Early Childhood Anesthesia Exposure and Neurocognitive Development: What Do We Know?

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Epidemiology of Anesthesia in Children

An estimated six million children receive anesthesia annually in the US. Among infants, defined as those under 12 months of age, the Nationwide Inpatient Sample data indicate that 1.5 million undergo surgery as inpatients each year in the US. Surgical anesthesia provides amnesia, analgesia, immobility and control of autonomic responses during surgical procedures. In the non-surgical setting, anesthesia in children provides safe and appropriate conditions for interventional procedures, imaging studies and long diagnostic procedures. The benefits of anesthesia in children include alleviation of pain, anxiety, maintaining stable vital signs and providing adequate conditions for surgery or the procedures in question. These benefits have accounted for the exponential increase in number of anesthetics administered in children in many different settings, and for many different procedures and to children of increasingly younger and younger age.

The widespread and growing use of anesthesia in infants and young children thus makes the safety of anesthesia in infants and children a major public health issue. This issue has become a matter of great concern with the evidence that anesthetics are neurotoxic in animal studies. The widespread and growing use of anesthesia in infants and young children thus makes the safety of anesthesia a major public health issue. It has generated and has become a concern to the public, government agencies and the anesthesia community

A conceptual framework for research related to the adverse health effects of anesthesia exposure *in vivo, in vitro and in populo* will be presented. We will provide an overview of the available clinical studies related to neurocognitive development and early childhood exposure to anesthesia, including the outline of two large scale ongoing clinical studies.

Is Anesthesia Neurotoxic to Infants and Children?

There are alarming evidence of anesthetic neurotoxicity from *in vitro* and *in vivo* animal studies which raises serious concern that the use of anesthetic agents in children may lead to long-term adverse neurodevelopmental outcome. The findings include abnormal behavior, attention, learning and memory tasks as well as social behavior in adult animals that had neonatal anesthesia exposure generated a great deal of interest from the media, public and parents. The FDA responded to these interests and convened a scientific advisory committee meeting in April, 2007. The purpose of the meeting was to discuss whether specific recommendations for changes in the use of anesthetic agents in infants and children are needed. At that time, there were non data from *in populo* studies, therefore the consensus from the advisory committee was that without data from clinical studies, the question of whether anesthetic agents are neurotoxic in children cannot be answered. On March 10th 2011, FDA held an advisory meeting to revisit this issue.

Clinical Studies of Neurodevelopmental Effects of Anesthesia Exposure During Early Childhood

From 2007 to today, a total of five clinical studies have been published, and they will be reviewed.

Two of these studies derived their data from the Olmstead County Birth Cohort. In both of these studies, the outcome used was learning disability (in math.. language and reading). Sprung et al. studied a cohort of 5,320 children to specifically determine the neurocognitive effects of prenatal /fetal exposure during labor and delivery. There were 4,823 who had vaginal delivery, 197 who had cesarean delivery under general anesthesia and 304 who had cesarean delivery under regional anesthesia. Fetal exposure to general anesthesia did not increase the risk for learning disability with the incidence of learning disability being comparable between those who had cesarean delivery under general anesthesia and those who had vaginal delivery. Using the same cohort, Wilder et al examined the effects of postnatal anesthesia before age four and found ~~showed~~ that learning disability (math, language or reading) was higher in those children with multiple anesthesia exposure and surgery before age 4. The Olmstead County birth cohort provides a large sample of study subjects. In addition, the investigators were able to obtain medical records to abstract information on anesthesia exposure. These are very significant strengths in both studies. But, there are also several limitations in these two studies with respect to the outcomes examined. In their analysis, the authors were careful to adjust for age, sex, birth weight, and maternal education, some of the known confounders in evaluating neurocognitive function. However, the demographics of the study cohort does not reflect the demographic, cultural and racial/ethnic diversity of the overall US population. In addition, the retrospective cohort had exposure to anesthesia from January 1976 to December 1982, a period during which the most commonly used anesthetic agents were halothane and nitrous oxide. Since the early 1980's, anesthesia practice has evolved and halothane is no longer in clinical use, and the popularity of the use of nitrous oxide has also declined. Therefore, based on the consideration of (1) relative lack of population diversity and (2) significant changes in anesthesia practice, the results of these two well-designed studies may not be generalizable to pediatric anesthesia practice in the US today. Another limitation of these two studies is the use of "learning disability" as the outcome measure. Learning disability is a categorical determination based on a discrepancy between a child's IQ and his/her actual achievement. It is not a specific neuropsychological outcome. In the state of Minnesota, where the study was conducted, learning disability can be identified using three different approaches, thus making the endpoints not standardized. Furthermore, the authors combined the three different types of learning disability in language, math and reading into a single outcome measure. Because language, reading and math is each subserved by discrete brain regions with distinct developmental trajectory, an unitary outcome of "learning disability" would be non-specific and could easily learning disability in any one specific area.

DiMaggio et al used the NYS Medicaid dataset and constructed a birth cohort of 383 children who underwent inguinal hernia repair during the first 3 years of life as the

exposed group. The unexposed cohort for comparison was a sample of 5050 children who were frequency-matched on age with no history of hernia-repair before age 3. Using the ICD-9 diagnostic codes for the exposed cohort to have an increased risk for such diagnosis by 2.3 fold (95% CI 1.3-4.1) compared to the unexposed cohort. As was the case with the Sprung and Wilder studies, one of the limitation of this study was the outcome measure used. It was non-standardized and therefore could easily subject to variations due to local practice patterns and potential misclassification from diagnostic coding. In addition, the study did not have an explicit variable of anesthesia exposure. While hernia surgery is not known to be associated with any specific conditions that give rise to abnormal neurocognitive function, it is still possible that there was bias from confounding due to indications for surgery. Unlike the Olmsted County population which was too homogeneous, the Medicaid population in the DiMaggio, by contrast, may be considered as a much higher risk cohort than the general population due to the criteria for eligibility to enroll in the Medicaid system is a low socioeconomic status.

Kalkman et al performed a survey of long term behavior after childhood surgery using the Child Behavior Checklist (CBCL) parental reports. Their study sample consisted of 243 individuals who were currently 12.5 to 15.8 years of age, and who had from 0-6 years of age. The authors reported that those who had anesthesia and surgery prior to 24 months of age appeared to be more likely to have "deviant" behavior than those who had surgery and anesthesia at an older age. However, the study sample size was inadequate to provide sufficient power to yield any statistically significant results, thus making this more of a pilot study for a larger study in the future.

While these retrospective cohort studies suggest early anesthesia exposure may be associated with late adverse neurodevelopmental outcome, a more recent study from the Netherlands failed to show any effects of anesthesia exposure on long term neurocognitive function using the Young Netherlands Twin Registry. They studied a total 1143 monozygotic twin pairs. They found exposure to anesthesia before age 3 significantly reduced educational achievement, but there were no differences between twins when they were discordant for anesthesia exposure. They therefore concluded that there was no causal relationship between exposure to anesthesia and cognitive performance later in life. The limitation in this study included the lack of comparative exposure data for the twins and data on the indications for surgery. The outcome measures used in this study are education achievement scores at age 12 and reports of behavior problems by teachers. Although the authors presented data that there was demonstrable correlation between IQ and educational achievement scores (in this case CITO scores), academic achievement scores cannot be considered as an objective neuropsychological outcome measure as they can be influenced by many different factors.

More recently, DiMaggio et al used the NYS Medicaid dataset and constructed a sibling cohort of children who had surgery/anesthesia prior to 3 years of age, and found an increased risk for later diagnosis of developmental and behavioral disorders (DiMaggio et al Anesth & Analg, in press). The same group, along with colleagues from Australian, has performed analysis of the Western Australian Raine birth cohort and the early results

suggested that early childhood exposure to anesthesia was associated with abnormal language development at age 10 years ((personal communication).

The available clinical studies, to date, have all been retrospective in nature. They often lack precise information in terms of age, agent, duration and dose. 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 are not direct using standardized and validated tools. Also, these study populations do no reflect a sampling of the population at large and therefore the findings may not be generalizable. At the present, results from *in populo* studies remain too sparse and too inconsistent for making any recommendations for specific practice guidelines or changes in pediatric anesthesia practice. However, these studies do all underscore the need for more definitive studies in which outcome endpoints are specific and comprehensive, assessments are prospective and direct, and the neuropsychological instruments used for assessment are validated and standardized.

Important Issues and Consideration in Clinical Studies of Anesthetic Neurotoxicity

The key questions that need to be addressed by clinical studies include what should be considered as adverse neurodevelopmental outcome and what should be considered as the age at risk.

Neurodevelopmental outcome could be assessed as the presence of neurodevelopmental disorders, such as autism, mental retardation, language delay, learning disability or attention deficit hyperactivity disorder. To date, studies examining the association of anesthesia exposure with neurodevelopmental outcome have adopted this approach. However, objective evaluation of neurodevelopmental abnormality requires direct assessment of neurocognitive functions using standardized neuropsychological instruments. Neuropsychological assessment in a developing child is very different than in adults. First, neuropsychological assessment instruments in children are age-specific and those available for the very young do not always predict later functions well. Second, many of the neurocognitive functions are not yet fully developed at the time of exposure. Therefore, pre-exposure “baseline” neuropsychological assessment of young children would not even be possible as in adults.

The age of vulnerability in children cannot be extrapolated easily from the clinical studies because cross species translation of brain development is still an area of ongoing study. The vulnerable period of injury has been consistently demonstrated to be during peak synaptogenesis. Therefore, our current understanding of human brain development may be informative in choosing the age most likely to be at risk for anesthetic neurotoxicity. In the human brain, there are significant regional differences in the timing for peak synaptogenesis. The earliest is in the primary sensorimotor cortex, occurring around birth. This is followed by the parietal and temporal association cortex, important in language and spatial attention, where peak synaptogenesis occurs at around 9 months. The last region to peak in synaptogenesis is in the prefrontal cortex, which occurs at age

2-3 years. Prefrontal cortex is key in executive function as well as integrative and modulatory brain function. Accordingly, since peak synaptogenesis occurs between birth and 2-3 years of age, it maybe appropriate to consider the vulnerability period for anesthetic-induced neurotoxicity to be up to 36 months of age in the developing human brain.

Currently, there are two large scale studies underway that attempt to address the question of anesthetic neurotoxicity in children. The GAS study is an international randomized trial comparing general sevoflurane anesthesia with regional anesthesia for infants undergoing inguinal hernia repair. The follow-up period will be for five years, with evaluation performed at age 2 years and 5 years. A total of 600 children will be enrolled for the study. The evaluation at age two years will be performed using the Bayley Scales for Infant Development-III, and the evaluation at age 5 years will include the Wechsler Preschool and Primary Scale of Intelligence-III and additional neuropsychological test within NEPSY II.

The PANDA (Pediatric Anesthesia and NeuroDevelopment Assessment) study is a multi-site study that will involve eight US study sites. It is an ambi-directional, sibling-matched cohort study that will enroll a total of 1,000 children or 500 sibling pairs. The period of anesthesia exposure will be before 36 months of age, and the exposure is limited to a single episode of general anesthesia for inguinal hernia repair in ASA I and ASA II patients. The study will perform an extensive neuropsychological battery (see Table 3) in children between age 8 and 15 years.

The results from the PANDA study will be applicable to children undergoing elective procedures, who are otherwise healthy, which constitute the great majority of children in the US. If anesthetic exposure is found to be without effects in the study patients, reassurance could be offered to millions of parents when their otherwise healthy children receive anesthesia for a limited duration. However, other patients who have significant co-morbidity or with more prolonged exposure or frequent exposure to anesthesia would still need to be examined. Should the study find anesthesia exposure to have deleterious neurocognitive effects, we must urgently consider alternate strategies in the timing and delivery of anesthesia care to young children as well as the development of novel anesthetic agents with different mechanisms of action with minimal or no side effects. In this case, the studies that would be needed are ones that would more specifically determine the age of vulnerability and examine the specific exposure variables related to types of anesthetic agents, drug doses and exposure duration.

While additional studies would still be needed depending on the findings from these large scale prospective studies, they should produce data that will contribute significantly in addressing whether the pre-clinical studies on anesthetic neurotoxicity are clinically relevant, and thus inform clinical decision making.

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