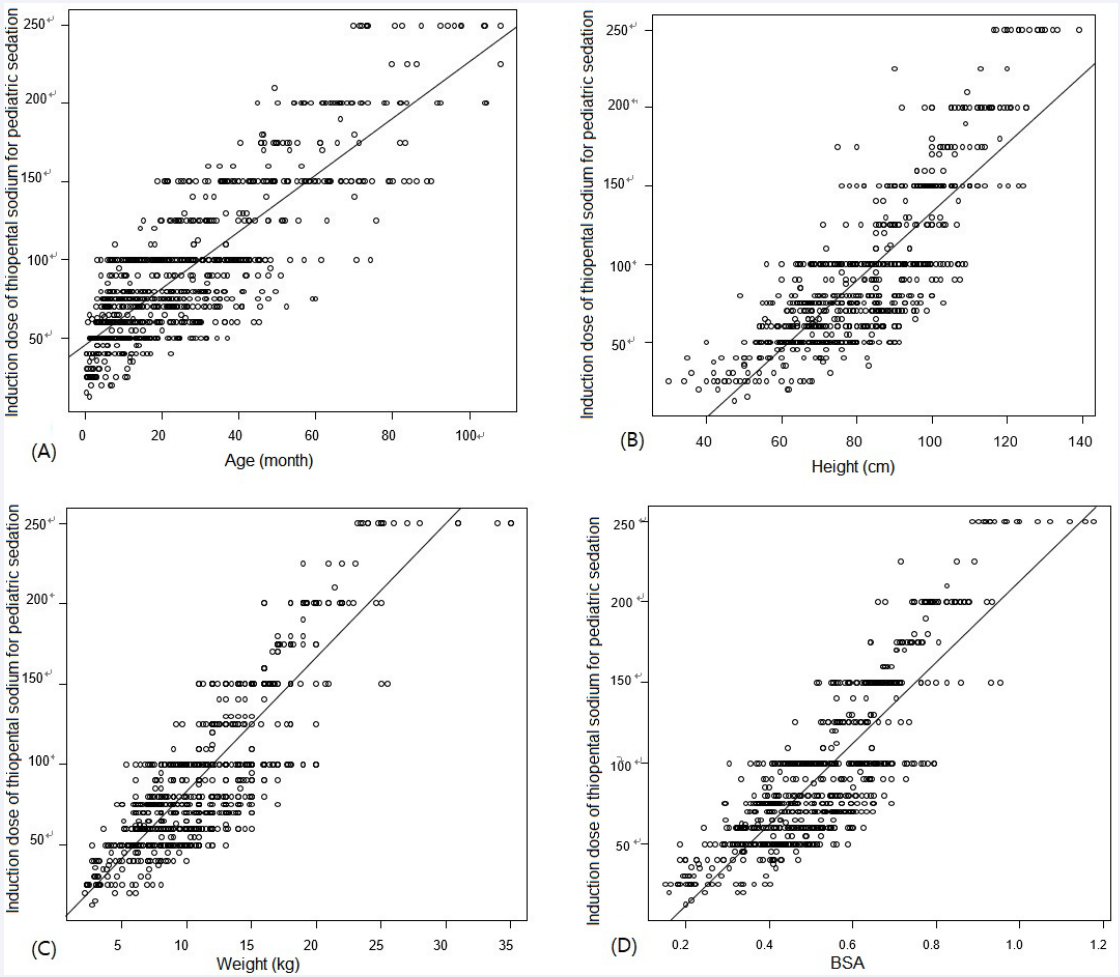

Figure 1 Simple linear regression between demographic characteristics and the dose of propofol needed to induce sedation in children undergoing radiological examinations. (A) Age, (B) height, (C) weight, and (D) body surface area (BSA).
BSA: body surface area

Table 2: Simple linear regression analysis between demographic data and dose of thiopental sodium required to induce sedation for children during radiologic examinations.

	Dose of thiopental sodium to induce sedation	
	β (SE)	*p*-value
Sex	0.729 (3.108)	0.815
Age(months)	1.808 (0.041)	<0.001
Height(cm)	2.183 (0.056)	<0.001
Weight(kg)	8.307 (0.172)	<0.001
BSA(m^2)	251.835 (5.572)	<0.001

BSA: Basal surface area

Table 3: Regression equations describing dose of thiopental sodium needed to induce sedationbetween age and other demograhics (height, weight and BSA).

Variable	equation	Adjusted R^2
Age, height	-8.84 + 1.98 × Age (months) + 0.86 × Height (cm)	0.709
Age, weight	14.15 + 0.80 × age (months) + 5.12 × Weight (kg)	0.738
Age, BSA	-8.15 + 0.78 × age (months) + 153.84 × BSA (m^2)	0.739

BSA: Basal surface area

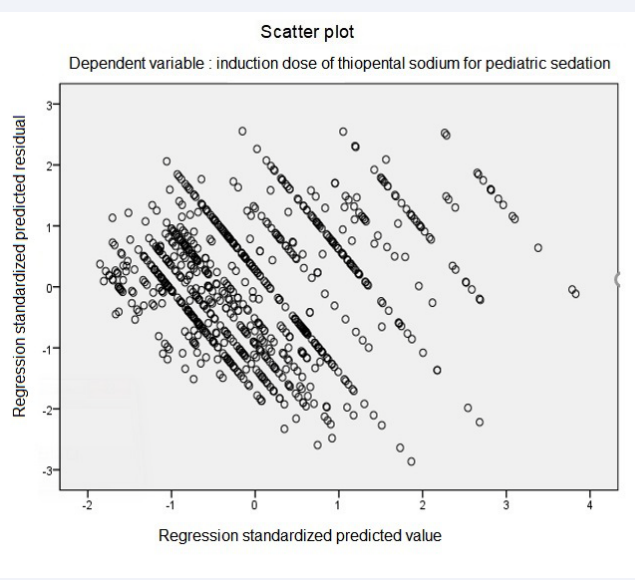

Figure 2 Residual plot of standardized and predicted values Dependent variable: induction dose of thiopental sodium for pediatric sedation.

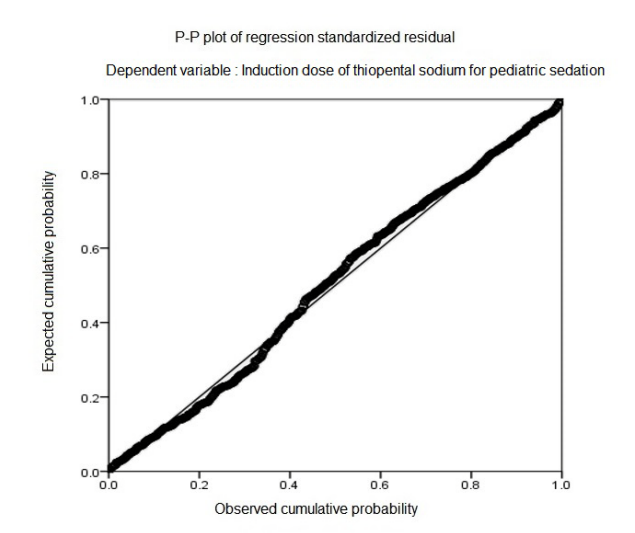

Figure 3 Probability–probability plot for the induction dose of thiopental sodium in children undergoing radiological examinations. Dependent variable: induction dose of thiopental sodium for pediatric sedation.

as having successful sedation and included in the regression analysis. The demographic data of patients are shown in Table 1.

The results of simple linear regression analysis between the pediatric sedation dose of thiopental sodium and each characteristic of the children, including sex, age, weight, height, and BSA, are described in Table 2. Age, weight, height, and BSA showed significant correlations with the pediatric sedation dose of thiopental sodium ($p< 0.001$). A scatter plot of the relationships between the pediatric sedation dose of thiopental sodium and each characteristic of the children is shown in Figure 1, in which the sloping line representing the dose of thiopental sodium increases with increasing age (A), weight (B), height (C), and BSA (D).

The VIFs of age, weight, height, and BSA were estimated at 5.833, 76.872, 254.889, and 533.184, respectively. The VIFs of weight, height, and BSA were determined to detect multiple collinearity, and were therefore impossible to analyze in the same model. Therefore, three models, including age and weight together, age and height together, and age and BSA together, were used, as shown in Table 3. The model including age and BSA together had the highest adjusted R-square value (0.739) and was therefore selected as the optimal equation for estimating the dose of thiopental sodium required to achieve successful sedation: induction dose of thiopental sodium (mg) = –8.153 + 0.799× age (months) + 153.844× BSA (m^2). In the equation, *p*-value of intercept, age and BSA was 0.064, < 0.001 and < 0.001 respectively.

In Figure 2, the dots appear to be random with no particular tendency, centering around zero. A P-P plot revealed that these points form a nearly linear pattern, indicating that normal distribution was a good model for this data set (Figure 3).

DISCUSSION

In this study, we reviewed the medical records of children successfully sedated with thiopental sodium and we performed a regression analysis on the relationship between the sedation dose and the different characteristics. The regression analysis showed that the sedation dose was significantly correlated with not only weight but also age, height, and BSA. Based on the multiple regression analysis equation, the formula for calculating the pediatric sedation dose of thiopental sodium was -8.153 + 0.799 × age (month) + 153.844 × BSA. This formula could help physician to determine the dose of thiopental sodium for pediatric sedation during radiologic examinations. However, physician should be careful of possible complications due to thiopental sodium in children.

In the current ASA guidelines, the thiopental dose for pediatric patients is based only on the weight of the child. However, weight may not reflect changes in the size and composition of the body as children grow. Previous studies have found that pharmacokinetic parameters, such as the volume of distribution and clearance, differ between adults and children [7-9]. It is reasonable that these aspects be considered when determining the dose of thiopental for pediatric sedation. As a result of simple regression analysis, we found that weight is not the only factor that affects the sedative effects of thiopental. Thus, the thiopental dose for pediatric sedation should be decided based not only on weight, but also on height, age, and BSA [10,11].

We performed the multiple regression analysis to evaluate how weight, height, age, and BSA affect the thiopental dose for pediatric sedation together. Based on the multiple regression analysis, a formula was developed to calculate the dose of thiopental sodium for pediatric sedation during radiologic examination. The formula was selected from among three regression models because it had highest value of R^2. In the present study, BSA was determined using the following equation:

$$\sqrt{\text{Weight}(\text{kg}) \times \text{Height}(\text{cm}) / 3600}$$

The formula used in present study suggested that age, weight, and height be considered together to determine the dose of thiopental sodium. The calculated dose means the dose of thiopental sodium administered in previous successful cases for children with same age, weight and height.

The formula developed in the present study can help physicians determine the dose of thiopental sodium for a successful pediatric sedation [12]. Because current guidelines for pediatric sedation propose a broad range of thiopental doses, deciding an appropriate dose can be challenging, particularly for physicians with less experience in pediatric sedation [6]. While, using the formula proposed in present study, physicians can calculate specific dose of thiopental sodium for children undergoing radiologic examinations. Because thiopental is not the first-choice drug for pediatric sedation, physicians have less experience using thiopental but it remains a useful sedative for pediatric sedation when propofol cannot be used (e.g.,, when there is a lack of availability, the patient has an allergy to the anesthetic, or when approval to use propofol in children cannot be granted [13]. The formula may be useful for these less experienced physicians to offer the referential dose of thiopental sodium based on the age and BSA of children [3].

The dose of thiopental sodium calculated using the formula developed in the present study is not an exact dose for inducing pediatric sedation. In our protocol, an initial loading dose of 2 mg/kg of thiopental sodium was administered, followed by an additional dose of 2 mg/kg at 1-min intervals until the loss of consciousness was achieved. In some children who need 3 mg/kg of thiopental sodium to achieve sedation, 4 mg/kg of thiopental sodium was injected because additional dose was 2 mg/kg. A greater dose of thiopental sodium than necessary to induce sedation may have been administered. Therefore, concern about the complications of thiopental, such as apnea and hypotension, may arise when using the formula developed in the present study.

However, this study was based on the medical records of children whose pediatric sedation was successful and without any complications associated with thiopental. Thus, complications of an excessive dose of thiopental sodium may be few when the dose of thiopental sodium is decided using the formula developed in the present study. Similarly, in the case of propofol, a high dose has proven effective for pediatric sedation without an increase of the adverse effects associated with propofol [2]. Nevertheless, physicians should monitor vital signs and respiratory function carefully because the possibility of an adverse event caused by a high dose of thiopental cannot be ruled out. Additional clinical studies assessing the clinical outcome when using the formula should be performed to prove the effect of the formula in pediatric sedation.

The dose of sedative drugs should be decided based on the type of examination or procedure because the required level of sedation differs accordingly. We only included cases of pediatric sedation during radiologic examinations such as MRI or CT, which require deep sedation to prevent any movement or analgesic effect during examination. It would be appropriate to apply the results of present study to children undergoing examination or procedures with the same sedation requirements. However, caution must be used when applying the results of the present study to examinations or procedures that need different levels of sedative or analgesic effect e.g., lumbar puncture, bone marrow aspiration, chemo port insertion).

The present study had several limitations. First, as a retrospective study, the data were collected from medical records of pediatric sedation, which are recorded in detail for quality improvement. Second, the medical records were recorded by a provider of pediatric sedation. Thus, it is possible that the data of the medical records could have been influenced by the recorder. Third, the data were collected from the medical records of children with an ASA classification of 1 or 2. Caution is necessary when applying the results of the present study to critically ill children who might be susceptible to complications caused by thiopental sodium. Fourth, possible effects of other medications that the children were taking on the sedative effect of thiopental sodium were not considered.

CONCLUSION

The induction dose of thiopental sodium for pediatric sedation during radiologic examinations should be determined based not only on weight but also on age, height, and BSA. The formula proposed in present study based on regression analysis might be used to calculate the referential dose of thiopental sodium to induce sedation in children undergoing radiologic examinations. Further clinical research to evaluate the clinical effectiveness of the formula developed in the present study should be performed to assess the outcomes.

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