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# Issues in Propofol Sedation for Pediatric Patients Using Target Control Infusion (TCI): Safety in Children 1-3 Years Old Versus Children Older than 3 Years of Age

**Tak Kyu Oh**[1], **Kyungho Kwon**[1], **Boram Park**[2] **and Woosik Eom**[1*]

[1]*Department of Anaesthesiology and Pain Medicine, National Cancer Centre, Republic of Korea*

[2]*Biometric Research Branch, Research Institute and Hospital, National Cancer Centre, Republic of Korea*

[*]**Corresponding author:** Woosik Eom, Department of Anesthesiology and Pain Medicine, National Cancer Center, 323, Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do 10408, Republic of Korea, Tel: +82-031-920-1703; Fax: +82-031-920-1465; E-mail: uchic@ncc.re.kr

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## Abstract

**Purpose:** Appropriate sedation is required when performing proton radiation therapy on pediatric patients. A target-controlled infusion (TCI) of propofol has recently been used for this purpose. However, there may be safety issues with the use of TCI in pediatric patients, as the initial bolus dose might be excessive for younger patients. To compare the safety and the incidence of adverse events between patients under and over 3 years of age undergoing sedation with a TCI (Paedfusor) model.

**Methods:** We performed a retrospective observational study by analyzing the medical records of patients who underwent a computer tomography simulation prior to beginning proton radiation therapy between January 2013 and December 2014. Patients were divided into those 1-3 years of age and those > 3 years of age. The incidence of adverse events was tabulated.

**Results:** Fifty-two patients-16 patients 1-3 years of age and 40 patients > 3 years of age-were included in the study. The adverse event incidence was the primary outcome. There was no statistically significant difference in desaturation ($p = 0.231$), nasopharyngeal airway insertion ($p = 0.366$), bradycardia ($p = 1.000$), and hypotension ($p = 0.578$). Additionally, there was no significant difference in sedation time, recovery time, propofol dose, and target concentration for induction or maintenance of anesthesia.

**Conclusions:** The use of propofol TCI for the induction and maintenance of sedation did not show an increased risk of adverse events in pediatric patients 1-3 years of age versus patients > 3 years of age.

**Keywords:** Propofol; Pediatrics; Manual infusion; Target-controlled infusion

## Introduction

When magnetic resonance imaging (MRI) or proton radiation therapy is performed on pediatric patients who are unable to cooperate, sedation is required. Propofol is widely used for sedation in such cases [1], however, the method of administration has undergone numerous changes. Previously, propofol was administered by repeated single infusions or continual infusion. However, pharmacokinetic advances have made it possible to use target-controlled infusion (TCI) techniques [2,3].

In the past, a continuous propofol infusion was not favored in pediatric patients between 1 month and 3 years of age because its safety had not been established. However, a study by Pessenbacher et al. in 2002 reported the use of propofol without problems in patients in this age group [4]. Subsequently, pharmacokinetic models were developed for efficient intravenous anesthesia and sedation in older pediatric patients as well. Sepúlveda et al. studied the use of various pharmacokinetic models for propofol administration in 1-26 month old pediatric patients, and reported the safety of propofol TCI use in these patients [5]. However, they concluded that most models overestimated the initial volume of distribution, and a larger than required initial bolus dose to reach the target concentration might be delivered [5] increasing the risk of adverse events. Furthermore, current data for the use of propofol sedation with TCI in pediatric patients less than 3 years of age is still lacking, and many clinicians in children's' hospitals still have concerns regarding the possibility of adverse events in these patients such as apnea, hypotension, and bradycardia. However, there have been no studies comparing the difference of risk for adverse events between children 1-3 years and children > 3 years of age. As a result, based on previous studies, using propofol TCI in patients under 3 years of age remains a challenge, since most pediatric TCI models have safety concerns regarding the large initial bolus required [4,5].

Therefore, the present study aimed to compare the safety and the incidence of adverse events with the use of propofol TCI to achieve sedation in pediatric patients 1-3 years of age versus patients > 3 years of age. We hypothesized that propofol sedation using TCI in pediatric patients 1-3 years would pose an increased risk of adverse events, because these younger patients might receive a larger initial bolus than needed and because younger patients have less predictable pharmacokinetics.

## Methods

The present study was a retrospective observational study conducted on pediatric patients requiring sedation while undergoing a computed tomography (CT) simulation for proton radiation therapy between January 2013 and December 2014. The analyses were conducted using electronic medical records with the approval of the Institutional Review Board for Health Science Research of the National Cancer Centre of Korea (IRB No. NCC2014-0026). Because it was retrospective observational study, the requirement for informed consent was waived by the IRB.

Children from 12-36 months old were classified into the young group, while children between 37 months and 15 years old were classified into the old group. The analysis was performed on pediatric patients who required sedation while undergoing a CT simulation before commencing proton radiation therapy. The children received proton radiation therapy about one week after CT simulation on an individual schedule using a target concentration determined by CT simulation [6]. Pediatric patients using opioid medication affecting their mental status were excluded from the data collection. Sedation was performed by an anesthesiologist in the Department of Anaesthesiology and Pain Medicine, National Cancer Centre, Korea. The sedation protocol for CT simulation was identical in all patients. Sedation was performed using propofol with a TCI protocol. The syringe pump used (Syramed uSP 6000, Acromed, Regensdorf, Switzerland) was compatible with the TCI Paedfusor model for sedation in pediatric patients aged 1-15 years old [7].

The patients underwent monitoring (non-invasive blood pressure monitoring, oxyhemoglobin saturation monitoring, electrocardiogram, and capnometry) appropriate for general anesthesia without premedication. Preparations were made for immediate endotracheal intubation and general anesthesia in the case of an emergency. After checking the initial vital signs, a continuous infusion of propofol 2% using TCI was commenced.

No patient had a history of prior propofol sedation, and the target concentration of propofol for induction started at 3 mcg/mL. When an appropriate level of sedation for the simulation was achieved with loss of consciousness and no patient movement, the target concentration was gradually increased for positioning and tight-mask fitting in 0.2 mcg/mL increments. The target concentration after completion of induction without breathing difficulties was defined as the target concentration for induction. After induction was complete, the patient's head was appropriately positioned for CT imaging, and during this time, the target concentration was gradually decreased towards the lowest concentration at which the patient was judged capable of maintaining self-respiration without movement. The adjusted dose was maintained until the end of the simulation. This concentration was defined as the target concentration for maintenance. For CT simulation all patients needed deep sedation at level -4 of the Richmond Agitation and Sedation Scale.

The primary outcome for this study was measuring the incidence of four types of adverse events: desaturation, nasal airway insertion, hypotension, and bradycardia. A desaturation event was defined as an oxyhemoglobin saturation dropping below 90% for at least 10 seconds, while nasopharyngeal airway insertion (Teleflex Medical Co., Westmeath, Ireland) was only performed when the patient was capable of self-respiration, but showed chest wall retraction or sleep apnea. Decreases in blood pressure or heart rate of more than 25% from the initial blood pressure and heart rate values immediately before sedation were defined as hypotension and bradycardia, respectively.

Sedation time was defined as the time from the start of the continuous infusion of propofol until the end of the infusion. Recovery time was defined as the time that sedation concluded to the time that the attending physician decided that the patient could leave the recovery room. According to the modified Aldrete scoring system, an appropriate state of consciousness, smooth breathing, normal cardiovascular vital signs, and normal movement were used as discharge criteria. The dose of propofol was recorded as the total amount of propofol used (mg) divided by the patient's body weight (kg) and sedation time (min).

### Statistical analysis

The characteristics of patients are summarized as median with 25th-75th interquartile ranges (IQR) for continuous variables, and frequencies with percentages for categorical variables. To compare the characteristics between groups, the Wilcoxon rank-sum test was used for continuous variables, and the Pearson chi-square test or Fisher's exact test was used for categorical variables. The primary outcome of the study was tested using the Fisher's exact test. The secondary outcomes were analyzed using the Wilcoxon rank-sum test. Significance was considered at two-sided significance level of 0.05. All statistical analyses were performed using the SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

Between January 2013 and December 2014, CT simulations for proton radiation therapy were performed for 56 pediatric patients, and all 56 patients were included in the retrospective analysis. Patient characteristics are summarized in Table 1. There was no difference in sex, proportion in prone position, and preterm delivery status between the young and old group, while there were significant differences between the two groups in the distribution of lesions, age (2.8 y vs. 6 y; $p < 0.001$), height (92.6 cm vs. 113.5 cm; $p < 0.001$) and weight (12.8 kg vs. 19.7 kg; $p < 0.001$).

| Characteristics | | Total (N = 56) | Young (N = 16) | Old (N = 40) | p-value |
|---|---|---|---|---|---|
| Sex | Female | 27 (48.2) | 6 (37.5) | 21 (52.5) | 0.310† |
| | Male | 29 (51.8) | 10 (62.5) | 19 (47.5) | |
| Age (Years) | median (IQR) | 6 (3-7) | 2.8 (2.7-3) | 6 (5-7) | |
| Height (cm) | median (IQR) | 105 (93.8-118.8) | 92.6 (86.6-97) | 113.5 (101.9-124.5) | |

| | | | | | |
|---|---|---|---|---|---|
| Weight (kg) | median (IQR) | 17.9 (13.7-22.9) | 12.8 (11.3-14.9) | 19.7 (17.0-25.5) | |
| Lesion | Eye | 6 (10.7) | 0 (0.0) | 6 (15.0) | 0.037‡ |
| | Abdomen | 1 (1.8) | 1 (6.3) | 0 (0.0) | |
| | Brain | 17 (30.3) | 7 (43.7) | 10 (25.0) | |
| | Brain with spinal cord | 31 (55.4) | 7 (43.7) | 24 (60.0) | |
| | Chest | 1 (1.8) | 1 (6.3) | 0 (0.0) | |
| Prone | No | 43 (76.8) | 12 (75.0) | 31 (77.5) | 1.000‡ |
| | Yes | 13 (23.2) | 4 (25.0) | 9 (22.5) | |
| Preterm | <=37 weeks | 6 (10.7) | 2 (12.5) | 4 (10.0) | 1.000‡ |
| | > 37 weeks | 50 (89.3) | 14 (87.5) | 36 (90.0) | |

† Pearson chi-square test
‡ Fisher's exact test
IQR = interquartile range

**Table 1:** Patient demographics.

There was no statistically significant difference between the young and the old group in the incidence of adverse events, the primary outcome (Table 2). There were no significant differences between the two groups in the incidence of desaturation events (6.3% vs. 0%; p = 0.286), nasopharyngeal airway use (18.8% vs. 12.5%; p = 0.676), incidence of bradycardia (6.3% vs. 7.5%; p = 1.000), or incidence of hypotension (6.3% vs. 12.5%; p = 0.662).

| Characteristics | | Total (N = 56) | Young (N = 16) | Old (N = 40) | p-value |
|---|---|---|---|---|---|
| Desaturation | Yes | 1 (1.8) | 1 (6.3) | 0 (0.0) | 0.286‡ |
| | No | 55 (98.2) | 15 (93.7) | 40 (100.0) | |
| Nasopharyngeal airway insertion | Yes | 8 (14.3) | 3 (18.8) | 5 (12.5) | 0.676‡ |
| | No | 48 (85.7) | 13 (81.2) | 35 (87.5) | |
| Bradycardia | Yes | 4 (7.1) | 1 (6.3) | 3 (7.5) | 1.000‡ |
| | No | 52 (92.9) | 15 (93.7) | 37 (92.5) | |
| Hypotension | Yes | 6 (10.7) | 1 (6.3) | 5 (12.5) | 0.662‡ |
| | No | 50 (89.3) | 15 (93.7) | 35 (87.5) | |

‡ Fisher's exact test

**Table 2:** Adverse events.

There was also no significant difference between the young and old groups in terms of the median value of sedation time (45 min vs. 70 min; p = 0.116) or recovery time (45 min vs. 50 min; p = 0.689) (Table 3). There was no significant difference in the median value of the target propofol TCI concentration used for induction (4.5 mcg/mL vs. 4.5 mcg/mL, p = 0.978) or maintenance (4 mcg/mL vs. 3.8 mcg/mL, p = 0.171) between the two groups. The dose of propofol used was not different between two groups (median value 0.3 mg/kg/min vs. 0.3 mg/kg/min, p = 0.277) (Table 3).

| Characteristics | | Total (N = 56) | Young (N = 16) | Old (N = 40) | p-value* |
|---|---|---|---|---|---|
| Sedation time (min) | Median (IQR) | 65 (40-77.5) | 45 (37.5-70) | 70 (45-82.5) | 0.116 |
| Induction (mcg $mL^{-1}$) | Median (IQR) | 4.5 (4-5) | 4.5 (3.8-5) | 4.5 (4-5) | 0.978 |
| Maintenance (mcg $mL^{-1}$) | Median (IQR) | 4 (3.1-4.5) | 4 (3.5-4.5) | 3.8 (3-4.5) | 0.171 |
| Propofol (mg $kg^{-1}$ $min^{-1}$) | Median (IQR) | 0.3 (0.2-0.3) | 0.3 (0.2-0.3) | 0.3 (0.2-0.3) | 0.277 |
| Recovery time (min) | Median (IQR) | 45 (40-55) | 45 (40-50) | 50 (40-55) | 0.689 |

*Wilcoxon rank-sum test
IQR = interquartile range

**Table 3:** Sedation profile.

## Discussion

The present study compared sedation using TCI between patients 1-3 years of age and pediatric patients > 3 years of age. The results showed that morbidity and risk were not increased with TCI use in younger children. A previous study showed that the use of TCI in pediatric patients between 3-26 months of age was possible, but that the majority of models, including the Paedfusor model used in our study, tended to overestimate the initial volume of distribution. This led to the injection of a larger initial bolus dose [5], resulting in a greater risk of adverse events compared with that observed in older patients. Our study compared patients up to 36 months of age with patients 37 months and older, and found no statistically significant difference in the target concentrations required for sedation during

induction between the two groups. There was no clinical evidence that a larger than required initial bolus dose was used for the younger age group when using TCI with the Paedfusor model, since our results did not reveal any statistically significant differences.

In our study, there was a significant difference between the two groups with regard to the distribution of lesions being treated with proton radiation therapy. However, the proportion of patients in the prone position was not significantly different, and there was no difference in the extent of the stimulation applied between the two groups; the difference in the distribution of lesions is unlikely to have affected our results. Additionally, because precise positioning and movement restrictions are important for any lesion for which proton radiation therapy is used [8], deep sedation was required in both groups, which restricts even minimal movements.

The present study has several limitations. The first is its retrospective design. The second is that the sample size of the younger age group was small compared with the older age group, which made objective and precise comparisons difficult. Third, we could not use end tidal carbon dioxide ($ETCO_2$) or respiratory rate (RR) as parameters of respiratory status because endotracheal intubation was not performed in all cases. For this reason, we used hypoxia and nasopharyngeal airway insertion as a measure of respiratory status, not $ETCO_2$ and RR.

Nevertheless, the present study has value in the field of pediatric radiation therapy, as it is the first clinical study to apply propofol TCI to pediatric patients ≤ 3 years of age and to compare these results with those seen in older patients. Moreover, this study is unique in comparison to previous studies because it used only one sedative agent - propofol - without the use of remifentanil or other analgesics.

In conclusion, despite concerns of overdose in pediatric patients ≤ 36 months of age, patients in the younger age group (12-36 months of age) underwent sedation for radiation therapy using propofol TCI as safely as did those in the older age group (37 months to 15 years of age). However, because children show different pharmacokinetic responses according to age, we believe that potentially more accurate sedation may be achieved with the development of specific TCI models reflecting these differences.

## Author's Contribution

TKO: Study design, interpretation of data, and writing of the first draft; KKH: Data collection; BRP: Data analysis; WSE: Study design, interpretation of data, and preparation of manuscript.

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