

Preterm Versus Term Children: Analysis of Sedation/Anesthesia Adverse Events and Longitudinal Risk

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Abstract

BACKGROUND AND OBJECTIVES: Preterm and former preterm children frequently require sedation/anesthesia for diagnostic and therapeutic procedures. Our objective was to determine the age at which children who are born <37 weeks gestational age are no longer at increased risk for sedation/anesthesia adverse events. Our secondary objective was to describe the nature and incidence of adverse events.

METHODS: This is a prospective observational study of children receiving sedation/anesthesia for diagnostic and/or therapeutic procedures outside of the operating room by the Pediatric Sedation Research Consortium. A total of 57 227 patients 0 to 22 years of age were eligible for this study. All adverse events and descriptive terms were predefined. Logistic regression and locally weighted scatterplot regression were used for analysis.

RESULTS: Preterm and former preterm children had higher adverse event rates (14.7% vs 8.5%) compared with children born at term. Our analysis revealed a biphasic pattern for the development of adverse sedation/anesthesia events. Airway and respiratory adverse events were most commonly reported. MRI scans were the most commonly performed procedures in both categories of patients.

CONCLUSIONS: Patients born preterm are nearly twice as likely to develop sedation/anesthesia adverse events, and this risk continues up to 23 years of age. We recommend obtaining birth history during the formulation of an anesthetic/sedation plan, with heightened awareness that preterm and former preterm children may be at increased risk. Further prospective studies focusing on the etiology and prevention of adverse events in former preterm patients are warranted.

Discussion

In this prospective analysis of patients 0 to 22 years of age undergoing procedural sedation/anesthesia, we determined that a considerable percentage (8.6%) of all children experienced an adverse event, with the most common adverse events associated with the airway and respiratory systems. Our data confirmed our primary hypothesis that preterm and formerly preterm patients would be at higher risk for adverse events during sedation/anesthesia. Our sensitivity analysis conducted in children 0 to 36 months of age suggests that postgestational age alone cannot explain the differences in frequency of adverse events. The small changes between the groups in this subanalysis suggest that there is an additive effect of preterm birth that cannot be solely explained by postgestational age. This implies there is a factor inherent to preterm children that places them at increased risk for the development of adverse events related to sedation/anesthesia. Our analysis suggests that preterm and formerly preterm patients undergoing

sedation/anesthesia for nonoperating room procedures should be considered a population at risk for the development of adverse events.

Both categorical and the locally weighted regression analysis suggest that this risk continues into adulthood; however, the exact reason is not clear. It is known that lung maturation is incomplete at birth and continues until 20 years of age with a further increase in alveolarization.^{16,17} Even moderate prematurity may adversely affect the maturation process, resulting in an increased incidence of respiratory disease later in childhood.^{18,19} Sedation/anesthesia may unmask subclinical pulmonary dysfunction, resulting in an increased likelihood of oxygen desaturation. Neurologic dysfunction commonly seen in preterm and former preterm infants may also play a role in the development of adverse events, including apnea and airway obstruction.

It is not surprising that the highest risk group included infants 0 to 6 months of age. Our subanalysis revealed that this age group was more than twice as likely to develop an adverse sedation/anesthesia event (OR 2.6, $P = .001$). Apnea was one of the most notable adverse events in this age group, particularly in preterm and formerly preterm infants. Formerly preterm and preterm infants 0 to 6 months of age were 5 times as likely to experience apnea, and this elevated risk was also demonstrated in the 24- to 36-month age group. Approximately 78% of infants in the 0- to 6-month age category received propofol, which is known to cause apnea. There is considerable variability in both the pharmacokinetics and pharmacodynamics of this drug, especially in preterm neonates, which may in part explain the occurrence of apnea.^{20,21} In addition, abnormal respiratory function frequently observed in the preterm population is complex and not completely understood. The immaturity of the respiratory and central nervous systems, altered carotid chemoreceptor responses to hypoxia and hyperoxia, numerous neurotransmitters, genetic predisposition, and laryngeal chemoreflexes are a few of the mechanisms that have been implicated in the development of apnea and respiratory abnormalities in the preterm infant.^{22–25} These factors may contribute to the development of airway and respiratory adverse events related to sedation/anesthesia.

Oxygen desaturation is one of the more common adverse sedation/anesthesia events that can result in significant morbidity or mortality. In our study, infants 0 to 6 months of age experienced the highest frequency of oxygen desaturation; however, no significant difference was noted between preterm and term groups (4.1% vs 3.1%; $P = .63$). We postulate that this is due to the higher oxygen consumption and limited physiologic reserve in all children <6 months of age. It is interesting to note a significant difference in oxygen desaturation developed in formerly preterm patients 7 to 18 months of age (OR 2.8; $P = .003$), suggesting there is an underlying pathology in the preterm group that predisposes them to hypoxia. The effect of age on the development of oxygen desaturation has been previously described by Côté et al.²⁶ These investigators reported that children undergoing inhalational general anesthesia, by either mask or endotracheal tube, were more likely to experience a major desaturation event (defined as oxygen saturation $\leq 85\%$ for >30 seconds). This occurred in ~28% of children 0 to 6 months of age, with a marked decrease in the 7- to 24-month age group (8.0%). They also examined the difference in oxygen desaturation between children 7 to 24 months of age and those >24 months and found no significant difference between the 2 groups. Although their study had a mean age less than ours, we found similar results. In our study, infants 0 to 6 months of age were significantly more likely to experience oxygen desaturation than older children, and no significant difference was found between the 2 older categories of children ages 7 to 24 months and 25 to 36 months ($P = .5$). This affirms that patients <7 months of age are at increased risk for the development of oxygen desaturation.

We investigated the possibility that preterm and former preterm patients required more invasive procedures than term children, requiring deeper levels of sedation or the administration of general anesthesia; however, our data suggest there was not a substantial difference between the 2 groups. Diagnostic procedures such as MRI scans and ABRs accounted for >60% of procedures experienced by preterm and former children, whereas MRI scans, upper endoscopies, and lumbar punctures accounted for >60% of procedures requiring sedation/anesthesia in term children. In light of the fact that esophageal endoscopy and lumbar punctures are more stimulating procedures, which could result in increased airway and respiratory adverse events, we could not conclude that preterm children experienced a higher percentage of adverse events solely owing to more invasive or painful procedures. Diagnostic procedures such as MRI scans may require a deep level of sedation or general anesthesia to obtain complete motion control that is necessary for adequate studies, in contrast to the variable level of sedation required for esophageal endoscopy and lumbar punctures, since the amount of movement that is tolerated during these procedures is not consistent. There were no significant differences in the occurrence of adverse events between the 2 groups undergoing computed tomography scans or upper endoscopies. In this instance, we believe the brief duration of the procedures decreases the exposure to risk. In addition, in patients undergoing upper endoscopy, the procedure itself may adversely impact the airway and respiratory systems, resulting in both groups experiencing a high rate of adverse events. Our findings suggest that the duration and level of sedation or administration of general anesthesia may be more important than the amount of stimulation.

It is well known that age is a predictor of adverse events during sedation and general anesthesia.^{5,8–10,27–32} This fact has been attributed to the variation in pharmacokinetics and pharmacodynamics of sedative and anesthetic drugs and to the limited physiologic reserve in children <1 year of age.^{20,21,32,33} We postulated that preterm children were more susceptible to experiencing adverse events at a younger age, but that the risk would decrease as they grew older owing to the increase in physiologic reserve that occurs with increasing age. The finding that a decrease in frequency of adverse events did not occur in formerly preterm patients as they reached adulthood was unexpected. The examination of the data by both categorical methods and nonparametric regression analysis revealed the same result; preterm and former preterm children are at higher risk for the development of adverse sedation/anesthesia events regardless of age at the time of the procedure. We postulated several possibilities for this finding, but as in any observational study, we cannot determine the cause. We suspect that the degree of prematurity may influence this outcome; however, we were unable to evaluate that possibility since the database does not collect information on the exact postgestational age at birth.

As previously noted, our analysis by age revealed a biphasic distribution in the frequency of adverse events. The increase in adverse events in preadolescent children has been previously reported in the sedation literature.^{27,34} Srinivasan et al reported an increase in adverse sedation events with the use of propofol in patients >12 years of age.³⁴ Green et al reported an unexpected increase in adverse sedation events with the use of ketamine in teenagers.²⁷ It is noteworthy that the increase in incidence of adverse events that occurs in infants and preteenage children corresponds to the well-described increase in minimum alveolar concentration in these age groups.^{35–37} It is possible that these children require higher doses of sedative/anesthetics agents, thereby decreasing the margin of safety. Furthermore, older patients who require sedation for these procedures may represent a selected group of individuals with behavioral or developmental pathology that places them at greater risk, since the ability to sedate this population is frequently more difficult.

Our findings were similar to those published by other investigators in several ways. Our analysis revealed that sedation/anesthesia adverse events were primarily related to airway and respiratory systems, the highest frequency occurred in infants <6 months, and an increase in the frequency of adverse events was noted in the preadolescent population. On the other hand, our longitudinal risk analysis demonstrated that preterm and former preterm children remain at increased risk into adulthood. To our knowledge, this has not been previously reported. This may be due to the fact that a history of prematurity may not be routinely obtained, since it has not been considered a risk factor for the development of an adverse event.

This study has several limitations, primarily related to its observational nature. These data were prospectively collected and retrospectively analyzed. As with all observational studies, observer bias may be present. The small number of patients who experienced uncommon adverse events, such as hypothermia, makes it challenging to draw any inferences from the data. Although it is plausible that hypothermia occurs more frequently in the preterm group receiving sedation/anesthesia in a non-thermal-controlled environment, the small number of children experiencing hypothermia in the entire database precludes any conclusion. Furthermore, organizations participating in this registry are primarily children's hospitals that are motivated to improve the quality of sedation/anesthesia care to children. The reporting institutions have sedation systems that are highly organized, have been in existence for more than 5 to 10 years, and practice under controlled circumstances. We also recognize that the sedations/anesthetics reported are almost entirely elective in nature. Data from emergency procedures could be significantly different. These are a selected group of providers and a limited range of procedures, and as such the data do not reflect pediatric sedation or anesthesia as it occurs randomly across the United States. Most importantly, we note that we do not know the degree of prematurity present in children classified in the preterm group. It is plausible that children born at 36 weeks' gestation have adverse event rates similar to those born at 37 weeks. If this is true, the risk of adverse sedation/anesthetic events would be higher in very premature (28–32 weeks' gestation) and extremely premature (<28 weeks' gestation) children. In addition, institutions involved in the research consortium are more likely to provide care to very and extremely premature children, resulting in the increased incidence of adverse events.

Observational studies such as this are essential tools in quality improvement initiatives. The advantage of studies conducted on large databases such as one developed by the PSRC includes the description of current practice at the national level, benchmarking, and the identification of trends and populations at risk. In addition, observational studies provide the ability to generate hypotheses for future randomized controlled studies. For example, it is known that children <60 weeks' postconception age receiving general anesthesia for surgical procedures are at increased risk for developing apnea perioperatively; however, the body of evidence supporting similar conclusions in children receiving propofol sedation is limited. Our data suggest that children receiving propofol for sedation/anesthesia and those born preterm are at increased risk for the development of apnea; however, the severity and duration of the apnea for diagnostic procedures is unknown.

Although the majority of patients in our study did not experience a serious adverse event with untoward outcomes, pediatricians and other health care professionals should be aware that diagnostic procedures frequently require sedation/anesthesia and expose children to the development of potentially serious adverse events. A risk/benefit assessment should be conducted before ordering elective studies, with patient age, birth history, and comorbidities taken into consideration.

Conclusions

Our longitudinal risk analysis of patients 0 to 22 years of age suggests that preterm and formerly preterm children are at increased risk for developing adverse sedation/anesthesia events. The highest risk group for the development of serious adverse events consisted of patients <6 months of age; however, an increase in the rate of adverse events was noted in the 10- to 13-year-old age group. These data suggest that age and history of prematurity should be considered during the development and implementation of a sedation/anesthetic plan.