Procedural Sedation Outside the Operating Room and Potential Neurotoxicity: Analysis of an At-Risk Pediatric Population

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ABSTRACT

OBJECTIVES: To determine the characteristics of children who met the risk criteria for potential neurotoxicity defined by the US Food and Drug Administration (FDA; 2016 warning) in a procedural sedation (PS) service.

STUDY DESIGN: A single-center retrospective review of all infants and children aged <3 years receiving PS outside the operating room from 2014 to 2016. Demographics, duration of, and the reason for PS were analyzed.

RESULTS: A total of 2950 patients with 3653 sedation encounters were included. Median age was 19 (range, 11−26) months. Most PS (86.4%) were for magnetic resonance imaging (MRI). The median number of sedation procedures per patient was 1 (25th−75th: 1−7), and median duration of sedation was 72 minutes (25th−75th: 55−98 minutes). Forty patients (1.4%) required prolonged sedations >3 hours, in a single encounter (median, [25th−75th] of 196 minutes [185−214 minutes]), and 298 patients (10.1%) had multiple sedation exposures during the study period. Overall, 327 patients, 11.1% (95% confidence interval, 10.0%−12.3%) required repeated and/or prolonged sedation. The most common reasons for repeated or prolonged sedation were MRI of the brain and neurologic concerns.

CONCLUSIONS: Multiple and prolonged PS commonly occurs outside the operating room in this young and potentially vulnerable population. Although certain imaging cannot be avoided, other cases may have the potential to be delayed until the child is >3 years old or to have alternate imaging that may not require prolonged PS. Family and provider awareness of the FDA warnings regarding potential neurotoxicity of sedation in all settings, both inside and outside the operating room, is critical.

KEYWORDS: children; drug safety; infants; sedation

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WHAT'S NEW?

The 2016 FDA warning about potential risk from prolonged or repeated sedative/anesthetic neurotoxicity in children ≤3 years of age occurs not only in the operating rooms but also in sedation services providing procedural sedation outside the operating rooms.

IN 2016, THE US Food and Drug Administration (FDA) released a drug safety communication warning about the use of general anesthetics and sedation drugs in young children and pregnant women.[1] The FDA warning specified that repeated or lengthy (defined as >3 hours) use of general anesthetic and sedation drugs during surgeries or procedures in infants and children younger than the age of 3 years or in pregnant women in the third trimester might affect the development of children's brains.[1] Despite convincing animal data, human studies have failed to provide strong evidence or are confounded by multiple factors about the impact of sedation and anesthesia on the neurocognitive development.[2] Further studies are ongoing with the SmartTots (www.smarttots.org) organization, a public−

private partnership between the FDA and the International Anesthesia Research Society coordinating and funding research to address issues of anesthesia/sedation affecting the developing brain of infants and children.[3]

In animal studies, the most commonly used general anesthetics such as sevoflurane and the intravenous (IV) agents such as benzodiazepines, barbiturates, propofol, and ketamine have been shown to potentially cause increased neuroapoptosis, dendritic cell damage, and long-term functional impairment of the central nervous system.[4] Most anesthetic/sedation neurotoxicity studies have focused on infants or children exposed to inhaled anesthetics or sedatives in the operating room (OR).[5-9] However, exposures meeting the FDA risk criteria may commonly occur outside the OR as well. For example, many children receive these agents during procedural sedation (PS), but data that describe these patients and quantify their exposures are sparse. It is important to describe the exposures in PS outside the OR because the characteristics/comorbidities of patients receiving PS may differ from those undergoing surgery. In addition, patients undergoing PS outside the OR are less likely than the surgical cohort to develop a stress/inflammatory response. Thus, the generalizability of the OR-based studies about anesthetic/sedative neurotoxicity, to PS outside the OR is limited, and should prompt sedation providers to delve deeper to explore the potential neurotoxicity risk encountered by this cohort. Furthermore, pediatric primary care providers, pediatric house staff, pediatric subspecialty providers, as well as other learners in pediatrics are major sources for referrals of children to PS. These pediatric care providers and learners are likely to be cognizant of the potential neurotoxicity concerns in children undergoing surgical procedures in the OR due to recent publications or concerns in the media, but are potentially less likely to be aware of prolonged or multiple exposures to nonvolatile agents such as propofol in PS outside the OR. This study also could serve as a call to arms, raising awareness if this concern does occur for certain children <3 years having PS outside the OR setting. One survey reported that anesthesia programs in US teaching institutions did not have a consistent management approach to the topic of pediatric neurotoxicity with anesthesiologists, anesthesia learners, surgeons, and other stakeholders.[10] In addition, a survey of European anesthesiologists reported that anesthesiologists from children's hospitals were less likely to routinely inform parents about neurotoxicity although they used more opioid-only anesthesia, especially in premature neonates.[11] The primary objectives of our study were to describe a large cohort of children <3 years of age undergoing multiple sedations and/or single prolonged sedations and to determine characteristics of children at risk based on the FDA criteria about exposure to general anesthetics or sedation.

METHODS

The institutional review board at Children's Healthcare of Atlanta in Atlanta, Georgia, approved this single-center retrospective chart review with a waiver of informed consent.

PATIENT SELECTION

Children's Healthcare of Atlanta is a quaternary care institution, which provides PS to >12,000 patients per year for various radiologic imaging and other procedures performed outside the OR. Data were obtained from the electronic medical records from January 1, 2014, to December 31, 2016. Inclusion criteria included all infants and children ≤3 years of age undergoing PS outside of the OR using IV sedation (Fig. 1).

Repeated PS was defined as >1 exposure in a child ≤3 years of age, and prolonged sedation was defined as a single sedation ≥3 hours in a child ≤3 years of age. Patients who received inhaled anesthetics for any procedure were excluded from the study. No detailed developmental assessment of the patient was made before the PS in this study other than routine screening for sedation.

SEDATION TEAM AND THE SEDATION PROCESS

The PS is administered by the sedation providers (ie, pediatric critical care, pediatric emergency care medicine physicians), who have privileges to administer deep PS. The sedation providers follow the American Academy of Pediatrics guidelines for deep PS.[12] Nurses trained in PS record the patient's vital signs every 5 minutes and assist the sedation process. Our institution follows the American Academy of Pediatrics guidelines for patient discharge after sedation.[12]

The sedation team refers children requiring PS to the anesthesia team based on a prescreening process if the child has any of the following: American Society of Anesthesiologists physical status ≥IV, a history of difficulty airway, abnormal facies, obstructive sleep apnea syndrome, body mass index of ≥95th percentile for age and sex, or complex congenital heart disease.[13]

For magnetic resonance imaging (MRI), the most commonly used medication is propofol (bolus followed by an infusion). Our institution has considerable experience in sedating patients even younger than 3 months of age.[14]

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all variables of interest and included counts and percentages, medians and ranges, or means and standard deviations, as appropriate. When applicable, percentages were accompanied by 95% confidence intervals. All data analysis was performed using SAS 9.4 software (SAS Institute Inc, Cary, NC).

RESULTS

During the study period, a total of 2950 patients ≤3 years of age with 3653 sedation encounters outside of the OR were identified. Overall, 327 (11%) of the 2950 patients required repeated and/or prolonged (>3 hours) sedation before 3 years of age. There were 40 (1.4%) patients who required prolonged sedation in a single encounter, and 298 (10.1%) who had repeated sedation exposures in the first 3 years of life. Only 11 patients had both repeated and prolonged sedation. Characteristics of

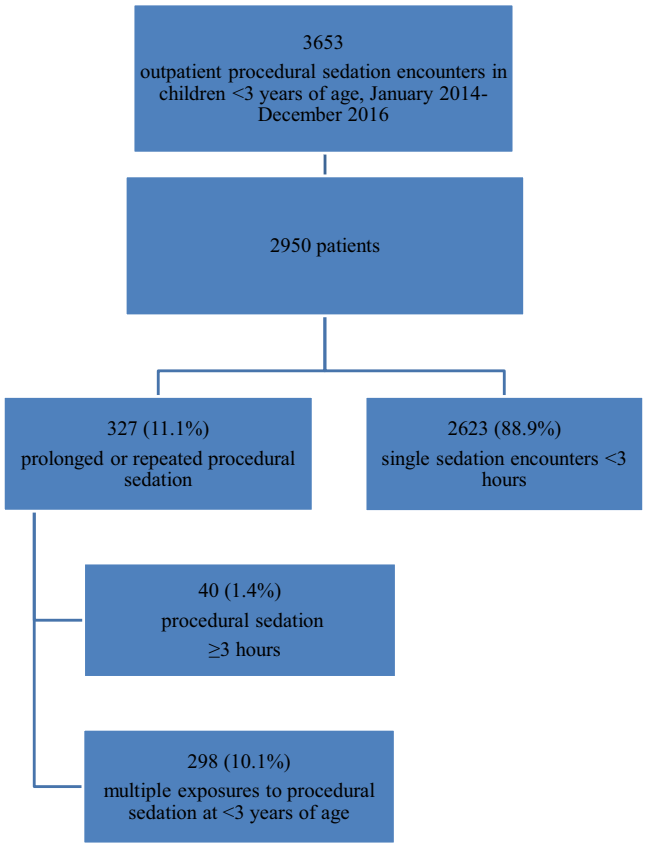

Figure 1. *Flow diagram describing search results for patients with procedural sedation who meet FDA risk criteria. FDA indicates US Food and Drug Administration.*

patients with prolonged and/or repeated sedation exposure as well as a synopsis of the medications and adjuncts used are shown in Table 1.

Figure 2 shows the underlying diagnosis leading to repeated or prolonged sedation. Children with neurologic diagnoses and malignancies, including brain and other extracranial solid tumors, typically had prolonged or repeated sedations.

A synopsis of medications and adjuncts used for PS is provided in Table 2. Propofol was the most commonly used agent in this cohort. Only 2 patients (0.3%) received dexmedetomidine.

Table 1. Characteristics of Patients With Prolonged and/or Repeated Pediatric Procedural Sedation Outside the Operating Room

Characteristic	No. (%) Sedation Events*	
	Prolonged Sedation (n = 40)*	Repeated Sedation (n = 789; 298 Patients)
Age at sedation, median (25th-75th), months	18.5 (8.7–31.2)	19 (11–26)
Weight at sedation, kg, median (25th-75th)	10.4 (8.0–13.3)	10.4 (8.5–12.3)
Outpatient†	38 (95.0)	764 (96.8)
ASA class		
I	15 (37.5)	94 (11.9)
II	19 (47.5)	288 (36.5)
III	3 (7.5)	65 (8.2)
Missing	3 (7.5)	342 (43.3)
Number of images during sedation, median (25th-75th)	2 (1–2)	1 (1–1)
>1 image in a single radiology procedure (MRI or CT scan)	21 (52.5)	NA
Duration of sedation, median (25th-75th), minutes	196 (185–214)	72 (55–98)‡
Sex, female	20 (50)	414 (54.5)

ASA indicates American Society of Anesthesiologists; MRI, magnetic resonance imaging; CT, computed tomography; and NA, not available.

*Number (%) unless otherwise noted.

†≤5% patients referred to the sedation services were inpatients.

‡Based on 741 sedation events.

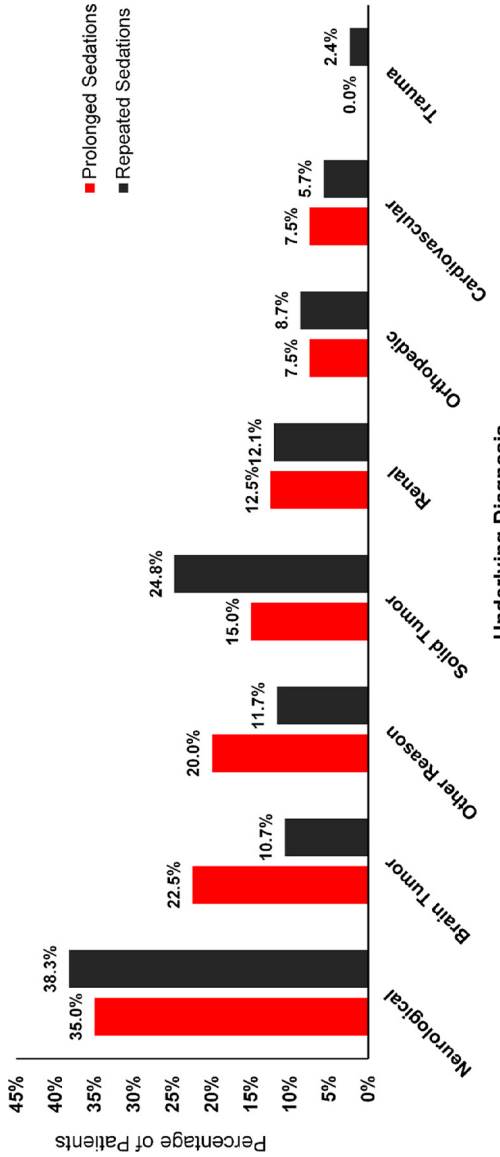

Figure 2. *Underlying diagnosis leading to repeated or prolonged sedation. Patients may have >1 underlying diagnosis, so percentages may add to >100%. Neurologic diagnosis included seizures, gait disturbances, unspecified spinal cord problems, neuromuscular weakness, and neurofibromatosis. Other underlying diagnoses included leukemia, hearing loss/evaluation for cochlear implant, gastrointestinal tract problems, hemangioma/port wine stain, tethered spine, unexplained swelling in head or neck, nystagmus, cellulitis, cysts, unexplained weight gain, and unexplained hypothermia.*

Table 2. Drugs Used for Sedation

Sedation Medication*	No. (%) Sedation Events
Prolonged sedation for imaging (n = 40 events)	
Propofol	40 (100)
Fentanyl	1 (2.5)
Repeated sedation for imaging (n = 789 events; 289 patients)	
Propofol	780 (98.9)
Fentanyl	12 (1.5)
Dexmedetomidine	2 (0.3)
Midazolam	26 (3.3)
Morphine	3 (0.4)

*Because >1 sedation medication could have been used, percentages add to >100%.

Imaging studies with repeated or prolonged sedation are shown in Figure 3. MRI of the brain, spine, abdomen, and pelvis were the most common imaging studies to result in prolonged or repeated sedation exposure. Approximately 105 of 327 (32%) patients undergoing imaging studies received IV contrast. We did not differentiate the duration of sedation between patients who received contrast versus those who did not receive contrast, nor did we capture information about patients who may have had procedures such as a lumbar puncture performed immediately after their imaging study, as it was evident from our experience that contrast administration or lumbar puncture prolongs sedation duration.

DISCUSSION

This study informs care providers, trainees, and other stakeholders such as referring physicians of the potential for infants and young children receiving PS outside the OR to be meeting the 2016 FDA warning for anesthetic/sedative exposure in children <3 years of age. Awareness by all stakeholders that children undergoing PS also could be at risk of potential neurotoxicity in such settings is necessary, given the rapid growth of PS outside the OR.[15] A recent retrospective analysis by Shi et al,[16] analyzing a geographic cohort, found that 1 in 7 children were exposed to at least 1 episode of general anesthesia before the age of 3 years and approximately 1 in 4 children who received general anesthesia met FDA criteria for potential neurotoxicity. Our study is the first to specifically focus on deep sedation provided in an outpatient setting and outside the OR.

Overall, 11.1% of our patients demonstrated prolonged or repeated PS, and a striking number (40 patients; 1.4%) underwent very prolonged single sedations (>3 hours). Bartels et al[17] reported that 13.7% of children <3 years of age undergoing general anesthetics were exposed for >3 hours. Although only 1.4% of our patients had single PS exposures >3 hours outside of the OR, a similarly significant portion met high-risk criteria based on multiple or prolonged sedations (11.1%). This highlights that while meeting high risk for different reasons, PS outside the OR remains a clear concern for meeting FDA at risk warning.

Most of these patients who needed prolonged sedation required it for neurologic or neuro-oncologic reasons.

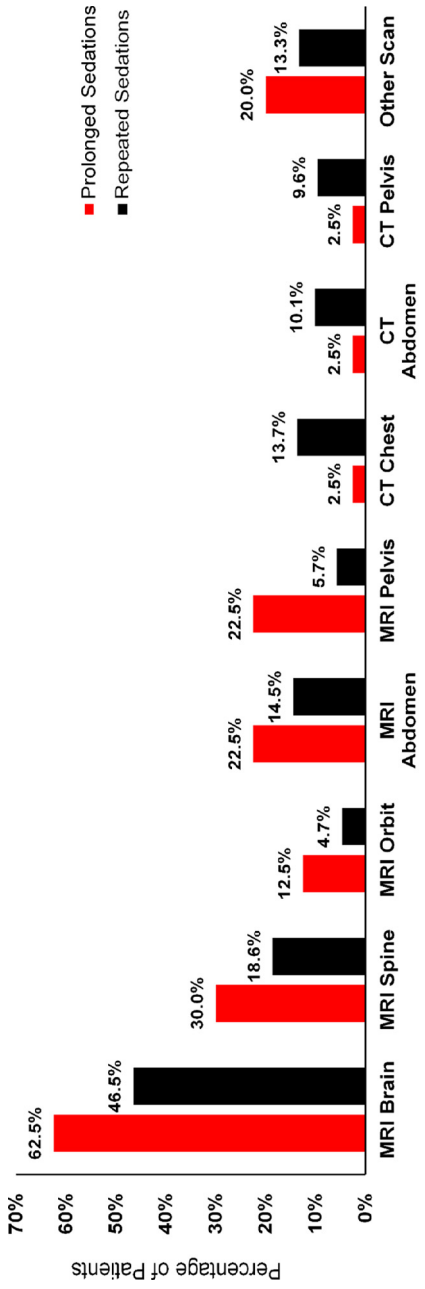

Figure 3. *Imaging studies with repeated or prolonged sedation. Because the patient may have undergone multiple imaging studies during a sedation encounter, percentages may add to >100%. Other imaging studies included magnetic resonance angiography; MRI of chest; CT of maxillofacial/sinus; CT of upper or lower extremity; total body CT scan; MRI of upper or lower extremity; and magnetic resonance venography of chest, head, neck, and/heart. MRI indicates magnetic resonance imaging; and CT, computed tomography.*

This finding is concerning because the underlying brain disease for which a study under PS is required (ie, diagnosis of a neurologic condition, brain tumor) may increase the brain's sensitivity to the sedatives used and the associated potential neurotoxic effects. However, these are cases when benefits might outweigh risks, especially when urgent or alternative diagnostics are not available. Unlike elective procedures in the OR, which could be delayed, radiologic imaging for cancer diagnosis, or follow-up examinations using PS may be necessary on a case-by-case basis even if it involves prolonged or repeated sedation.[18] Although parents of children with cancer, etc, may not have a choice to delay the exposure to PS, the family should be engaged by the providers including the pediatrician and other clinicians involved in the child's care in an open discussion of the FDA warning about potential neurotoxicity. Explaining risk/benefits as well as alternatives available to PS may help reassure families and perhaps certain procedures can be delayed or shortened, or alternatives considered, that limit the amount of sedation time and potential risk in this vulnerable population. Discussion with pediatric radiologists about the best imaging study for the patient's disease or shortening the imaging protocol when possible could potentially decrease the exposure time to sedation. Alternative procedures that may not require prolonged sedation also may be considered. However, such studies as computed tomography scans have their associated risks (ie, radiation exposure).[19] In addition, providers must discuss with families and other stakeholders the risks and benefits of delaying fully elective procedures until the patient is out of the FDA recommended at-risk period.[18]

Parents should specifically ask specialists if neuroimaging for disorders such as developmental delay or other disorders are critically necessary if the child has no seizures or headaches and has otherwise normal findings on the neurologic examination.[20] If the procedure is deemed essential, at what age and with what potential immediate and longer-term sedation risks should this occur? The results of this study should help families and providers better assess these questions, open communication, as well as raise awareness that the FDA warnings are applicable and risks potentially exist to the developing brain. Families and all stakeholders need to be fully aware and informed.

It is not surprising that propofol was the most commonly used drug for sedation in this study because our institution is primarily a propofol-based sedation program. Propofol in animals has been shown to potentially cause neuronal apoptosis.[21] The use of propofol for PS is widespread because of its favorable pharmacodynamic profile, low rates of serious adverse events, a shorter onset of sedation, and faster recovery time compared with other sedatives.[22,23]

Only 0.3% of our sedation encounters used dexmedetomidine. Although this finding is most likely because our sedation program is primarily a propofol-based sedation service, it could also be because the sedation providers needed their patient to be deeply sedated for a longer

MRI, which may not be possible with dexmedetomidine alone. Recent studies have shown good success with the use of dexmedetomidine for short MRI, and its use could potentially decrease exposure to commonly used sedatives like propofol.[24-26] Furthermore, dexmedetomidine has been shown to have potential neuroprotective effects in animal models of brain injury.[27,28] The exact role of dexmedetomidine or other agents needs to be further explored, especially for prolonged imaging studies and for the risks with its use in the neonatal and premature cohorts for PS.[29]

In light of our of prolonged/repeated exposures to anesthesia/sedation, the use of nonpharmacologic techniques for imaging studies such as swaddling, sucrose pacifier, and papoose/vacuum devices and assistance of child life specialists should be considered, although none of these techniques have been shown to be superior to sedation.[30] The use of nonpharmacologic techniques or sedation using dexmedetomidine are potential strategies that sedationists can use in their practice whenever possible. Further research will be needed to see if such strategies decrease the risk of exposure to propofol.

Our study has several limitations. It is a single-center retrospective study with relatively small sample size, but it comes from one of the largest sedation services for children in the nation. Although the data used in our analysis predate the FDA's 2016 warning for potential neurotoxicity, sedation physicians in our group were unaware of this retrospective analysis, and hence there was no change in sedation practices of these physicians during or after the study period. Our goal was not to see the impact of FDA warning on our practice but rather to see how our sedation practice aligned with FDA's concerns on potential neurotoxicity outside the OR. The duration of sedation for a given procedure or multiple exposures to sedation were captured from patients' electronic medical records, as documented by both the sedation providers and the sedation nurses, and thus offers a double check to the accuracy of the duration of the sedation. Despite the retrospective nature, this study still has the largest cohort of patients meeting FDA risk criteria for abnormal brain development from exposure to PS outside the OR setting, of which we are aware. The retrospective nature also allowed us to evaluate actual practice among a large group of providers. Furthermore, the FDA warning was issued based primarily on convincing evidence from animal studies.[4,31] Because of the retrospective nature of our study, we do not have follow-up information on the neurocognitive performance of our study cohort and, for the same reason, we did not compare the characteristics/outcomes of our study cohort to those who had OR exposures. It was not the intention of this study to assess the long-term neurocognitive development of the study cohort over time, and further studies are needed to determine the long-term impact of prolonged or repeated sedation exposure. It is also probable that some of these patients could have had previous exposure to general anesthesia (eg, for central line placement or tumor removal), which could potentially further add to the risk of total exposure to sedatives. Many of these patients may have undergone additional general anesthesia, or sedation exposures at outside institutions, which would only further increase the actual extent of children in our cohort for which repeated or prolonged sedations before age 3 years of life is a concern. We did not evaluate adverse events in the cohort described in this study, as multiple other studies have reported on the adverse events when propofol is used for PS outside the OR.[22,32]

We also acknowledge that there are no data in the anesthesia literature that provide a definitive link between exposure to sedative/anesthesia in the developing brain and long-term harm. In fact, in a recent press release, the American Society of Anesthesiologists assures parents that anesthesia provided during one brief surgery is safe and urges parents to make decisions about delaying of surgery with their child's surgeon and anesthesiologist.[33]

The impact of the FDA warning of the sedative/anesthesia risks for brain development issued in 2016 remains unknown, especially in the PS arena. Our study highlights the potential exposure to risk in young children undergoing PS. The use of propofol and other sedatives outside the OR by nonanesthesiology providers is expanding and outpacing the work done by even pediatric anesthesiologists. It is therefore vital for pediatric sedation providers and referring physicians, including community pediatricians, to pay specific attention to FDA's potential risk criteria that may be overlooked in the PS arena.[34] It is also critical that providers fully inform families and engage them in the decision process, weighing risks/benefits of the sedation, obtaining and timing of the underlying procedure and educating everyone on the FDA warnings.

CONCLUSIONS

In a large-volume PS program, many children met the FDA's neurotoxicity risk criteria for prolonged duration of sedation/anesthesia or multiple exposures to sedatives before 3 years of age in non-OR settings. In this subset of potentially at-risk patients, appropriateness of the imaging or delayed imaging should be considered when the procedure is elective or not critical in a child aged <3 years. Both pediatric care providers (including trainees), and families must be fully aware and informed of the potential neurotoxicity risks of sedation at an early age and balance them with the benefits of the proposed procedure or alternatives. In light of FDA warnings and our findings that children are meeting the FDA's at-risk criteria in non-OR settings, further research also is needed to evaluate the possible long-term neurodevelopmental effects of exposure to sedatives in this vulnerable population.

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