Anesthetic Neurotoxicity — Clinical Implications of Animal Models

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General anesthetic and sedative drugs are administered to millions of infants, toddlers, and preschool children each year to facilitate life-saving surgery and other essential surgical or medical procedures. In the past two decades, mounting data from animal and observational human studies have raised concerns that general anesthetics may cause neurotoxic changes in the developing brain that lead to adverse neurodevelopmental outcomes later in life. To address the growing concern about the potential adverse consequences of general anesthesia in young patients, in 2009 the Food and Drug Administration (FDA) established a public–private partnership with the International Anesthesia Research Society (IARS) called Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots, or SmartTots.[1]

In 2012, the FDA, SmartTots, and the American Academy of Pediatrics released a consensus statement that summarized the state of knowledge and presented several key recommendations. Although there were insufficient data at that time to draw any firm conclusions about an association between exposure to anesthetics and subsequent learning disabilities in children, the consensus statement recommended that elective surgical procedures performed under anesthesia be avoided in children less than 3 years of age. The statement also called for further research to better define the risk. Various nonclinical studies have been undertaken since then, and on the basis of their results, the consensus statement is now being revised to convey a heightened level of concern.

More specifically, since the original statement was released, new studies have confirmed that commonly used anesthetics and sedatives that either increase inhibitory γ-aminobutyric acid (GABA) receptor activity (e.g., propofol, etomidate, sevoflurane, desflurane, and isoflurane) or block excitatory glutamate receptors (e.g., ketamine) produce profound neurotoxic effects in laboratory animals.[2] The injectable anesthetic propofol, most commonly used to induce a rapid loss of consciousness, causes apoptosis of neurons and oligodendrocytes in the brains of fetal and neonatal macaque monkeys.[3] Similarly, the commonly used inhaled anesthetic isoflurane induces widespread apoptosis in the neonatal primate brain. The glutamate receptor antagonist ketamine, when administered as a single dose over a prolonged period (24 hours) during a sensitive phase of brain development, causes long-lasting deficits of memory and attention in primates.[4] Studies involving species ranging from nematodes to nonhuman primates have revealed histologic changes and, in some cases, impaired performance on behavioral tests.[2] Factors that influence the extent of injury include age at the time of drug exposure and cumulative anesthetic dose.[2] Histologic changes include widespread apoptosis and cell death, a reduction in the number of synapses, changes in neuronal morphology, and impaired neurogenesis in the hippocampus.

The compelling evidence from animal models is supported by a small number of observational studies in children who underwent anesthesia early in life. Although these observational studies offer conflicting results and are confounded by multiple factors, they suggest that some such children may have deficits in learning and school performance.[5] For example, in an observational matched-cohort study in children born between January 1, 1976, and December 31, 1982, in Rochester, Minnesota, those exposed to anesthesia before 2 years of age were compared with unexposed controls in terms of specific risk factors for learning deficits. Exposure to multiple (but not single) episodes of anesthesia and surgery significantly increased the risk of learning disabilities (hazard ratio, 2.12; 95% confidence interval, 1.26 to 3.54), even when overall health status was taken into account. A similar pattern was observed for decrements in tests of achievement and cognition.

In June 2014, SmartTots convened a meeting to review the data from animal and human studies that have accumulated

since release of the original consensus statement. The participants concluded that the current data from animal studies are now sufficiently convincing that large-scale clinical studies are warranted. The group produced a new statement recommending that surgical procedures performed under anesthesia be avoided in children under 3 years of age unless the situation is urgent or potentially harmful if not attended to. The statement also emphasizes the need to determine whether anesthetic and sedative drugs cause brain damage in infants, toddlers, and children (www.smarttots.org/resources/consensus.html). In particular, randomized clinical trials are needed to determine whether general anesthetics impair neurocognitive development.

There are multiple challenges to achievement of this goal, which will require years to complete. For example, investigators will have to differentiate between the adverse effects of surgical trauma and those specifically associated with the use of anesthetic agents. Control participants can be randomly assigned to receive a local or regional anesthetic, but only a limited number of relatively brief surgical procedures will be amenable to regional anesthetics. Furthermore, regional anesthesia in children is often complemented by the use of low doses of anesthetics for sedation so that the children can tolerate prolonged periods of immobility. The FDA and SmartTots support the notion of a large, prospective, multicenter trial to determine whether a sedative drug such as dexmedetomidine, which has not been shown to be neurotoxic in animal studies, could be used in combination with reduced doses of a standard anesthetic drug to improve outcomes. Properly designed studies could assess cognitive performance at multiple time points after anesthesia and permit probing of potential deficits in distinct cognitive domains. Further animal studies are also essential in order to elucidate underlying cellular mechanisms and identify additional mitigating strategies.

Many important fundamental questions remain to be answered, and we believe that a combination of animal studies and well-designed clinical trials is needed. For example, are certain pediatric patient populations at higher risk? Does the extent of anesthetic-induced neurotoxic effects depend on the cumulative dose? Do underlying diseases or inflammatory processes increase the risk of brain injury? Can diagnostic biomarkers be developed to measure the incidence and extent of brain injury? Can strategies or interventions be developed to reduce harm?

The mounting evidence that anesthetic agents cause neurotoxic effects in the developing brains of laboratory animals increases the urgency of the need for large-scale clinical studies to answer these and other questions. SmartTots has taken a first step by establishing an international working group of experts who will generate data on animal models that can inform the design and execution of appropriate clinical trials. In the meantime, we believe that parents and care providers should be made aware of the potential risks that anesthetics pose to the developing brain. While we await clinical studies that can definitively determine whether anesthetics cause injury in humans, surgeons, anesthesiologists, and parents should consider carefully how urgently surgery is needed, particularly in children under 3 years of age.

This article has not been endorsed by the groups that endorsed the 2014 consensus statement.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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