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MINISYMPOSIUM: MINIMIZING SEDATION IN PEDIATRIC MRI

Pediatric anesthesia and neurotoxicity: what the radiologist needs to know

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Abstract The use of cross-sectional imaging in the pediatric population continues to rise, particularly the use of MRI. Limiting motion artifact requires cooperative subjects who do not move during imaging, so there has been an increase in the need for pediatric sedation or anesthesia. Over the last decade, concern has increased that exposure to anesthesia might be associated with long-term cognitive deficits. In this review we report current understanding of the effects of anesthesia on the pediatric population, with special focus on long-term developmental and cognitive outcomes, and suggest how radiologists can use new technologies or imaging strategies to mitigate or minimize these potential risks.

Keywords Anesthesia · Children · Developmental delay · Magnetic resonance imaging · Neurotoxicity · Sedation

Introduction

Use of cross-sectional imaging in the pediatric population continues to rise, particularly the use of MRI [1, 2]. The myriad benefits of cross-sectional imaging include precise identification of anatomy in pre-surgical planning; sensitive evaluation for life-threatening injury in trauma; detection and accurate diagnosis of disease, including systemic disease spanning multiple body systems; and follow-up evaluation of surgical repair, interval healing, disease progression and treatment effect. Achieving diagnostic-quality imaging requires image optimization across multiple realms, including limiting interference from imaging artifact. Limiting motion artifact requires cooperative subjects who can hold still on command; thus there has been a concomitant increase in the need for pediatric sedation or anesthesia to fulfill this demand. In a 12-year study at one university medical center, researchers found a growth rate in pediatric CT and MRI of 8.1% with an essentially equal 8.5% increase in anesthesia care during imaging [3]. In practicality, the clinical requirements in the pediatric population necessitate levels of sedation that most commonly fit the definitions of deep sedation or general anesthesia. In this review we use the terms "sedation" and "anesthesia" to refer to the use of pharmacological agents to ensure adequate patient conditions for MRI.

When approached in a systematic manner, modern pediatric anesthesia care for children undergoing imaging appears to be extraordinarily safe [4]. However over the last decade concern has increased that exposure to anesthesia might be associated with long-term cognitive deficits [5]. As a result, strategies that reduce anesthesia exposure at an early age could have significant clinical value [6]. In this review we report current understanding of the effects of anesthesia on the pediatric population, with special focus on long-term developmental and cognitive outcomes.

Sedation medications and adverse events

Pharmacological strategies for achieving immobility during imaging encompass a spectrum of interventions from oral anxiolytics to general anesthesia with intubation. However,

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younger children typically require the use of general anesthesia in order to produce acceptable image quality. Currently in the United States, anesthesia for cross-sectional imaging is primarily the purview of the anesthesiologists or specially trained designees, including nurses [7, 8]. A structured approach includes appropriate use of medications (with a particular emphasis on limiting side effects) and efficient anesthesia administration [9].

The ideal sedation agent for use in pediatric imaging is easy to administer, fast-acting, predictable, rapidly reversible and well-tolerated. The most common classes of medication used for imaging procedures historically have been benzodiazepines, opioid analgesics, intravenous anesthetics (propofol, ketamine), inhalational anesthetics (e.g., sevoflurane), selective alpha-2 agonists (dexmedetomidine), barbiturates (chiefly pentobarbital) and hypnotics (e.g., chloral hydrate). These medications have been thoroughly reviewed [10, 11]. Much of the literature on these agents' use in children focuses on optimization of agent and dose [12–15]. Longer-acting agents such as chloral hydrate and pentobarbital have fallen out of favor. In recent years, propofol has been the predominant agent of choice, occasionally supplemented by a benzodiazepine such as midazolam [4].

A sizeable body of literature has examined the rate of adverse events occurring during pediatric sedation. These studies have found a wide range in the incidence of adverse events, varying from <1% to >10% [16–18]. Although the incidence of adverse events in some of these studies was quite high, they included a wide range of practices including the use of older anesthetic agents such as pentobarbital.

More recent data indicate that when approached in a systematic and well-organized manner, anesthesia for MRI is extremely safe. The Pediatric Sedation Research Consortium collected data on adverse events in pediatric sedations performed outside the operating room, of which greater than 60% of the studied sedations occurred for imaging. Their analysis included data pertaining to more than 30,000 sedations at 26 international sites. They found a complication rate of 5.3%, with oxygen desaturations below 90% for at least 30 s comprising nearly half of all reported events [4]. Despite this relatively high adverse event rate, it was notable that serious adverse events were rare, and there were no reported deaths. The authors concluded that the low rate of serious events was attributable to the use of a highly motivated and organized pediatric sedation service and that safety was related to the ability to effectively manage less serious events.

In other studies, developmental disability [19] and underlying respiratory illness [20] were found to confer additional risk for adverse event during sedation for imaging, whereas the rate of adverse events remained independent of patient gender, age and weight across multiple series. A systematic review of 118 case reports of adverse sedation events in pediatrics concluded that drug overdoses and drug–drug interactions were the most frequent root causes of adverse events, particularly when three or more agents were used concurrently, regardless of agent used or route of administration [21].

Anesthesia and neurotoxicity

Over the last two decades, concern has mounted that exposure to all currently available anesthetic agents (including sedatives) might be neurotoxic in young animals during periods of synaptogenesis and rapid central nervous system (CNS) cell growth. Animal studies comprise the preponderance of literature evaluating direct neurotoxicity of sedation medications [22, 23]. Studies of rodent and non-human primate models have revealed immediate neurotoxic effects including accelerated apoptosis and increased neuronal cell death [24, 25]. In addition to neuronal cells, the supporting stroma of the CNS is also affected. Evidence of concomitant oligodendrocyte cell death introduces a plausible mechanism by which even brief exposure to anesthetic agents could lead to long-term structural CNS changes [26]. These neurotoxic effects have been observed in animal models exposed to inhaled and intravenous anesthetics with actions on both the γ-aminobutyrate (GABA) and N-methyl-D-aspartate (NMDA) receptors. In addition to histological findings, animal models consistently exhibit evidence of cognitive deficits, primarily in the domains of learning and memory. Anesthesia-exposed rats exhibit deficiencies in performance in water maze testing as well as recollection memory [27]. In addition to deficits in memory, specific patterns of behavior might be adversely affected by early anesthesia exposure. Female rats exposed to general anesthesia at an early age appear to develop sexually normally and produce healthy offspring [28]. However, these rats exhibit extremely poor maternal nurturing behavior and their offspring suffer high mortality rates from maternal neglect [29, 30].

Translation of these results to human populations poses significant challenges. There are species-specific differences in development, including the timetable of brain maturation and the window of peak vulnerability to anesthetic exposure [31, 32]. In addition, it is difficult to compare anesthetic regimens between laboratory protocols and clinical anesthesia conditions in human infants. Despite these limitations, it is generally well accepted that early exposure to anesthesia causes permanent structural and functional changes in the CNS of laboratory animals. However, whether early

anesthesia exposure causes meaningful harm in humans remains uncertain [33, 34].

Long-term effects: neurodevelopmental or cognitive risks?

Evaluation of anesthesia-related neurotoxicity in the human pediatric population is predominated by observational case–control and retrospective cohort study designs [35, 36]. The vast majority of these studies evaluate cognitive or neurodevelopmental outcomes in children exposed to surgical anesthesia as compared to age-matched non-exposed cohorts [37–41].

Some studies reveal no identifiable link between anesthesia exposure and negative neurodevelopmental or cognitive outcomes. For example, a decade-long cohort study in the Netherlands followed more than 1,100 monozygotic twin pairs with varying histories of early anesthesia exposure. Although there were greater rates of cognitive problems in concordant twin pairs in which both twins had early exposure to anesthesia compared to unexposed concordant pairs, they identified no statistical difference in the rates of learning disabilities between the 71 discordant twin pairs in which only one twin had early anesthesia exposure [42]. This study of monozygotic twins controlled for many confounding variables including genetic variability, birth history including prematurity, and in utero toxic exposures; however interpretation of this paper is limited by a lack of details regarding anesthetic administration. A recent large database study from Denmark found no statistically significant difference in long-term academic performance between children with and without a history of exposure to anesthesia and surgery at an early age [43]. A retrospective study of children who underwent urological surgical procedures prior to 6 years of age similarly showed no statistically significant difference in the rates of behavioral disturbances in children operated on before or after age 24 months [44].

Other studies have revealed differences in development and cognition between anesthesia-exposed and non-exposed cohorts. A Mayo Clinic study of greater than 5,000 children in Olmstead County, MN, found an increased risk of learning disabilities in children with two or more anesthesia exposures prior to the age of 4 years [45]. An additional study of children from the same population confirmed repeated early anesthesia exposures as a risk factor for learning disability later in childhood [46]. In another study, Ing et al. [47] found significant domain-related language deficits and other cognitive deficits in a cohort of exposed children in Australia.

Lack of an identifiable phenotype of anesthetic neurotoxicity has also limited human research. Of particular interest to radiologists, MRI and fMRI studies are beginning to shed light on this issue. Taghon et al. [48] demonstrated that fMRI might be a useful tool in the investigation of anesthetic neurotoxicity by demonstrating activation differences in the cerebellum, cingulate gyrus and paracentral lobule between groups of exposed and unexposed children. Backeljauw et al. [49] found decreased performance intelligence quotient (IQ) as well as structural CNS changes in the form of lower-gray-matter density in the occipital cortex and cerebellum. An objective model of potential anesthetic neurotoxicity would be of enormous value. Such a model would help to determine whether there are permanent changes in the human CNS after exposure in clinical scenarios. In addition, an objective phenotype would aid in understanding potential mechanisms of neurotoxicity as well as provide a template to judge the efficacy of potential mitigating strategies or antidotes.

An oft-cited criticism of the existing clinical studies of anesthesia and neurotoxicity, irrespective of study result, is that by comparing populations that have had anesthesia during surgery to those that have not had anesthesia, the surgical exposure itself serves as an undeniable confounder. It is possible that either the need for surgery, the surgical experience, per se, or demographic characteristics of groups of children requiring early infant surgery might influence later tests of cognitive function. Multiple approaches to address this limitation are underway. In Iowa, a study by Block et al. [50] found marked decreases in elementary school test performance in children who had received general anesthesia for pyloromyotomy, hernia repair or circumcision. At our own institution, a study of 265 children who underwent spinal anesthesia for the same procedures revealed no relationship between infant spinal anesthesia and very poor elementary school performance [51]. Currently multiple international centers are engaged in a similar study under the General Anesthesia Spinal Anesthesia (GAS) group — a prospective, randomized trial comparing cognitive outcomes in infants undergoing inguinal hernia repair under either general anesthesia or spinal anesthesia [52]. At the 2-year interval, the GAS study revealed no association between 1 hour of sevoflurane and adverse neurodevelopmental outcomes compared with infants who underwent the same surgical procedure with spinal anesthesia [53, 54].

Conclusion and next steps

While the diagnostic and prognostic benefits of cross-sectional imaging in the pediatric population are robust, the cost–benefit analysis of using sedation to acquire diagnostic imaging remains complex. The clinical relevance to pediatric populations of anesthetic agent-related neurotoxicity in the form of accelerated neuronal cell death seen in rodent and non-human primate models is uncertain [55]. Furthermore, as astutely delineated by Flick and Warner [56], the observational studies on infant and early childhood exposure to

anesthesia and negative neurodevelopmental outcomes later in life are inherently challenging to interpret. These concerns are addressed in consensus statements from the U.S. Food & Drug Administration and other stakeholders including the American Academy of Pediatrics and the American Pediatric Surgical Association [57, 58]. Radiologists who perform scans that require the use of anesthetic and sedative drugs should familiarize themselves with these statements.

Inherent to the discussion of limiting the potential harmful effects of anesthesia on the developing brain are the non-pharmacologic approaches to management of pediatric patients during image acquisition and their relative effectiveness. Imaging simulation and play preparation have been in use for more than 20 years [59, 60] and demonstrate continued success [61, 62]. Stimulation-reduction techniques and feeding neonates and infants immediately prior to MRI have proved effective [63], with a growing evidence base [64]. Cincinnati Children's Hospital Medical Center demonstrated measurable success reducing sedation of pediatric patients undergoing cross-sectional imaging, by using varied strategies including child-life specialists, video and audio technologies, and moving light shows projected within the imaging suites [65]. In their initial study of children under 7 years of age, the Cincinnati team observed statistically significant decreases in sedation utilization of 34.6% for MRI and 44.9% for CT [65].

Some children undoubtedly require the use of anesthesia to provide suitable conditions for high-quality scans. At present time, our understanding of the potential neurotoxic effects of anesthetic drugs is not sufficient to allow recommendation of one agent vs. another (e.g., inhalational anesthesia vs. propofol). The vast majority of the commonly used anesthetic agents in children have been shown to be of concern in animal models. However, alpha-2 agents, including dexmedetomidine, are not thought to be neurotoxic, and dexmedetomidine might even be neuroprotective in animals [66]. Dexmedetomidine has been successfully used for MRI; however it has a higher failure rate than propofol, has been associated with motion artifact, and has a longer recovery time [67].

Recent advances in image acquisition techniques, including dramatic improvements in isotropic 3-D imaging with the ability to reconstruct images in orthogonal planes, offer pediatric radiologists the opportunity to re-evaluate MR protocols and potentially realize significant time savings without image degradation, and substantially reduce anesthesia times. In addition, development of MR sequences that are less motion-sensitive might allow less anesthesia to be employed for certain clinical indications.

Whereas exposure to some form of anesthesia for surgery is obligatory, in radiology we have the opportunity to apply tools and technologies to systematically reduce rates of pediatric anesthesia exposure. Regardless of what the future demonstrates about correlations between early exposure to anesthesia and neurotoxicity and neurodevelopmental and cognitive impairments, it is not difficult to agree that unnecessary anesthesia exposure, like unnecessary radiation, is a thing to be avoided. We support the priority adoption of an ALARA (dose as low as reasonably achievable) principle for anesthesia such that in the acquisition of pediatric imaging we would apply a multifaceted approach to reduce imaging sedation as much as is reasonably achievable.

Compliance with ethical standards

Conflicts of interest None

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