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REVIEW ARTICLE

Anesthetic neurotoxicity: what to tell the parents?

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Summary

Over the past decade, numerous preclinical and retrospective human studies have reported that the provision of anesthetic and sedative agents to infants and children may be associated with adverse neurodevelopmental outcomes. These data have gained widespread attention from professional and regulatory agencies, including the public at large. As such, pediatric anesthesiologists are being increasingly questioned by parents about the risks of anesthetic agents on their children's neurocognitive development. To impart a framework from which anesthesiologists may address the apprehensions of parents who actively bring up this issue, we review the data supporting anesthetic neurotoxicity and discuss its strengths and limitations. As many parents are not yet aware and do not actively raise these concerns, we also discuss whether such a conversation should be undertaken as a part of the consent process.

Introduction

Within the span of a single generation of pediatric anesthesiologists, the approach to neonatal anesthetic care has changed from a belief that the provision of analgesia, hypnosis, and amnesia to the neonate was not only unnecessary but represented a quantifiable risk given the widely held assumption that neonates neither experienced pain, nor possessed the capacity for memory formation, nor demonstrated evidence of higher order cognition. However, with improved methods of monitoring, safer anesthetic drugs and delivery systems, and better understanding of both the response of neonates to procedural pain as well as the potential consequences of leaving such responses untreated, the field rapidly developed a care standard not unlike that of the adult, where the pharmacologic provision of amnesia, hypnosis, and analgesia is standard (1–4). As such, the pendulum of anesthetic drug provision swung from its nadir to a position where multiple anesthetic agents were administered to neonates as a matter of routine.

Over the past several years, however, many have begun to question whether the pendulum has swung too far and the need for anesthesia in the neonates should be reassessed (1). Numerous preclinical and retrospective human data have questioned the safety of anesthetics on the developing human brain. While once restricted to a relatively small group of individual clinicians and researchers, debate over the risks of anesthetics has now reached a wide audience, including professional organizations inside and outside of anesthesiology, including the United States Food and Drug Administration (FDA), the European Medicines Agency, and increasingly the lay public. As such, pediatric anesthesiologists are being increasingly confronted with questions regarding the safety of the drugs that, in effect, define their profession. Answering such questions first involves understanding the evidence in support of anesthetic neurotoxicity, its potential shortcomings, and current research addressing this issue.

The evidence

Data supporting anesthetic neurotoxicity have been present in the literature for over 10 years (5–7). These data originate from mechanistic studies of fetal alcohol syndrome, an accepted, well-defined, and permanent neurotoxidrome (8). In brief, it was found that exposure of developing rodents to ethanol, a known *N*-methyl-D-aspartate (NMDA) receptor antagonist and γ-aminobutyric acid (GABA) receptor agonist, during a critical period of development resulted in

widespread neuroapoptosis of the central nervous system (9). Given that most anesthetic agents are believed to exert their effects via these receptors, the data were subsequently reproduced using established anesthetic agents and neurodegeneration was described using a wide variety of molecular and histologic techniques (10). These abnormalities, however, were without defined developmental significance, until a landmark study reported long-term cognitive deficits in developing rodents exposed to a combination of midazolam, nitrous oxide, and isoflurane (11). These data have subsequently been reproduced in a wide variety of species using many of the anesthetic agents in common clinical use (10).

Although criticism regarding dose, duration, degree of clinical monitoring, and generalizability of rodent data to humans remains (12,13), many of these concerns have been addressed by large animal models utilizing nonhuman primates. At present, seven published studies have reported neuroapoptosis in response to anesthetic exposure in developing monkeys, all using monitoring standards similar to that of children undergoing operative procedures (14–20). Perhaps most importantly, one developmental study reported long-term neurocognitive deficits in monkeys exposed to 24 h of ketamine, effects that were persistent several years after exposure (17). Recently, the belief that the histiologic changes induced by anesthetic exposure are restricted to neurons has been challenged. Degeneration of oligodendrocytes has also been reported in developing monkeys, suggesting that the spectrum of anesthetic neurotoxicity may be wider than previously assumed (14). At the same time, there have been many attempts to prevent the histiologic and developmental abnormalities induced by anesthetics, many of which have been successful in the laboratory. These protective techniques include, but are not limited to, hypothermia (21), melatonin (22), dexmedetomidine (23), lithium (24), erythropoietin (25), xenon (26,27), bumetanide (28), and environmental enrichment (29). However, it has not yet been demonstrated in monkeys that prevention of histiologic abnormalities induced by anesthetic exposure prevents the aforementioned behavioral consequences. Indeed, while isoflurane has been reported to both induce (14,16) and not induce (19) histiologic injury in monkeys, the developmental consequence of isoflurane exposure has not yet been reported in this species. As such, it has not yet been established that the absence of histiologic changes can serve as an adequate marker for the complete absence of neurocognitive injury, which may complicate the development of neuroprotective strategies.

In contrast to the hundreds of preclinical studies in animals is the relative dearth of reports studying the neurodevelopmental effect of anesthetics in humans. While the prospective randomized controlled trial is the gold standard for determination of cause and effect, cost, length of time from exposure to the measured outcome, and ethical considerations have made such studies prohibitive with regard to anesthetic neurotoxicity. As such, the extant literature is based upon a very limited number of epidemiologic studies, all but one of which is retrospective (30–43). These studies exhibit significant variability due to varying population selection, comparators, definition of anesthetic exposure, timing of anesthetic exposure, outcome measurements, and findings. Some of the retrospective studies encompassed a period during which halothane, a drug no longer used in the United States, was the primary anesthetic agent used, and standard monitoring devices (such as the pulse oximeter) were not available (34,35,40,41,43). All the retrospective studies involved analysis of databases composed of one of three primary sources: administrative data, single-center data, and data from a single geographic area (birth cohorts). While data derived from these data sets have been valuable, they also have significant weaknesses that temper conclusions derived from such records (5,44). Common to all is the fact that these databases were not constructed for the purpose of studying the desired outcome, and therefore, each data set has implicit strengths and weaknesses. While administrative data possess the strength of having large number of patients available for study, such data sets have been criticized for lacking detailed information about the anesthetic and surgery and being unable to control for the effects of migration patterns and educational experience (5,32,33,44). While single-center data often possess detailed medical information about the anesthetic, they are weakened by the presence of relatively small numbers of patients for analysis as well as the possibility of increased comorbidities in their subjects confounding the results (referral bias) (31,36,39). Birth cohorts have had the benefit of avoiding referral bias and providing detailed socioeconomic, educational, and medical information, but the specific constitution of such cohorts may not be generalizable to pediatric populations at large (34,35,37,38,40,41,43).

With regard to outcome measurement, comprehensive neurocognitive tests are the gold standard for both determining the presence or absence of neurologic deficits as well as quantifying their magnitude. However, such exams are often prohibitively expensive and thus have been reported in a single study utilizing an existing birth cohort assembled to study child development in Australia (38). The remaining studies utilized data from

individual or group-administered tests of achievement (GTA), teacher/parent rating scales, and diagnostic codes. Unlike individual tests of achievement, GTAs are intended to serve as sensitive tests to screen large numbers of subjects but lack the specificity necessary for diagnostic precision. Diagnostic codes, in contrast, are biased in the opposite direction; they provide specific diagnostic information, but are frequently inaccurate, lack sensitivity, and may miss cognitive delay observed in nonclinical settings. Lastly, parent/teacher reports are overtly subjective, and information on their sensitivity and specificity is completely lacking with respect to the outcomes of interest.

Despite these shortcomings, of the approximately dozen studies evaluating for the presence of anesthetic neurotoxicity in children, eight report an association between neurocognitive outcome and exposure to anesthetics. However, the degree of the purported association remains weak, with the majority reporting hazard ratios less than 2. Hazard ratios of this magnitude are frequently secondary to factors other than the exposure (confounders) and are significantly weaker than associations that are widely accepted in the pediatric literature, such as prone sleeping and sudden infant death syndrome (hazard ratio 12.9) as well as salicylate use and Reye syndrome (hazard ratio 26) (5,44). Nevertheless, even a modest effect, if real, could have profound public health consequences given the millions of anesthetics that are provided to children around the world each year.

Information for parents

What then can be said to parents based on the available evidence? While the weight of preclinical data on anesthetic neurotoxicity is overtly concerning, results from animal studies must be extrapolated to humans with great caution. One need not look further than penicillin, perhaps one of the greatest drug discoveries in the history of medicine, to learn of the disparate effects drugs have on animals as opposed to humans. Penicillin is profoundly toxic, to the point of inducing fatal enterotoxemic and hemorrhagic syndromes, in both guinea pigs and rabbits, two mammals commonly used in laboratory research at the time this drug was discovered (45–48). Had the initial testing of penicillin been conducted in these species, this incredibly important drug likely might never have been used in humans. As a more recent example, fluoroquinolone antibiotics have been shown to cause irreversible degeneration of articular cartilage in a wide variety of juvenile animals including dogs, mice, and guinea pigs, an effect that has not yet been demonstrated in humans despite worldwide utilization of these drugs (49–51). Similar caution must also be extended to anesthetic neurotoxicity, given that its purported mechanism primarily involves neuronal cell death. While much attention has been given to the fact that many neurons die by apoptosis as a normal part of growth and development (as much as 50–70%), comparatively little has been given to those neurons that survive (10,52). Unlike the cellular lining of the gastrointestinal system that is effectively replaced by mitosis every few days, neurons do not replicate and are thus among the longest living cells within the body. The lifespan of human neurons can be over 100 years; neurons of a mouse in captivity live for 2 years, a small fraction of their human counterparts. Such an observation suggests a considerable difference in the magnitude of neuronal survival mechanisms between these two species, a magnitude that also may govern how the neurons respond to stress and injury. This may help explain why the described neurotoxic effects of anesthetics in rodents are particularly robust, while evidence in humans is comparatively weak. As such, preclinical data can neither prove nor disprove that anesthetics cause neurodegeneration in humans and have limited capacity to assuage a concerned parent or disquiet an indifferent one.

What can be said with regard to the human studies? At best, these studies have not ruled out the possibility that anesthetic neurotoxicity exists in humans. This, of course, is a far cry from stating that it has been 'ruled in'. While concerning, retrospective human data remain hypotheses-generating, rather than conclusion-generating, even under the best of circumstances, given that such data can reveal only associations. Parents (and some clinicians) often misunderstand the difference between association and causation. An illustrative example is the association between gray hair and death (53). While gray hair is certainly associated with death, it does not cause death; interpretation of such an association is, as in all retrospective analysis, subject to confounders in which the studied factor may only serve as a marker for the causative factor, in the above example that of age. Nevertheless, while epidemiologic studies rarely provide great confidence in the strength of an association, the human data do provide some assurance that single, brief anesthetic exposures may be safe (34,35,37,40,43). There are no data that would indicate that a change of anesthetic practice should be undertaken and may have unintended consequences secondary to delaying necessary surgery or changing anesthetic practice to one that is unknowingly more risky.

As there is not yet certainty within the medical community that there is a real risk posed by anesthetics, there does not seem to be a compelling medical argument to actively bring up the purported risk with patients and their parents as part of the consent/assent process. Such a discussion would be of unclear benefit, particularly to those undergoing nonelective surgery, and may induce unnecessary and unwarranted concern on the part of the parent. The effect of preoperative discussions of anesthetic risk on ameliorating parental anxiety has been reported in a number of studies, and unlike comparable studies in adults, detailed information regarding anesthesia has not been associated consistently with decreased parental anxiety (54). In one illustrative study, while ~50% of parents reported that the anesthetic was the most anxiety-provoking aspect of their entire perioperative experience, the discussion of anesthetic risk had no effect on alleviating parental anxiety in 50% of parents and was reported to increase anxiety in an additional 25% (55). Nevertheless, some practitioners are beginning to question whether there is a legal responsibility to discuss the possibility of anesthetic neurotoxicity. In the United States, laws governing the consent process originate at the state level and are largely split between two different consent standards—the professional standard and the materiality standard (56). In states governed by the professional standard, physicians are required to disclose risks that a reasonable physician would in the same situation; this is also termed the majority standard since one must disclose what the majority of one's peers would under similar circumstances. In contrast, states governed by the materiality standard require physicians to disclose risks that would be considered material to the patient. Therefore, consent in these states is not governed by standard medical practice but rather by what patients, and in this case, their parents would want to know—undoubtedly, a far more subjective standard. While physicians do not need to disclose risks believed to be speculative, the legal system, particularly in states governed by the materiality standard, may allow a patient or parent to sue a physician for failing to disclose such a risk. However, in order for such a litigation to be successful, it would need to be shown that the harm occurred as a direct result of anesthetics given, rather than any other comorbidities or environmental exposures such as the surgery itself—a difficult, perhaps nearly impossible, standard given our current knowledge on this subject matter.

Parental desire for anesthetic information has been studied and virtually all studies report that the vast majority of parents want to know about the risks of anesthesia, including severe and rare risks such as death (57). When parents are further queried regarding what the specific content of perioperative conversations should be, it has been reported that parents most often want detailed information on readily apparent, short-term concerns—notably pain, nausea, anesthetic induction, and emergence (58). With regard to children, their desire for information has also been studied and similar themes emerge; the majority of children want comprehensive perioperative information, but mostly with regard to well-defined, largely short-term problems (59). Indeed, it is notable that the four most common concerns of children have been reported to involve perioperative pain, its severity, treatment, and duration. As such, for both children and their parents, the extant literature on the discussion of anesthetic risk largely studied risks that are accepted and short-term, rather than those that are hypothetical and long-term. It is thus difficult to extend these data to the issue of anesthetic neurotoxicity.

So what do we tell the parents of our patients when asked whether their children are at risk of adverse neurocognitive outcomes as a result of anesthesia? How do we address their concerns based on the available evidence? SmartTots, a partnership between the International Anesthesia Research Society and the FDA, released a statement intended for parents. Below is an excerpt. The entire statement is available on the SmartTots website (http://www.smarttots.org/aboutus/drRoizensAdvice.html):

> In the United States alone, more than 1 million children, 4 years of age and under, undergo surgical procedures requiring anesthesia annually. While most children appear to recover well, findings from these animal studies call for further research to ensure the safety of every child undergoing anesthesia. Until this determination can be made, children requiring surgery essential to their health should proceed as directed by their physician. Young children usually do not undergo surgery unless the procedure is vital to their wellbeing. Therefore, postponing a necessary procedure may itself lead to significant health problems, and may not be an option for the majority of children.

In the United States, the FDA has addressed this issue in two separate advisory committee meetings evaluating the data supporting anesthetic neurotoxicity. It was the opinion of both committees that the data were neither sufficient to warrant a change in practice nor sufficiently compelling to require that the FDA directly communicate with the American public. Subsequently, a consensus statement intended for the public on the use of

anesthetics in children was crafted by SmartTots/FDA with broad input from a variety of stakeholders. The statement has since been endorsed by a large number of professional societies including the American Academy of Pediatrics, the American Society of Anesthesiologists, the European Society of Anesthesiologists, the Society for Neuroanesthesia and Critical Care and the Society for Pediatric Anesthesia. The consensus statement (available at http://www.smarttots.org/resources/consensus.html) asserts that 'it would be unethical to withhold sedation and anesthesia when necessary' and that clinicians should 'recognize that current anesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures'. The most recent consumer update from the FDA was released in 2013 and approached the purported developmental risks of anesthetics from a somewhat different perspective (available at http://www.fda.gov/forconsumers/consumerupdates/ucm364078.htm). Rather than a discussion involving the risks of anesthetics themselves, the update concluded that caretakers "must talk to their pediatrician or other health care professionals about the risks and benefits of *procedures requiring anesthetics* and weigh them against the known risks of not treating certain conditions." As such, the update represents somewhat of a departure in that while sedation and anesthesia for invasive procedures was treated as obligatory, the procedure itself not necessarily so. Indeed, while the FDA update maintained that children do not usually undergo invasive procedures "unless the procedure is vital to their health," such a statement may evoke controversy and discussion about which surgeries, invasive procedures, and imaging studies result in data that are simultaneously practice-changing for the provider and outcome-changing for the patient. Clearly, more research is needed about the risks of anesthesia and surgery on children, but in the absence of more compelling data, it remains our duty to do what is right for our patients and minimize whatever risks they may face. Given what we know about pain perception in our youngest and most vulnerable patients, our care of infants and children undergoing surgery must continue to provide amnesia, hypnosis, and analgesia. Changes in practice intended to minimize an unknown and as yet undefined risk will inevitably lead to unintended risk and the inevitable adverse outcomes that follow. Three studies are currently underway that may serve to illuminate and clarify the true risk of the neurodevelopmental effects of anesthetic exposure in neonates including; the GAS study (General Anesthesia Spinal Anesthesia Study) prospectively compares the neurodevelopmental outcomes among young infants exposed to either general or spinal anesthesia for hernia repair, the Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) study, a retrospective–prospective study of children undergoing hernia repair using a sibling design and the MASK (Mayo Anesthetic Safety in Kids) study also a retrospective–prospective matched birth cohort study of children exposed once and more than once. These studies will begin to report results over the next 2 or 3 years. It is hoped that our ability to advise parents will be greatly enhanced by the information gleaned. It is, however, not unlikely that none of the aforementioned studies will be in any way conclusive. Significantly more both human and animal studies will need to be completed before the issue is finally resolved.

As families vary in regard to what information is desired, it is the authors' practice to take an individualized approach by discussing anesthetic risks in general terms and inviting parents and older children to ask for additional, more specific information. No mention of anesthetic-related neurologic injury is typically made unless parents or children specifically ask. Those parents that ask about this issue typically have read or heard something in the media or have seen something on-line. In our community, the MASK study has been publicized sufficiently to raise concerns among some parents. Prior to the study, parental questions regarding anesthetic injury were relatively uncommon. When asked, it is our practice to place the unknown risk of neurologic injury in the context of all risk associated with anesthesia and surgery with an emphasis on the low rate of harm associated with anesthesia and the lack of compelling data clearly implicating anesthetic drugs in subsequent cognitive deficits. Although unsatisfying, until more precise information becomes available little more can be provided to parents and the public at large.

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Disclosures

Dr. Flick currently serves as Chair of the Anesthetic and Analgesic Drug Products Advisory Committee, has conducted research under contract for the US FDA, is Co-Primary Investigator on a federally funded grant (U.S. National Institute of Child Health and Development), and serves as an advisor to SmartTots.

Conflict of interest

No conflicts of interest declared.

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