

Anesthetic Neurotoxicity to the Fragile Young Brain: Where Do We Stand?

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Abstract

There is no doubt of the benefits of anesthesia in children which has allowed surgical procedures to be performed in the youngest infants, alleviating of pain, anxiety and maintaining stable vital signs. We also believe that anesthesia has indirectly improved quality of life and in many cases accounted for the saving of many young lives. However, in view of conflicting evidence, it is imperative to invest in future studies, based on scrupulous methodology that can undoubtedly translate the association between anesthesia and adverse neurocognitive outcomes in children. But while more and better-designed studies are being conducted, we have the obligation to be judicious and adopt a protective strategy for our young patients. Although we think there is no evidence to postpone or cancel truly urgent surgeries in young children, it seems to be reasonable that at least on children with less than 6 months, but preferably up to 3 years of age, the decision of proceeding to surgery should count the matter of anesthesia-related neurotoxicity as a possible cost. When necessary, anesthesia and surgery should be kept to the minimum time possible. Also, the avoidance of the agents most implicated, as toxic in animal studies such as ketamine, isoflurane and nitrous oxide seems wise [41, 42]. As millions of children can be affected worldwide by this yet to explain possible phenomenon there is urgent need and place for a great deal of translational research so we can finally understand the association between neurotoxicity to the young brain and anesthesia, thus devising mitigating strategies. As Albert Einstein would say, "If you always do what you always did, you will always get what you always got."

Keywords: Anesthesia neurotoxicity; Anesthetics neurotoxicity; Anesthetics behavioural changes

Is Anesthesia Safe to Young Brains?

Advances in neonatal and pediatric surgery and intensive care demanded for increasing general anesthesia requirements in small infants, as well as the need for prolonged infusions for sedation.

General anesthesia results from a complex pharmacological interaction of different drugs, many with still incompletely known mechanisms [1]. Consequently, their immediate and long-term effects are not completely understood.

Traditionally, anesthetic drugs' effects were thought to dissipate as early as the end of their administration, without prospective effects on children development [2]. Since fifties, a concern about anesthetic consequences in the developing brain started to rise due to studies that have showed that vinyl ether, cyclopropane or ethyl chloride administration to young children could cause long-term personality changes [3].

During the past three decades, strong evidence from animal studies have questioned the anesthetic safety profile on central nervous system development, and inflamed debate surrounds the negative effects of anesthesia in the developing brain. In fact, animal studies to date reveal very robust and consistent data concerning anesthesia-induced neurotoxicity in immature mammals and rodents.

Considering the universal and serious possible impact of this issue in pediatric health care, the Food and Drug Administration (FDA) established a partnership with the International Anesthesia Research Society (IARS), called SmartTots (Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots), to specifically address and make recommendations on this matter.

Animal Studies: From Animals to Humans?

In a recent review, Sanders et al identified 55 rodent and 7 primate studies on anesthesia neurotoxicity, stressing consistent and robust data on anesthetic drugs toxicity on developing brain [4].

Evidence implicates most of anesthetics used in current practice, independently of their mechanism of action. Gamma-amino butyric acid (GABA) agonists (volatile anesthetics, propofol, benzodiazepines), as well as n-methyl-d-aspartate (NMDA) antagonists (ketamine and nitrous oxide) have been implicated in animal neuronal apoptosis and impaired synaptogenesis [5-7], resulting in long-term cognitive and behavioral alterations [5,6].

Animal studies also address sedative protective agents such as dexmedetomidine, an α_2 -adrenoreceptor antagonist. On the opposite of the previous stated drugs, dexmedetomidine has not shown neurotoxic properties, even reducing isoflurane-induced neuroapoptosis in neonatal rats [8]. Also clonidine, with a similar acting mechanism protects against ketamine neuroapoptosis and behavioural changes [9].

Other drugs as xenon [10], melatonin [11] and β -estradiol [12] are pointed out in animal studies as possible neuroprotective agents [6], although further studies are warranted to confirm their potential.

Animal studies so far have included different mammal species, not only rodents, as well as bigger mammals as piglets and nonhuman primates [4,6,13].

Piglets appears as an interesting model to parallel human brain development, as synaptogenesis occurs pre- and post-natally, as well as in humans. Two studies with piglets demonstrated isoflurane-nitrous oxide induced apoptosis [4,14].

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Seven recent studies reported neuroapoptosis after anesthetic exposure in developing monkeys, using similar monitoring than in humans [15]. One of these studies reported long-term neurocognitive defects, persisting for several years, on primates exposed to 24 hr ketamine [16]. Another reported neuronal and oligodendrocytes apoptosis in fetal and neonatal monkey brains after propofol administration [17].

Limitations of Animal Studies: How to Translate?

Despite the robust data on anesthesia neurotoxicity in developing animal brains, it is extremely difficult to extrapolate from animal studies to clinical practice.

Recently, Pound and Baker reaffirmed this conviction on a BMJ analysis about translation of conclusions from animal studies to human neurosciences, raising a heated debate on this issue [18].

To begin with, anesthetic protocols, drug doses and management and monitoring in animal studies are extremely different from human clinical practice. Most studies proved greatest negative effects in very young animals submitted to higher doses and longer exposure to anesthetic drugs than the usual practice in humans [1,5]. This inflated doses and prolonged exposures have even caused high mortality rates, which reflects the strongly different techniques used in animals' anesthesia when comparing to human protocols [6].

On the other hand, neurodevelopmental timings and stages differ significantly between humans and animal models. The most vulnerable period to the development of anesthetic neurotoxicity certainly overlaps the period of maximum synaptogenesis and neuronal differentiation, and this critical stage occurs in different time frames according to each species, respecting their life span and natural development.

Maximum neuronal development in rats seems to peak on the seventh day after birth, which comparing directly to the matching development peak in humans, is equivalent to human neonates during the final gestation phase (from 32 to 36 weeks) [19].

Despite the undeniable limitations, animal studies strong data cannot be ignored and were sufficient to raise the awareness on this issue.

Human Studies: Do We Know Enough?

In fact, during the past few years, the amount of solid data arising from both animal and *in vitro* studies has mounted increasing concern around anesthesia-induced neurotoxicity to the young. This phenomenon and the possibility of long-lasting neurobehavioral consequences had to be clarified. In 2007, Food and Drug Administration held a scientific advisory board to discuss specific recommendations on this matter, but at the time no clinical study had been specifically designed to address it, and the question remained unanswered.

From 2009 to the present, observational clinical studies have showed little consistent results, with some reporting an association between early exposure to anesthesia and adverse neurocognitive outcome whereas others do not [6,20].

In fact, these contradictory conclusions might be explained by the methodological problems inherent to the studies.

First, these study populations do not reflect a sampling of the population at large and therefore the findings may not be generalizable. Whether some authors claim to have worked on a large sample yet too

homogenous [21,22], others might have faced a higher than normal risk population [23].

On the other hand, as virtually all these studies are retrospective they often lack precise information in terms of age, agent, duration and dose.

Also the outcomes are not defined by the investigators and probably do not provide an objective measure of neurocognitive function. The outcome endpoints used in these studies included learning disability, diagnosis of developmental delay and parent reports of behavior. These outcome measures lack specificity and in most cases the assessments did not use standardized and validated tools.

This "outcome matter" was sharply addressed by Ing et al. [24] in 2014, which showed that when assessing cognition in children with early exposure to anesthesia, the results may depend on the outcome measure used. In their study Neuropsychological and International Classification of diseases, 9th Revision, Clinical Modification-coded clinical outcomes showed an increased risk of deficit in anesthesia-exposed children, whereas academic achievement scores did not. The authors believe this may explain some of the contradictory results available in the literature. As Flick et al. [25] stated in their editorial, the studies using academic performance and teach-parent rating scales as endpoints for comparison tend to negative [26,27] results whereas those using individual tests of neurocognitive performance have been more uniformly positive. Also the use of ICD-9 or other administrative data as an end point may lead to erroneous conclusions as errors in coding are ubiquitous, providing an important source of bias [28]. Nevertheless the awareness of the problem, it seems to be of difficult resolution.

The age issue should also not be ignored. Children have a stepped cognitive evolution and the tools used to assess it should be age-specific, and those available to the very young not always predict function later in the future. Furthermore, it can be difficult to establish a pre-exposure profile, as cognitive functions are often not fully developed at the time of anesthetic exposure [29].

Another pitfall seems to be the identification of the young brain's most vulnerable period to the anesthetic neurotoxicity, as there are significant regional differences for peak synaptogenesis in humans. Although clinical importance remains to be substantiated, results to date do indicate that exposure of animals to general anesthesia during active synaptogenesis is most detrimental [30-34] showing that anesthesia-induced neurotoxicity is strongly age-dependent? Thus, it is essential to determine when synaptogenesis peaks in the developing human brain. The parietal and temporal association cortex areas are responsible for language and spatial attention and seem to be in peak synaptogenesis around 9 months whereas the prefrontal cortex responsible for key executive functions would be the last region to peak around 2 to 3 years of age. Accordingly, since peak synaptogenesis occurs between birth and 2-3 years of age, it may be appropriate to consider the vulnerability period for anesthetic-induced neurotoxicity to be up to 36 months of age in the developing human brain [29].

While the human studies have used heterogeneous retrospective approaches, they provide sufficient preliminary evidence to cause concern in clinicians and parents alike. Even so, the scientific community finds itself drifting in contradictory and confounding evidence.

The Large Scale Clinical Studies: High Expectations?

To better address this subject there are currently three ongoing large-scale prospective studies.

The Pediatric Anesthesia and Neuro-Development Assessment (PANDA) study investigators will assess neurodevelopment of children age 8 to 15 year-old who have been submitted to inguinal hernia repair before 3 years of age, and compare them with unexposed sibling [35].

Researchers from Children's Hospital Boston are collaborating with researchers from nine other centers in the United States, as well as centers in Canada, Australia, Europe, and the United Kingdom, to collect data from 720 infants to be enrolled in the GAS study, a Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in Infants. Authors will test for a difference in preschool IQ between children who received sevoflurane or neuraxial bupivacaine for inguinal hernia repair when they were 26 – 60 weeks and the follow-up time is 5 years. Enrollment has been completed, but final analysis results are not expected before 2017.

Unfortunately, in these two studies, investigators will test for an effect of exposures that are probably too brief to have an effect in a study population that may be substantially composed of children who can also be too old to be sufficiently susceptible.

The third study is the Mayo Safety in Kids (MASK) in which children with multiple, single, and no anesthesia exposure are sampled for neuropsychological testing between the ages of 8 and 12 years or 15 and 19 years during the period 2012-2016. The results of this testing will be compared among children with different anesthetic exposure histories. Authors expect to delineate a phenotype of anesthetic-associated human neurotoxicity. They also aim to compare the effects of anesthetic exposure in children and nonhuman primates performing nearly identical behavioral tasks [36].

Within the next few years we believe that the results of these and possibly other prospective, well-designed, large-scale and multi-site studies might shade some light on this still too foggy matter.

Is It the Time for a Change of Practice?

Authors seem to agree that although animal data are solid and sufficient to disturb the more relaxed minds, its verification in humans is still lacking. There is in fact not enough evidence to support an obvious change in clinical practice, or make guidelines on this subject, and new data from prospective studies are still pending.

Some small prospective studies have already tried to analyze the influence of the type of anesthesia in the incidence of immediate adverse neurocognitive outcomes such as delirium [37], emergence agitation [38] and abnormal behavior [39]. These studies tend to demonstrate that intravenous anesthesia might have a less harmful profile than inhalational anesthesia. In fact, some authors advance that in the future intravenous anesthesia will supersede inhalational anesthesia in the pediatric surgical population [40]. Although this subject warrants attention and further investigation, we believe that until the quality and quantity of human data improves, no change in practice can be supported.

What Can We Do?

There is no doubt of the benefits of anesthesia in children which has allowed surgical procedures to be performed in the youngest infants, alleviating of pain, anxiety and maintaining stable vital signs. We also believe that anesthesia has indirectly improved quality of life and in many cases accounted for the saving of many young lives. However, in view of conflicting evidence, it is imperative to invest in future studies, based on scrupulous methodology that can undoubtedly translate the

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As millions of children can be affected worldwide by this yet to explain possible phenomenon there is urgent need and place for a great deal of translational research so we can finally understand the association between neurotoxicity to the young brain and anesthesia, thus devising mitigating strategies. As Albert Einstein would say, "If you always do what you always did, you will always get what you always got".

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