ORIGINAL CLINICAL RESEARCH REPORT

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Age-Stratified Propofol Dosage for Pediatric Procedural Sedation and Analgesia

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Background: Procedural sedation and analgesia (PSA) for diagnostic and minimally invasive therapeutic procedures has become common practice in children of all ages. Based on our clinical experience, we suspected an inverse relation between age and dosage. However, a schedule for age-stratified propofol induction and maintenance dosage for PSA was not available and could be helpful to many anesthesiologists as a reference.

Methods: We performed a retrospective cohort study of children who received procedural sedation at the Wilhelmina Children's Hospital (WKZ), a tertiary pediatric hospital part of the University Medical Center Utrecht (UMCU), between June 2007 and December 2020. We studied whether the induction (mg·kg^{-1}) and maintenance (mg·kg^{-1}·h^{-1}) dosage is age-dependent using linear regression models.

Results: A total of 6438 pediatric procedures were retrieved from Anesthesia Information Management Systems (AIMS). A total of 5567 records were available for induction dose analysis and 5420 records for analysis of the maintenance dose. After adjustment for sex, American Society of Anesthesiologists (ASA) physical status classification, opioid administration, and diagnostic or interventional, we obtained a coefficient of −0.11 (95% confidence interval [CI], −0.12 to −0.11) for age (years) from a multivariable linear regression model for propofol induction dosage (mg·kg^{-1}) and a coefficient of −0.36 (95% CI, −0.39 to −0.34) for age (years) for propofol maintenance dosage.

Conclusions: We found a noteworthy inverse age-effect on propofol dosage for both induction and maintenance of pediatric procedural sedation. Furthermore, our study revealed that remarkably higher propofol sedation doses were needed for infants and toddlers than previously expected and reported. (Anesth Analg 2023;136:551–8)

KEY POINTS

- **Question:** Should we adjust the propofol induction (mg·kg^{-1}) and maintenance (mg·kg^{-1}·h^{-1}) dosage for age during pediatric procedural sedation and analgesia (PSA)?
- **Findings:** Age-stratified propofol induction and maintenance dosage for PSA is strongly recommended.
- **Meaning:** Infants and toddlers need a higher propofol induction and maintenance dose compared to older children for PSA.

GLOSSARY

AIMS = Anesthesia Information Management Systems; **ASA** = American Society of Anesthesiologists; **BMP** = bone marrow puncture; **CI** = confidence interval; **CT** = computed tomography; **ID** = identification; **IV** = intravenous; **LP** = liquor puncture; **MRI** = magnetic resonance imaging; **PET** = positron emission tomography; **PICU** = pediatric intensive care unit; **PRIS** = propofol infusion syndrome; **PSA** = procedural sedation and analgesia; **REML** = residual maximum likelihood; **RT** = radiation therapy; **SD** = standard deviation; **STROBE** = Strengthening the Reporting of Observational Studies in Epidemiology; **UMCU** = University Medical Center Utrecht; **WKZ** = Wilhelmina Children's Hospital

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The demand for procedural sedation and analgesia (PSA) for diagnostic and minimally invasive therapeutic procedures in pediatric medicine continues to increase. The aim of PSA is to prevent pain and fear during these procedures and to increase the therapeutic and diagnostic success rate. Propofol has been used for anesthesia since 1989. The anesthetic properties of propofol (2,6-diisopropylphenol) were first reported in 1973.[1] Later, due to its favorable early onset and short recovery profile, propofol has been increasingly used for procedural sedation in adults and children.[2] While pediatric propofol dosage ranges for general anesthesia have been described in more detail, observational reporting about propofol dosage administered during pediatric procedural sedation is limited.[3–5] We hypothesized that an inverse relation between age and propofol dosage would be present. Since procedural sedation with propofol has become common practice for diagnostic and minimally invasive procedures in children, we aimed to study whether propofol dosage is age-dependent and if necessary create a reference age-stratified propofol-dosing schedule. Therefore, we retrospectively evaluated the required induction ($mg \cdot kg^{-1}$) and maintenance ($mg \cdot kg^{-1} \cdot h^{-1}$) dosage for PSA in a large cohort with all pediatric age categories included.

METHODS

Study Design

We performed a retrospective cohort study of all children who received PSA between June 2007 and December 2020 at Wilhelmina Children's Hospital, a tertiary pediatric hospital that is part of the University Medical Center Utrecht (UMCU) in the Netherlands. PSA was used for diagnostic procedures (eg, magnetic resonance imaging) and minimally invasive procedures like gastrointestinal endoscopic procedures (upper, lower, and combined), bone biopsies, bone marrow, and lumbar punctures. The institutional review board of the UMCU reviewed the study plan and found that it was not subject to the Dutch act on medical research involving human subjects and waived the need for informed consent. The study was conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (2013) and good clinical practice. This article adheres to the STROBE guidelines.

PSA Protocol

PSA is provided by either a pediatric anesthesiologist or a sedation practitioner with direct or indirect supervision of an anesthesiologist. In our institution, a sedation practitioner is a certified anesthetic nurse who additionally followed a 2-year PSA training with a special emphasis on pediatric deep sedation. The sedation practitioner is allowed to provide PSA outside the operating room to children with an American Society of Anesthesiologists (ASA) physical status classification of ≤2 within the framework of the PSA protocol. During PSA, the patient is monitored for proper head and neck position and airway patency by direct observation. The level of sedation is assessed by the Modified 5-level Ramsay scale. In the majority of procedures, a sedation level of 3 to 4 on the Ramsay scale was targeted, and some movement was allowed. In a subset of procedures, like radiation therapy (RT) or diagnostic scanning, movement of the involved area was not accepted, and Ramsay level 4 to 5 was targeted. Electronic monitoring consists of pulse oximetry, electrocardiogram, noninvasive blood pressure, and capnography with a dual nasal cannula that can simultaneously provide oxygen and obtain carbon dioxide sampling during spontaneous breathing. Supplemental oxygen is routinely provided.

The facilities' PSA protocol advises a propofol induction dosage of 2 to 3 $mg \cdot kg^{-1}$, and other sedatives are not included. The maintenance dose of propofol is adjusted to maintain an adequate level of sedation. Furthermore, analgesic treatment (including opioids, preferably alfentanil before painful stimuli and acetaminophen for postoperative analgesia) is administered depending on the procedure and the clinical view of the sedation provider. After the procedure, the patient is transferred to the recovery unit for observation until discharge criteria are met.

Data Collection and Handling

All PSA case information was stored in the electronic Anesthesia Information Management System (AIMS) (Anstat, Carepoint). The AIMS automatically registers vital parameters derived from the anesthesia monitor. Observations and medications (bolus and continuous infusions) are manually entered by the PSA provider. Complications were also registered in the AIMS. An automated email with reminder was sent to the sedation provider if the registration was not completed. From the AIMS database, we collected descriptive variables such as sex, age, weight, type of procedure, use of opioids, sedation duration, and dosage of propofol per minute for each PSA registration and registered complications. To calculate the administered propofol induction dose, we selected the total amount of propofol in milligrams given during the first 5 minutes after the initiation of propofol administration. The total dose included registrations of propofol bolus and continuous infusions as, in some cases, the targeted level of sedation was reached with a high continuous propofol infusion rate.

The propofol maintenance dose was calculated in milligrams per minute for procedures that lasted >5 minutes and took bolus and continuous infusions

into account. We only used the first hour of the PSA procedure to calculate the maintenance dose. The maintenance dose was calculated as average propofol infusion rate from minute 5 to 60 after the start of propofol administration. An induction dose calculation <0.8 or >8 mg·kg^{-1} was considered an outlier. A maintenance dose <6 or >30 mg·kg^{-1}·h^{-1} considered an outlier.

To calculate the maintenance dose, we divided the dose per minute by the weight of the patient, and weight of 0 and >150 kg was recoded as missing and considered as outliers. Procedures were ranked to their invasiveness. Procedure group 0 contains diagnostic imaging and RT, group I endoscopic procedures, group II diagnostic punctures and biopsies, group III ablation for cardiac arrhythmias, group IV intra-articular injection, and group V miscellaneous. We also performed a subanalysis to study the influence of repeated exposure to propofol in children who received RT. These patients received multiple PSA procedures in a short time period, and all procedures in the first 30 days after initiation of RT were used.

Statistical Analysis

Statistical analyses were performed using R (2.11.1, 4) in RStudio Version 1.1.456 2009–2018. We calculated sample size for the null hypothesis that propofol dosage is independent of age using the *pwr* package version 1.3–0 with correlation power calculation with arctangh transformation using an alternative effect size of 0.1, 90% power, and alpha = 0.01. According to this calculation, we needed a sample size of 1480 procedures. Quantitative parameters were calculated as mean and standard deviation (SD) for normally distributed variables. For categorical parameters, we calculated frequencies with percentages. Correlation coefficients (Pearson) were calculated for the relation between age and PSA propofol induction and maintenance dose with the corresponding *P* value. To adjust the relationship between age and PSA propofol dosages for potential confounders, we performed a multiple linear regression analysis and present the coefficients with 95% confidence intervals (CIs). To analyze the RT dataset with repeated PSA procedures, we used mixed effect models using the *lme4* package 1.1–27.1 with "time in days after the start of RT" and "age" as fixed effects and subject ID as a random effect for 2 separate models explaining propofol induction and maintenance dose.

RESULTS

A total of 6438 pediatric PSA registrations in 2368 unique patients were retrieved from the AIMS. The number of PSA registrations per patient showed an evident Poisson distribution with 1345, 292, 161, 124, and 86 patients having, respectively, 1, 2, 3, 4, and 5 PSA registrations. For 82 patients, more than 10 PSA procedures were registered in the AIMS. A total of 5567 PSA registrations were available to calculate age-stratified induction dose, and 5420 PSA registrations were available for the age-stratified maintenance dose. Database processing is depicted in Figure 1, and patient characteristics are described in Table 1. The PSA providers reported 21 complications in the automated complication database. These complications were scored as laryngospasm 7 (0.1%), hypoxemia 3 (0.05%), bronchospasm 1 (0.02%), bradycardia 3 (0.05%), hypotension 1 (0.02%), aspiration/vomiting 3 (0.05%), and a subcutaneous IV access 2 (0.03%). All reported complications were scored as temporarily without the need for PICU admission. PSA propofol induction doses in mg·kg^{-1} per age category are plotted in Figure 2.

In all age categories, except for the infant category, the number of available PSA procedures to calculate both induction and maintenance dose was around 300. PSA was less frequently provided in infants (0–1 year category) with <100 cases available to calculate average induction and maintenance dose. Figure 2

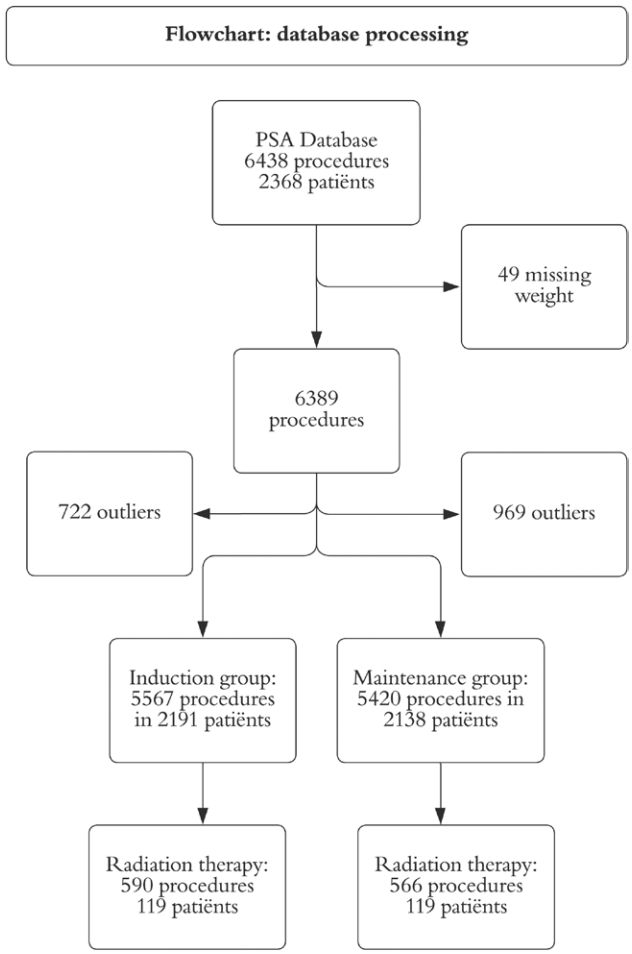


Figure 1. Flowchart of the data processing. PSA indicates procedural sedation and analgesia.

Table 1. Patient Characteristics of the Pediatric PSA Procedures

Characteristic	Induction group (n = 5567)	Maintenance group (n = 5420)
Sex, males (%)	3094 (55.6)	3015 (55.6)
Age, mean (SD), y	7.9 (5.3)	7.9 (5.3)
Weight, mean (SD), kg	31.7 (20.4)	31.6 (20.3)
ASA score, n (%)		
1	556 (10.0)	537 (9.9)
2	3143 (56.5)	3071 (56.7)
3	295 (5.3)	285 (5.3)
4	3 (0.0)	(0.0)
Missing	1570 (28.2)	1524 (28.1)
Opioids administration	4590 (82.5)	4514 (83.3)
Alfentanil	4553 (82.1)	4477 (82.6)
Sufentanil	40 (0.7)	40 (0.7)
Duration of PSA procedure, mean (SD), min	31 (15)	31 (15)
Diagnostics and interventions performed (%)		
Endoscopic imaging[a]	741 (13.3)	731 (13.5)
Punctures (BMP, LP)	2560 (46.0)	2524 (46.6)
Imaging scans (MRI, PET, CT)	373 (6.7)	363 (6.7)
Radiation therapy	684 (12.3)	655 (12.1)
Other	1209 (21.7)	1147 (21.2)
Induction dose, mg·kg^{-1}, mean (SD)	3.4 (1.2)	Not calculated[b]
Maintenance dose, mg·kg^{-1}·h^{-1}, mean (SD)	Not calculated[b]	15.0 (4.6)

Abbreviations: ASA, American Society of Anesthesiologists; BMP, bone marrow puncture; CT, computed tomography; LP, liquor puncture; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, procedural sedation and analgesia; SD, standard deviation.

[a]Endoscopic gastrointestinal imaging; upper tract, lower tract, and combinations all together.

[b]Not all cases were used for calculation of the maintenance and induction dose.

shows a decrease in PSA propofol induction dose over time that corresponds with a Pearson correlation coefficient of $r = -0.538$ ($P < .001$). A similar negative relation between age and propofol dosage for PSA is also observed in Figure 3 and corresponds with an $r = -0.470$ ($P < .001$).

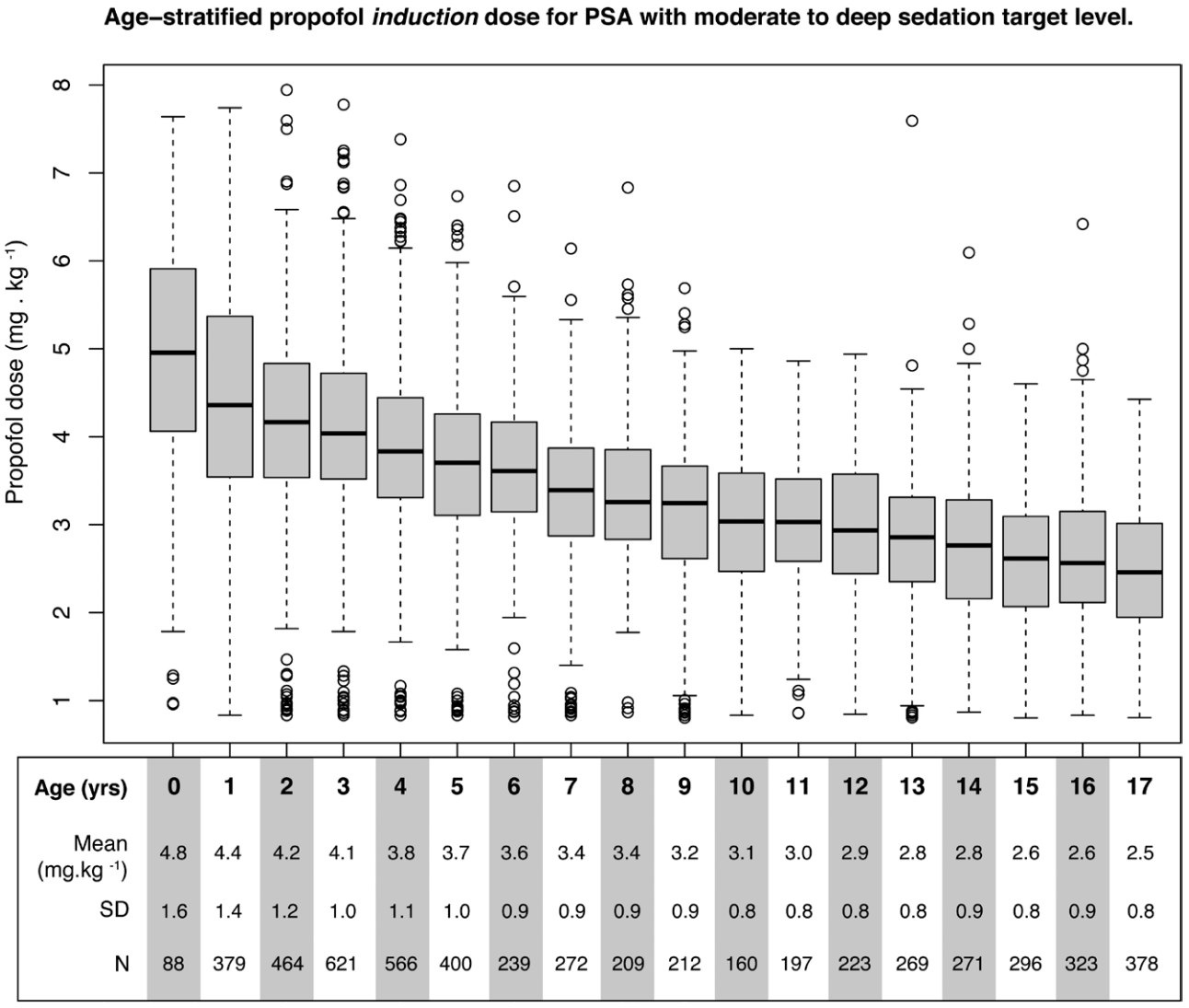
From our simple linear regression analyses, the following PSA propofol dosage formulas could be derived; induction dosage (mg·kg^{-1}) = 4.39 + (−0.119 [95% CI −0.124 to −0.114] * age [yrs.]), maintenance dosage (mg·kg^{-1}·h^{-1}) = 18.22 + (−0.403 [95% CI, −0.424 to −0.384] * age [yrs.]). The results from our multiple linear regression analyses are presented in Table 2 and incorporate sex, opioid administration, ASA class, and type of procedure as potential confounding factors.

In the subanalysis with RT patients, we explored the effects of repeated exposure to propofol during PSA. The cohort consisted of 119 patients with 590 PSA procedures for induction and 566 PSA procedures for maintenance dose calculations. Spaghetti plots displaying the relation between days after start of RT and propofol dosage are added as Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/E38, and Supplemental Digital Content 2, Figure 2, http://links.lww.com/AA/E39. A mixed effect model for propofol induction dose was fitted by REML with a fixed intercept of 5.19, fixed effects "number of consecutive days after RT start" 0.005 (−0.005 to 0.014), age −0.21 (−0.27 to −0.15), and "patient ID" as random effect. For maintenance dose, intercept 21.1, and the fixed effects "number of consecutive days after RT start" 0.03 (−0.01 to 0.07), "age in years" −0.72 (−0.95 to −0.49), and "patient ID" as random effect. Residuals were checked, and qqplots were generated.

DISCUSSION

This study aimed to explore the association between propofol dosage and age in children receiving PSA provided by a pediatric anesthetic team. We studied the propofol induction and maintenance dosage in a cohort of children from 0 to 17 years old and found a clear inverse relation: an older child needed a lower weight-adjusted propofol dose for both PSA induction and maintenance. These age-related differences were also consistent after accounting for possible confounders in a multiple regression analysis. To our knowledge, this is the largest retrospective PSA cohort reporting on propofol dosage in children of all ages (0–17 years). Furthermore, our study revealed that remarkably higher propofol induction and maintenance dosages for PSA were needed for infants and toddlers than previously reported and advised. In a subanalysis with pediatric patients who were repeatedly exposed to PSA with propofol, we were unable to detect a clear tolerance effect.

Our findings of an inverse relation between age and propofol dosage for pediatric PSA were consistent with a few previously published smaller cohort studies.[5–7] However, the absolute induction and maintenance dosages in our cohort were considerably higher with a more prominent age-effect. Most published pediatric PSA cohorts included <100 patients, categorized age in 3 or 4 groups with infants and toddlers

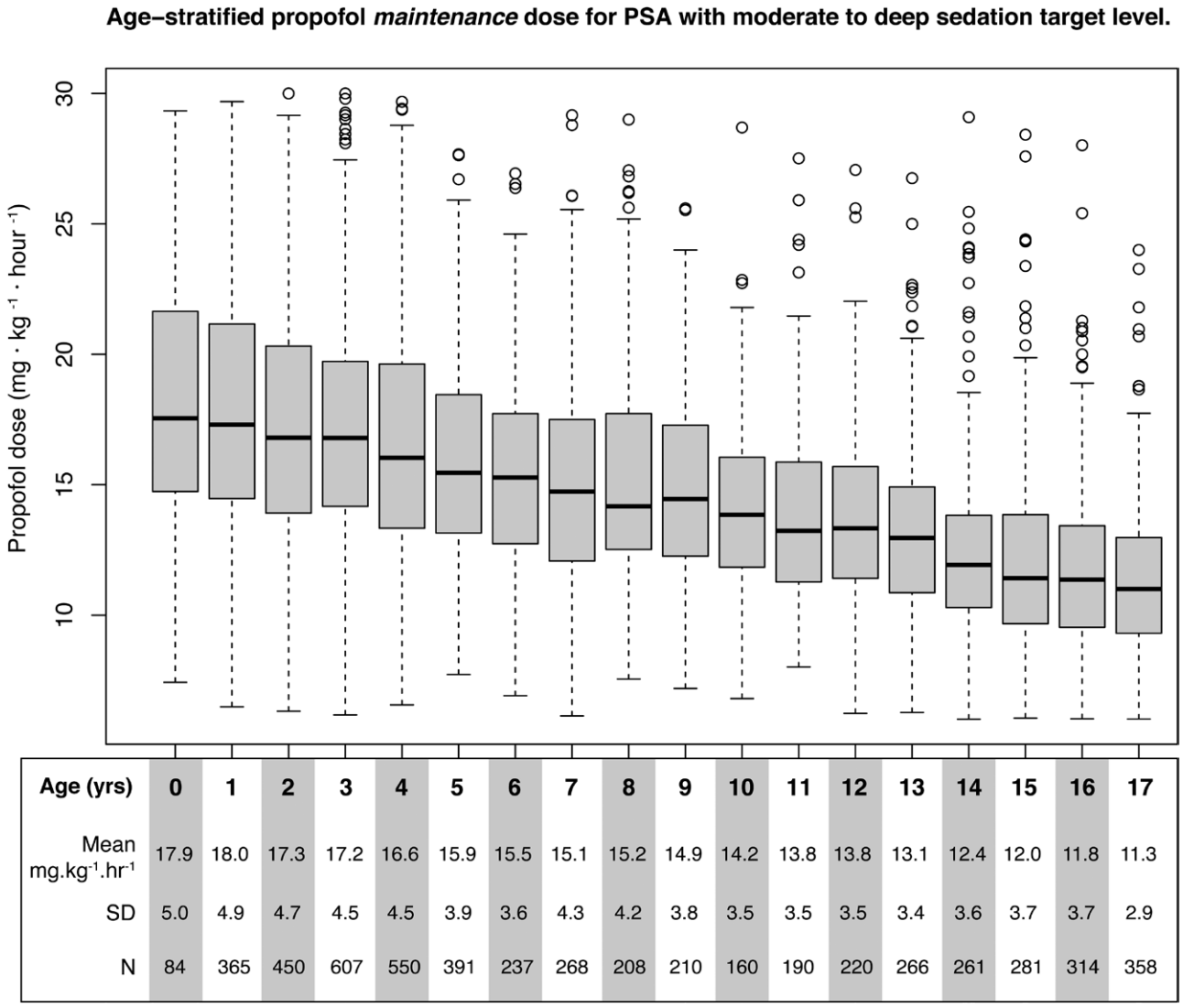


Age (yrs)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Mean (mg.kg -1)	4.8	4.4	4.2	4.1	3.8	3.7	3.6	3.4	3.4	3.2	3.1	3.0	2.9	2.8	2.8	2.6	2.6	2.5
SD	1.6	1.4	1.2	1.0	1.1	1.0	0.9	0.9	0.9	0.9	0.8	0.8	0.8	0.8	0.9	0.8	0.9	0.8
N	88	379	464	621	566	400	239	272	209	212	160	197	223	269	271	296	323	378

Figure 2. Age-stratified propofol induction dose for PSA with moderate to deep sedation target level. PSA indicates procedural sedation and analgesia; SD, standard deviation.

underrepresented. The largest cohort was published by Khalila et al.[7] They evaluated induction dose and found a clear age effect. However, in this study, infants, toddlers, and complex (ASA > 3) patients were sedated by an anesthesiologist, while the remaining patients received propofol sedation from the pediatric gastroenterologist. The administered weight-adjusted induction dose was significantly higher when an anesthesiologist was present. In our cohort, PSA was provided always by an anesthetic team member with direct or indirect supervision of a pediatric anesthesiologist. A few small cohort studies did not find an age effect on PSA propofol dosage.[4,8–10] In these studies, age was also categorized in larger groups and with infants and toddlers underrepresented. The recoding into age groups results in regression to the mean and blunting of the maximum age effect on propofol dose. This may explain why an age effect was not detected in these studies.

In this study, we report on the propofol maintenance dose for PSA in children of all ages. Many adult sedation practitioners or anesthesiologists might feel uncomfortable by an average maintenance dose of 18 $mg \cdot kg^{-1} \cdot h^{-1}$ and may question whether a patient would still breathe adequately. Publications on propofol maintenance dose for pediatric PSA are scarce. However, Scheiber et al[11] and Buehrer et al[12] concluded that 10 $mg \cdot kg^{-1} \cdot h^{-1}$ is a safe and adequate maintenance dose for PSA in pediatric RT. Scheiber et al[11] documented an average propofol maintenance dose of 7.4 ± 2.2 $mg \cdot kg^{-1} \cdot h^{-1}$ in patients 19 to 42 months of age. We observed a mean maintenance dose of 17.7 ± 4.8 $mg \cdot kg^{-1} \cdot h^{-1}$ for the age of 0 to 2 years. The manufacturer of propofol advices on a dosage of 12 $mg \cdot kg^{-1} \cdot h^{-1}$ (4.9–23.6 $mg \cdot kg^{-1} \cdot h^{-1}$) for children <2 years old for maintenance of pediatric anesthesia not PSA.[13] Propofol dosage was considerably higher in our cohort of PSA procedures and was clearly dependent on age.



Age (yrs)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Mean mg.kg^{-1}.hr^{-1}	17.9	18.0	17.3	17.2	16.6	15.9	15.5	15.1	15.2	14.9	14.2	13.8	13.8	13.1	12.4	12.0	11.8	11.3
SD	5.0	4.9	4.7	4.5	4.5	3.9	3.6	4.3	4.2	3.8	3.5	3.5	3.5	3.4	3.6	3.7	3.7	2.9
N	84	365	450	607	550	391	237	268	208	210	160	190	220	266	261	281	314	358

Figure 3. Age-stratified propofol maintenance dose for PSA with moderate-to-deep sedation target level. PSA indicates procedural sedation and analgesia; SD, standard deviation.

There are multiple hypotheses to explain the inverse relation between age and propofol dosage in pediatrics: Children and adults differ in body composition, and the body undergoes physiological maturation and changes in terms of height, fat composition, and weight. Furthermore, changes in hepatic and renal function and the number of gamma-aminobutyric acid A-receptors are described.[1] Studies also show a higher concentration of propofol at half-maximal effect in children compared to adults.[13] Coadministration of opioids reduces the propofol dose due to its synergistic effect.[1,13] However, in our multivariable model, opioid administration is associated with an increased propofol dose, while, more likely, this is due to unexplained confounding in procedural coding for painful procedures. For invasive punctures (eg, bone biopsies, bone marrow, and lumbar punctures), opioids and deep sedation are frequently provided. Furthermore, it might be explained by the PSA provider who might deepen the sedation and give opioids simultaneously when reactions motoric and nonmotoric are noticed.

Limitations

Our retrospective cohort study has some limitations. First, we defined induction as the first 5 minutes of PSA, and hereafter, dosing was considered for PSA maintenance. This approximates real induction and maintenance in all cases but is not an exact reflection as we do not exactly know when and what targeted sedation level was reached. Different sedation practitioners might have targeted different levels of sedation. Another limitation for the calculation of propofol dosage is that the registration, bolus, and continuous infusions are manually entered in the AIMS with an undefined time delay and potential human error. However, it is more likely that bolus infusions given are missing in the registration, and we potentially

Table 2. Effects of Age on Propofol Dosage During Pediatric PSA

Model	Coefficient for age (y) (95% CI)	Variables	Estimates (95% CI)
Crude propofol induction dose model[a] (mg·kg^{-1})	−0.12 (−0.12 to −0.11)	(Intercept)	4.39
Adjusted propofol induction dose model[b] (mg·kg^{-1})	−0.11 (−0.12 to −0.11)	(Intercept)	4.45
		Sex (male)	−0.02 (−0.07 to 0.03)
		ASA 3/4	0.001 (−0.12 to 0.12)
		Opiates	0.18 (0.09 to 0.27)
		Procedure group 1	−0.08 (−0.20 to 0.05)
		Procedure group 2	−0.32 (−0.42 to −0.22)
		Procedure group 3	−1.34 (−1.61 to −1.08)
		Procedure group 4	−0.20 (−0.41 to 0.01)
		Procedure group 5	−0.48 (−0.59 to −0.38)
Crude propofol maintenance dose model[a] (mg·kg^{-1}·h^{-1})	−0.40 (−0.42 to −0.38)	(Intercept)	18.22
Adjusted propofol maintenance dose model[b] (mg·kg^{-1}·h^{-1})	−0.36 (−0.39 to −0.34)	(Intercept)	17.74
		Sex (male)	0.28 (0.07 to 0.49)
		ASA 3/4	−0.75 (−1.23 to −0.28)
		Opiates	0.17 (−0.21 to 0.55)
		Procedure group 1	−1.23 (−1.74 to −0.72)
		Procedure group 2	0.24 (−0.16 to 0.64)
		Procedure group 3	−3.99 (−5.21 to −2.77)
		Procedure group 4	1.71 (0.85 to 2.57)
		Procedure group 5	−1.15 (−1.57 to −0.74)

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; EP, electrophysiology; PSA, procedural sedation and analgesia.

[a]Crude coefficient calculated with a linear regression model.

[b]Adjusted for sex, ASA, opioid administration, and diagnostic or interventional procedure group (reference = imaging/radiation therapy), group 1 = endoscopic imaging, group 2 = punctures (eg, bone marrow, bone, and lumbar) group 3 = EP study and ablation, group 4 = intra-articular injection, group 5 = miscellaneous in a multivariable linear regression model.

underestimated the induction dosage. The high maintenance dosage for PSA made the authors reflect on the risk of propofol infusion syndrome (PRIS). This has been described after propofol doses of 4 mg·kg^{-1}·h^{-1} for >48 hours.[14,15] Hemphill et al[16] conducted a literature review and analysis on PRIS in adults and children. They demonstrated a linear relationship between PRIS and the accumulative dose of propofol in adults. However, this relationship was not observed in the pediatric population.[16] It is unclear whether short-term sedation with high-dose propofol increases the risk of PRIS in children. We did not perform calculations for dosage in procedures with a duration >60 minutes. Neither did we study adverse events. The pediatric anesthesiologist responsible for the PSA procedure is requested to register a complication after every case by an email reminder. PRIS was never reported. However, due to the nature of this registration, we are unable to conclude on the safety of our pediatric propofol maintenance dose.

CONCLUSIONS

We found a noteworthy inverse age-effect on propofol dosage for both induction and maintenance of pediatric procedural sedation. Furthermore, our study revealed that a remarkably higher propofol sedation dose was needed for infants and toddlers than was expected and previously reported. The provided age-stratified propofol dosage schedule can be used by trained anesthesiologists and sedation practitioners as reference for pediatric PSA.

DISCLOSURES

Name: Huib van Dijk, MD.
Contribution: This author helped analyze the data and write the manuscript.
Name: Mark P. Hendriks, MD.
Contribution: This author helped write and revise the manuscript.
Name: Marga M. van Eck-Smaling, BSc.
Contribution: This author helped initiate the research project and is responsible for data collection.
Name: Leo van Wolfswinkel, MD, PhD.
Contribution: This author helped build the database; is responsible for data storage, report, and collect from the archive; and helped revise the manuscript.
Name: Kim van Loon, MD, PhD.
Contribution: This author helped initiate the research subject, form the research question, supervise data analyzed, and write and revise the manuscript.
This manuscript was handled by: James A. DiNardo, MD, FAAP.

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