RESEARCH ARTICLE

Association of BMI With Propofol Dosing and Adverse Events in Children With Cancer Undergoing Procedural Sedation

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ABSTRACT

OBJECTIVES: Obesity increases the risk of complications during pediatric procedural sedation. The risk of being underweight has not been evaluated in this arena. We therefore investigated the association of BMI with sedation dosing and adverse events in children across a range of BMIs.

METHODS: A total of 1976 patients ages 2 to 21 years old with oncologic diagnoses underwent lumbar punctures and/or bone marrow aspirations. All children received a standard adjunctive dose of ketamine before sedation with propofol. Weight categories were stratified by BMI percentile: underweight <5%, normal weight 5% to 85%, overweight >85%, and obese >95%. Dosing and adverse events (hypoxia, apnea, bradycardia, or hypotension) were reviewed.

RESULTS: There were no differences in propofol dosing for procedural sedation between patients who were normal weight and underweight. However, children who were overweight and those who were obese used less propofol compared with children who were normal weight ($P < .01$). Children who were underweight had a higher proportion of adverse events overall relative to those children of normal weight ($P < .001$). In contrast, there was not an increase in adverse events for patients who were overweight and obese.

CONCLUSIONS: Children who are overweight and children with obesity who require deep sedation can undergo successful sedation with lower propofol dosing relative to children of a normal weight. This dosing strategy may help to mitigate the risks associated with sedating patients who are obese. Notably, children who were underweight had an increased rate of complications despite receiving an equal amount of sedation compared with patients who were normal weight. This should alert the clinicians to the risks associated with sedating children who are underweight.

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Obesity remains a widespread and significant health concern facing American children. At the present time, 17% of children and adolescents with obesity are defined by a BMI ≥95th percentile for age and sex. Furthermore, nearly one-third of children who are overweight are classified by a BMI >85th percentile.[1]

With the rise in pediatric obesity, clinicians must continue to familiarize themselves with the challenges that accompany caring for a child with obesity. Obesity leads to a wide array of comorbidities that must be considered in the acute care setting. Additionally, vital procedures such as airway management and the establishment of intravenous access can become complicated in a child with an obese body habitus.[2] Lastly, obesity has been associated with an increased risk of adverse events in children undergoing procedural sedation.[3]

Clinicians must also be aware of pharmacologic adjustments, which may be needed for patients with obesity. This includes many sedative and analgesic agents that are extremely fat soluble, thus altering their volume of distribution in patients with obesity.[4] Dosing regimens for patients with obesity include dosing on the basis of actual body weight, ideal body weight (IBW), and adjusted body weight (ABW). Unfortunately, there is little consensus regarding the appropriate drug dosing for several classes of medications, including those used for procedural sedation.[5] Furthermore, at the present time, there are limited data available by which to guide medication dosing for pediatric patients with obesity.[6]

On the opposite end of the spectrum, children who are underweight and/or malnourished also have an increased risk of adverse outcomes when hospitalized.[7] The effect of being underweight on procedural sedation has not been previously evaluated. Therefore, the purpose of the current study is to investigate the effect of BMI on propofol dosing and rate of adverse events in children with cancer, of varying weight categories, who underwent procedural deep sedation for painful procedures. Propofol is an intravenous sedative-hypnotic agent that is used for induction and maintenance of deep sedation and general anesthesia.[8] It produces the sedative effect by activating the γ-aminobutyric acid A receptor, inhibiting the N-methyl-D-aspartate receptor, and modulating calcium influx through slow calcium ion channels. Propofol has many properties (including a rapid onset, a short duration of action with rapid recovery time, and minimal adverse effects) that makes it an ideal agent for pediatric sedation in the outpatient setting. Emerging data support the safety and efficacy of using propofol outside the operating room for pediatric outpatient procedures and interventions by qualified physicians trained in sedation and advanced airway management.[9,10] We hypothesize that children who are underweight and children with obesity will have different propofol requirements and higher rates of adverse events during deep sedation when compared with children with normal weight.

METHODS

This study was a retrospective review approved by our institutional review board. The records of pediatric oncology patients ages 2 to 21 years old undergoing deep sedation from January 2010 to December 2015 were reviewed. The majority of our study population were outpatients, but occasionally inpatient cases were conducted as well. This includes both inpatient and outpatient procedures. Sedation was administered for lumbar puncture (LP), bone marrow aspiration (BMA), or both procedures combined. Sedation was performed by physicians and nurses trained in pediatric critical care medicine while a pediatric oncology physician or nurse practitioner performed the procedure itself. An initial adjunctive dose of ketamine was given to all patients, with a dosing regimen of 0.5 mg/kg body weight for patients weighing ≤20 kg and 0.25 mg/kg for patients weighing >20 kg.

Intermittent bolus doses of propofol were given at the discretion of the sedation physician to achieve deep sedation level (level 4) on the basis of the Ramsay Sedation Scale to facilitate the procedure. The typical dosing regimen for propofol at our institution is an initial 1 to 2 mg/kg propofol bolus at the start of sedation with additional 0.5 to 1 mg/kg doses as needed thereafter. There was no unique dosing method used for patients who fell into the underweight or obese weight categories; propofol dosing for these patients was based on the decision of the sedation physician.

Data collected included patient age, sex, height, weight, doses of ketamine and cumulative dose of propofol (mg/kg) administered for the procedure, and any adverse events that occurred, in addition to the American Society of Anesthesiologists (ASA) classification. All patients were either classified as ASA physical status I or II per the ASA physical status classification system. Adverse events included hypoxemia (pulse oxygen saturation <90%, requiring the administration of supplemental oxygen), apnea (requiring bag-mask ventilation), bradycardia (>20% reduction in pre-sedation heart rate), and hypotension (>20% reduction in pre-sedation blood pressure).

BMI was calculated for each patient, and then BMI percentage for age and sex was determined by plotting on the appropriate BMI curve by using the Centers for Disease Control and Prevention BMI-for-age growth chart. Weight categories were defined as the following: underweight as BMI <5th percentile, normal weight as BMI 5th to 84th percentile, and overweight as BMI >85th percentile. A subcategory of patients within the overweight class were identified as obese, with a BMI >95th percentile.

Data are presented as mean and SD for continuous data and as frequency for categorical data. Comparisons of the log-transformed propofol dosing among BMI categories were made by using 1-way analysis of variance testing, and with 2-way analysis of variance for BMI category, procedure group, and their interaction. Comparisons of the frequency of adverse events in each BMI category were evaluated with χ^2 tests. A logistic regression analysis was used to assess the effect of BMI category on adverse events. A P value of $< .05$ was considered statistically significant.

RESULTS

A total of 1976 pediatric oncology patients undergoing deep sedation were included in this review. One hundred percent of procedures were successfully completed. There were no significant differences in age across weight and procedure categories. There was a higher proportion of male patients across all categories. Patient characteristics are further outlined in Table 1.

Our results comparing propofol dosing requirements for deep sedation among the various weight classes are summarized in Table 2. Children who were overweight and children with obesity required significantly lower doses of propofol per kilogram of body weight to achieve deep sedation for BMA and combined BMA plus LP procedures when compared with children with a normal weight. Furthermore, children with obesity required significantly lower doses of propofol compared with children with a normal weight for LP. In contrast, there was no difference in propofol dosing between children who were underweight and children of a normal weight.

Adverse events were compared among children of varying weight categories. The overall incidence of adverse events during deep sedation was significantly higher in children who were underweight compared with children with a normal weight (10.6% vs 3.5%, $P < .001$). There was no difference in the incidence of adverse events among children of a normal weight, children who were overweight, and children with obesity. No serious adverse events (such as endotracheal intubation, respiratory or cardiac arrest, failure to complete the procedure, or admission to a higher level of care) were noted. In Tables 3 and 4, we outline the rate of adverse events by weight class and procedure. Furthermore, in a logistic regression analysis, being underweight yielded a higher risk for hypoxia (odds ratio [OR] 3.18 [1.70–5.92], $P < .0003$) and apnea (OR 3.24 [1.76–5.94], $P < .0001$) when compared with being normal weight.

TABLE 1 Demographic Comparisons of Patients According to Procedure and Weight Categories

Procedure and Weight Category	*n*	Average Age, y	Boys, %
LP			
Normal weight	797	8.2	72.0
Underweight	91	11.8	83.5
Overweight	550	9.4	66.6
Obese	302	10.2	67.7
BMA			
Normal weight	181	9.6	69.1
Underweight	27	9.0	82.6
Overweight	105	10.9	53.3
Obese	54	11.3	54.7
LP and BMA combined			
Normal weight	108	7.9	76.9
Underweight	18	11.1	94.4
Overweight	98	9.3	54
Obese	50	9.1	62

DISCUSSION

In this study, we evaluated the effect of BMI on propofol dosing and adverse events during deep sedation in pediatric oncology patients. Our findings regarding both children with obesity and children who are underweight merit discussion. First, the link between obesity and complications in children undergoing general anesthesia has been well described,[11–13] but the impact of obesity on pediatric procedural sedation is a relatively new concept. In 2014, Scherrer et al[3] used the Pediatric Sedation Research Consortium database to show that childhood obesity is an independent risk factor for adverse events during procedural sedation. In their analysis, the use of propofol was associated with an increased rate of adverse events in obese children, but the exact dose of sedative medications is not described.

Furthermore, pediatric obesity poses significant challenges in drug dosing, and the proper mechanism by which to dose certain classes of medications is not always known, including dosing regimens for sedatives and anesthetics. Options include dosing by total body weight (TBW), IBW, and ABW, in which ABW = IBW + 0.4 (TBW − IBW).[6] Data are conflicting and scarce with regard to guiding propofol dosing in obese children. Olutoye et al[14] performed a prospective study of children with obesity undergoing general anesthesia with propofol and found that children with obesity required smaller doses of propofol relative to children of normal weight. In contrast, the authors of other studies have recommended TBW for weight-based propofol dosing.[15,16] Our retrospective study reveals that children with obesity can be successfully sedated with significantly less propofol on a per weight basis compared with children with a normal weight, thus suggesting that perhaps dosing propofol by IBW may be a

TABLE 2 Cumulative Propofol Dosing (mg/kg TBW) for Deep Sedation Among BMI Categories

BMI Category	Lumbar Puncture	Bone Marrow Aspiration	LP and BMA
Normal weight	2.57 (±1.21)	3.85 (±2.06)	5.26 (±2.18)
Underweight	2.59 (±1.69)	3.82 (±2.05)	4.98 (±1.84)
Overweight	2.42 (±1.22)	3.20 (±1.56)*	4.42 (±2.19)*
Obese	2.12 (±1.11)*	2.72 (±1.56)*	4.08 (±2.12)*

Data reported as mean ± SD.
* $P < .01$ compared with normal weight category.

TABLE 3 Incidence of Adverse Events Among BMI Categories During Deep Sedation

BMI Category	Overall Events, %	Lumbar Puncture, %	Bone Marrow Aspiration, %	LP and BMA, %
Normal weight	3.5	2.6	3.9	5.6
Underweight	10.6*	6.6*	11.5*	28.0*
Overweight	4.0	2.9	8.6	7.1
Obese	4.6	3.3	11.1*	2.0

* $P < .05$ compared with normal weight category.

more appropriate dosing strategy for deep sedation involving children with obesity.

In our study, we also sought to investigate the relationship between BMI, propofol dosing, and complications during pediatric deep sedation. In our study population, there was no difference in adverse events among children with a normal weight and children with obesity. Concurrently, as noted above, children with obesity required significantly lower amounts of propofol to achieve successful sedation. This finding held true across all 3 procedures. One may conclude that clinicians possibly can mitigate the risks associated with sedating children with obesity by utilizing propofol at doses that are less than those based on TBW. Successful deep sedation can still be achieved at these lower doses.

Notably, children who were underweight in our study had a significantly higher rate of adverse events compared with children with a normal weight, despite an equal per-kilogram dose of propofol. To our knowledge, this is the first study to reveal an association between underweight status and an increased risk of sedation-related complications. Furthermore, when compared with children with obesity, children who were underweight were at higher risk of adverse events during deep sedation (OR 2.49 [1.24–4.98], $P < .01$). The causes for this association merit further study. Children who are underweight have worse clinical outcomes when acutely ill,[17] and malnourishment with a negative nitrogen balance can lead to respiratory muscle weakness.[18] Such weakness may predispose to hypoventilation, hypoxia, and apnea during deep sedation. Second, as a lipophilic drug, propofol circulates into adipose tissue as part of its volume of distribution. With children who are underweight having less adipose tissue and thus a smaller peripheral compartment, more circulating propofol is available to cross the blood-brain barrier, again predisposing them to hypoventilation and apnea. This could explain why our underweight cohort had such a higher rate of complications despite an equivalent dose of propofol compared with children with a normal weight. This finding and biologic explanation should prompt clinicians to consider administering a smaller dose of propofol to children who are underweight and malnourished instead of a standard propofol dose that is based on TBW.

TABLE 4 Distribution of Adverse Events Among BMI Categories During Deep Sedation

Procedure and Weight Category	Adverse Event		
	Desaturation, No. of Patients (%)	Apnea, No. of Patients (%)	Hypotension, No. of Patients (%)
LP			
Underweight	6 (6.6)*	3 (3.3)	0
Normal weight	19 (2.4)	2 (0.3)	3 (0.4)
Overweight	5 (0.9)	0	0
Obese	9 (3.0)	0	2 (0.7)
BMA			
Underweight	2 (7.4)*	1 (3.7)	1 (3.7)
Normal weight	7 (3.9)	1 (0.6)	0
Overweight	3 (2.9)	0	0
Obese	6 (11.1)*	0	0
LP and BMA			
Underweight	5 (27.8)*	0	0
Normal weight	6 (5.6)	1 (0.9)	1 (0.9)
Overweight	6 (5)	0	0
Obese	0	0	1 (2.0)

* $P < .05$.

Our study is limited by its retrospective nature. However, the study population consists of a large number of children who are undergoing similar procedures. Although we did not directly report the type of cancers in our study population, the majority of oncology patients undergoing these procedures in our institution suffer from hematologic malignancies, mirroring the incidence of pediatric cancer seen in the general population.

Additionally, propofol dosing varies based on physician discretion to achieve the desired depth of sedation, which could have influenced total doses of propofol given per patient. Thus, our study population is relatively homogeneous in terms of underlying disease process. Sedation was administered via an institutional protocol, with there being a difference in adjunctive ketamine dosing depending on the patient's weight, as noted in the Methods section; however, our logistic regression analysis did not show a significant effect from this difference in ketamine dosing. Lastly, recovery time from sedation is an outcome of interest but was not investigated in our study.

CONCLUSIONS

BMI is an important factor to consider when administering deep sedation to pediatric patients. Extremes at both ends of the BMI spectrum should prompt awareness. Utilizing lower doses of propofol may mitigate the potential for adverse events

that accompany sedating children with obesity. Successful sedation is still achieved at these lower doses. Notably, children who are underweight are at an increased risk for complications during deep sedation, and thus heightened awareness and vigilant monitoring are required for this patient population.

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