**Anesthesia and Neurodevelopment in Children**

*Time for an Answer?*

**Editor’s Note:** This is the first in a three-part series of Editorial Views regarding design of clinical trials to address the effect of anesthesia on the developing brain. Animal studies have suggested that anesthetic exposure could affect neurocognitive development, and there is an urgent need for clinical trials to determine whether this effect occurs in humans. This series presents the opinions of three world thought leaders in the possible designs of such clinical trials.

*James C. Eisenach, M.D.*, Editor-in-Chief

RECENT animal studies have suggested that anesthetics may be toxic to the immature developing brain.1–3 In rodents, γ-aminobutyric acid receptor agonists and N-methyl-D-aspartic acid receptor antagonists, including ketamine, isoflurane, midazolam, and nitrous oxide, induce dose- and age-dependent neuronal apoptosis and neuronal cell death in vitro.1,2 with the most prominent effects being observed at postnatal day 7, which interestingly is also the peak period for synaptogenesis. Ketamine produces similar age- and dose-dependent neurotoxicity in nonhuman primates.3 Alarmingly, these in vitro findings were shown to have long-term functional consequences resulting in deficits in memory, learning, attention, and motor function in adult rats after neonatal exposure to anesthetics.2 Comparable data are not yet available in nonhuman primates. Although the dose and duration of anesthetic exposure used in most laboratory studies are substantially higher than those used in children, these findings are nevertheless of serious concern.4,5 Moreover, recent work indicates that neurotoxicity could indeed occur with doses within the human range.6

According to the 2004 National Hospital Discharge Survey, close to three million children in the United States receive anesthesia for surgical procedures, and many more require anesthesia and sedation for dental procedures and imaging studies. Given this large exposure vulnerability for so many infants and children to agents that seem to be neurotoxic to animals, it is critical to understand whether such toxicity also occurs in children exposed to anesthesia. This concern prompted the US Food and Drug Administration to hold an Advisory Committee meeting in March 2007 to review the data on neurotoxicity and determine whether changes in anesthesia practice should be recommended.7 Although no changes in anesthetic practice were recommended, the panel did recommend that studies to determine whether anesthetics are developmental neurotoxins in children should be urgently performed. The concerns raised by both the animal studies and the Food and Drug Administration’s response have generated media interest resulting in sensational headlines and reports on the potential “brain damage” children might sustain from exposure to anesthesia.

Because there has been no clinical study specifically designed to examine the effect of anesthesia on neurocognitive function in children, it is therefore reasonable to look to other studies that may inform the debate. Studies that can tangentially address this issue include neurodevelopmental outcome after surgery in groups such as premature infants and infants with congenital cardiac defects.8–21 In premature infants, neurodevelopmental outcome was worse in those who had surgery for ligation of patent ductus arteriosus compared with those who were treated medically.17 Similarly, very low-birth-weight infants and premature infants who had surgery for necrotizing enterocolitis fared worse neurodevelopmentally than those who did not have surgery.18 The Boston Circulatory Arrest Trial examined neurodevelopment in infants who had repair of congenital cardiac defects and found that these children had normal or only very modest decreases in full scale intelligence quotient (IQ) but had specific deficits in memory, language skills, attention, and visuospatial skills.8–16,22,23 These studies, however, contain many confounding variables that make it impossible to separate the effects of anesthesia from surgery and comorbid conditions. The comparison of outcomes in a group of relatively healthy children who had tympanostomy either before age 3 yr or up to 9 months later is therefore of particular interest. At follow-up, the two groups did not differ in their neurodevelopmental or neurocognitive function at age 6 yr.24,25 Therefore, although these studies provide some reassurance that anesthesia exposure before age 3 yr does not adversely affect neurodevelopment, they do not directly address the issue of anesthetic neurotoxicity because
they were not designed to examine the effect of anesthesia per se, but were a comparison between children who received anesthesia at two different ages. Indeed, none of the aforementioned studies could specifically address the potential effects of anesthesia on neurodevelopmental outcome.

The absence of clinical data to address this critically important public health issue underscores the need for more rigorous and definitive studies to examine whether anesthetic agents cause neurotoxicity in children. Such studies may have many different possible approaches: experimental, observational, prospective, or retrospective. Perhaps not one single study could provide the answer to the question, and data may need to be generated from various sources that converge to answer the research question. To be more precise, the research question should be directed to address the effects of anesthetic exposure on neurodevelopment in children with and without surgery. The two most important design considerations for such a study are the identification of the appropriate endpoints to use to determine whether neurotoxicity exists and the choice of the epidemiologic design. In addition, the successful implementation of such a study must consider feasibility issues and the cost and duration for the study.

Taking all of these considerations into account, we propose a study with a mixed epidemiologic design using a retrospective historical cohort that had anesthesia exposure during early childhood before age 3 yr, and a prospective follow-up for direct assessment of outcome. The neurodevelopmental outcome measures will include global IQ and targeted areas of neurocognitive function, including attention, memory, behavior, and motor function. The comparison group will be developmental age–matched siblings without history of anesthesia exposure. The assessment will be performed within a specified age range in late childhood for both the index and the comparison group using validated age-specific instruments.

With respect to identifying the appropriate endpoints, the existing findings from animal studies, mostly on rat pups, cannot be directly extrapolated to children who receive anesthesia because of interspecies differences in brain development and in the brain’s age- and dose-dependent vulnerability to injury. In addition, anesthetic neurotoxicity may be modulated by noxious stimuli such as occurs during surgery. Nevertheless, the preclinical data do provide consistent and irrefutable evidence that anesthetic exposure can produce negative neurodevelopmental consequences. The specific areas in which deficits were identified in rodents could be translated to corresponding neuropsychological functional domains in humans and could be readily measured in children by trained professionals using a wide range of available and well-established developmental neuropsychological tests.

In addition, we might also apply the lessons learned from a variety of clinical neurodevelopmental studies in considering which endpoint measures might be relevant in studying the neurotoxic effects of anesthetic agents in children. Studies of developmental outcomes related to environmental neurotoxins have used a wide range of endpoint measures, including mental and motor development, intelligence quotients, behavioral deviations, and quality of home environments. Both large-scale national studies of brain development in normal children and studies of neurodevelopment outcomes after surgery have also used similar ranges of endpoint measures, including intelligence, verbal and nonverbal abilities, memory, attention, multidomain development, and behavioral pathologies. It is important to note that these defined endpoints involve specific developmental domains and are not the same as a global measure of intelligence. In the Boston Circulatory Arrest Trial, even in situations of significant physiologic injuries, decrements in general IQ scores were extremely modest, and deficits were only detected using a targeted examination that assessed specific areas such as executive function, memory, and attention. In human studies, although it would be informative to have an IQ measure, more specific information can only be obtained by evaluating defined developmental domains. Assessment could be selective for the specific domains of interest and does not necessarily require a complete battery of neuropsychological testing. Although these studies did not specifically address the question of anesthesia neurotoxicity, they do demonstrate the value of examining global as well as domain-specific outcome measures. The need to perform long-term follow-up assessment is illustrated by the results from neurobehavioral outcome studies in children after surgery and anesthesia. The overwhelming majority of these clinical studies have consistently identified minor behavioral regressions followed by recovery within a month. Therefore, they have been limited to assessment of short-term rather than long-term neurodevelopmental consequences.

Therefore, based on the findings in the preclinical anesthetic neurotoxicity studies and other developmental neurotoxicity studies in children, we propose to assess the neurodevelopmental endpoints by direct assessments of both global intelligence measures and specific domain measures in executive functioning, attention, memory, and motor development. Because human development is impacted by complex interactions, interpretation will also require the appraisal of social, behavioral, and family function. The rationale for using direct assessment for these outcome measures is that the data will be specific, consistent, and complete with respect to the research question. Unlike using a clinical diagnosis, which not only may lack standardization and uniform criteria but may only point to significant and serious conditions, direct assessment allows for detection of...
more subtle, though important, functional deficits. For example, a diagnostic endpoint of attention deficit hyperactivity disorder would exclude more subtle attention dysfunctions that are, nevertheless, suboptimal for age and impact on learning, such as poor selective and sustained attention abilities, self-regulation, and monitoring. We further propose that the assessment be performed in a single session later in childhood, at least 3 yr after exposure, to determine the long-term outcome. To perform the assessment in a single session would mean that the comparison of these outcome measures between the exposed and unexposed groups could be performed using the same age-specific instruments during a defined developmental period. This would eliminate the methodologic challenge of interpreting data obtained using different age-specific instruments across sequential developmental periods in childhood. Poor predictability over time of widely used and respected instruments for infants and young children, e.g., the Bayley Scales of Infant Development, is well documented and would constitute a significant limitation.

The second important consideration in study design is the choice of the epidemiologic approach. Direct and prospective neuropsychological evaluation would provide the most valid information. However, useful data derived from direct but nonprospective neuropsychological evaluation may be available in certain life-course birth cohorts constructed over the past 50 yr in the United States and elsewhere. Because almost all birth cohort studies have some information on child health and development and are likely to have surgical histories, this has the appeal of providing answers relatively quickly. Several of the more recent birth cohort studies, including the MoBa-Norway cohort constructed in 1999 and the National Child Study initiated in 2006, are particularly attractive because they would not involve any significant changes in anesthesia practice in children and therefore exposure history to obsolete agents, as would be the case with some of the older birth cohorts. However, these birth cohorts have not completed their enrollment, and any data from these studies may not be available for some time to come.

Direct and prospective neuropsychological evaluation could be performed as a randomized controlled trial or as an observational study. Because surgery without anesthesia is not an ethical or acceptable option, a placebo-controlled randomized clinical trial is precluded. Observational studies could be performed with either a prospective cohort or a retrospectively assembled exposed and unexposed cohort, which is then followed and assessed, in a prospective fashion. The approach of prospective assessment of a retrospective cohort has been successfully used in studies of childhood cancer survivors and on the effect of tympanostomy on childhood development. Creating a cohort with anesthesia exposure having occurred in the past has a number of distinct advantages. First, there would be a large number of potential subjects. Second, if only subjects who have sufficient quality of documentation are enrolled, the actual dose and duration of anesthetic exposure could be examined. Third, one could use age-specific, validated assessment tools for the direct assessment of outcomes. Fourth, the comparison is within a well-defined developmental period and not across ages of different developmental periods. It is difficult to make comparison across ages representing different periods of physiologic and psychological development, because the predictive value from one age group to another is relatively weak with the currently available age-specific neuropsychological assessment tools. Finally, this approach offers economy in the time required to obtain initial results, and in the potential cost of the study because there will be no need to budget for extensive follow-up.

All of the preclinical data have consistently demonstrated that neuronal apoptosis and degeneration in response to anesthetic exposure were developmental age dependent, with the greatest vulnerability occurring during the period of synaptogenesis. We therefore propose to assemble a retrospective cohort that had anesthetic exposure before age 3 yr, a period for synaptogenesis in humans.

The choice of comparison group is perhaps the most important consideration in this study design. In our proposed design, the comparison group consists of siblings who had no anesthesia exposure. Parental education and socioeconomic status are two of the most important confounding factors to control for in any study involving evaluation of neurocognitive function. For this reason, the adoption of siblings as the comparison group has been widely used in psychiatric research. In using the sibling as the comparison group, one important consideration is the intersibling differences in IQ that may exist. Though a recent study has documented a difference in IQ based on the birth order of siblings when they were tested as adults, other sibling studies have shown little intersibling differences in intelligence when testings were performed at ages 4, 7, and 11 yr. Although intersibling differences in more subtle aspects of brain functioning related to learning and behavior are less known, these data do strongly suggest that the choice of age for testing is important in the study design when sibling comparison groups are used for studies examining neurocognitive function as an outcome.

It is clear that a study to determine whether anesthetics are neurotoxic in children is urgently needed. The proposed epidemiologic design would be efficient and feasible and would yield reliable and valid outcome data. The neurodevelopmental endpoint measures for the proposed study, including tests of memory, attention, motor function, and behavior, are chosen based on extrapolating the deficits identified in the available though limited animal data, while incorporating the experiences from other developmental neurotoxicity studies. The assessment will be performed within a specified age range in...
late childhood for both the index and the comparison group using validated age-specific instruments. Finally, the study is designed to detect modest effects of anesthetic agents on the neurodevelopmental outcome in the context of surgery. Therefore, a relatively large sample size for such a study would be anticipated, which could be more effectively achieved with a multisite design.

Irrespective of the epidemiologic design, distinguishing the effects of anesthesia from the effects of surgery represents a daunting challenge to clinical researchers. Our proposed study design may be the most appropriate and immediate approach to perform an observational study to address the research question of anesthetics as potential developmental neurotoxins. With the proposed study design, if there is no difference in any neurodevelopmental outcome between groups, then that is strong evidence that anesthesia does not produce neurotoxicity, but if the results show any evidence for any difference between exposed and unexposed groups in any neurodevelopmental outcome, then no definite conclusion can be made that this effect is due to the surgery or the anesthesia.

In the context of history of anesthesiology as a specialty, once before, the anesthetic scientific community had answered a pressing question of anesthetic toxicity and safety. Forty years ago, the National Halothane Study was the largest epidemiologic study ever performed up to that time. It was a multisite study that used a retrospective cohort design, similar to the study proposed here. The results of The National Halothane Study significantly influenced anesthetic practice and assured the public of the safety of the anesthetic agent halothane.48 We believe, 40 yr later, it is once more time for a major anesthesia-related epidemiologic study. It is both a responsibility and an opportunity for the specialty of anesthesiology. It is our responsibility to address this critical public health issue related to pediatric anesthetics. It is also an opportunity for us to lead the way in translational research from developmental neuroscience to population child health.

Lena S. Sun, M.D.,* Guohua Li, M.D., Ph.D., Ph.D., M.P.H.,† Charles DiMaggio, Ph.D., M.P.H.,‡ Mary Byrne, Ph.D., M.P.H.,§ Virginia Rauh, Sc.D., M.S.W.,§ Jeanne Brooks-Gunn, Ph.D., Ed.M.,§ Athina Kakavouli, M.D.,# Alastair Wood, M.D.,** Co-investigators of the Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) Research Network†† Departments of Anesthesia at the University of North Carolina, University of New York, New York, New York, New York, Issi@columbia.edu. †Department of Anesthesiology and Epidemiology, §School of Nursing, ‡Department of Population and Family Health, ††School of Public Health, ††Teachers' College and Department of Pediatrics, #Department of Anesthesiology, Columbia University, **Departments of Neurology and Pediatrics, Vanderbilt University, Nashville, Tennessee; Department of Internal Medicine and Department of Pharmacology, Weill Cornell Medical College, New York, New York. ††See appendix.

The authors acknowledge the contribution of all of the guest participants of the First Columbia University–Morgan Stanley Children's Hospital of New York Symposium on 'Neurodevelopment and Anesthesia in Children,' held on May 5, 2008: Cynthia Salorio, Ph.D. (Assistant Professor, Department of Physical Medicine and Rehabilitation, Johns Hopkins School of Medicine, and Pediatric Neurologist, Department of Rehabilitation and Department of Neurophysiology, Kennedy Krieger Institute, Baltimore, Maryland); Gregory Crosby, M.D. (Associate Professor, Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Boston, Massachusetts); Randall Flick, M.D., M.P.H. (Assistant Professor, Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota); Michael M. Todd, M.D. (Professor and Head, Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, Iowa); David Bellinger, Ph.D. (Professor, Department of Neurology, Harvard Medical School, Boston Children’s Hospital, Boston, Massachusetts); Alan J. Moskowitz, M.D. (Professor, Department of Medicine and Department of Health Policy and Management, and Co-Director, InCIOHR, Columbia University, New York, New York); Ezio Susser, M.D., Dr.P.H. (Anna Cheskin Gelman and Murray Charles Gelman Professor and Chair, Department of Epidemiology, Mailman School of Public Health, Professor, Department of Psychiatry, Columbia University).

The authors also acknowledge other significant contributors to the design and development of the PANDA Study Research Network: Charles Dean Kurth, M.D. (Professor, Departments of Anesthesia and Pediatrics, University of Cincinnati College of Medicine, and Anesthesiologist-in-Chief and Director, Department of Anesthesia, Cincinnati Children's Hospital, Cincinnati, Ohio); Annetine Geligus, Ph.D. (Professor, Department of Health Policy and Management and Surgical Science, and Co-Director, InCIOHR, Columbia University); William J. Greeley, M.D., M.B.A. (Professor, Departments of Anesthesiology and Pediatrics, University of Pennsylvania School of Medicine, and Anesthesiologist-in-Chief and Chair, Department of Anesthesiology and Critical Care Medicine, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania); Charles Schleien, M.D. (Professor, Departments of Pediatrics and Anesthesiology, Columbia University, and Director, Pediatric Intensive Care Unit, Morgan Stanley Children’s Hospital of New York–Presbyterian, New York, New York); Charles J. Stolar, M.D. (Rudolph N. Schulz Professor, Departments of Surgery and Pediatrics, Columbia University, and Surgeon-in-Chief, Morgan Stanley Children’s Hospital of New York–Presbyterian, Pennsylvania); Joseph R. Tobin, M.D. (Professor and Chair, Department of Anesthesiology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina); and Alastair Wood, M.D. (E.M. Papper Professor and Chairman, Department of Anesthesiology, Columbia University).

The authors thank Barbara Lang, B.S. (Administrative Assistant, Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York), for her excellent editorial assistance.

References

19. Anesthesiology, V 109, No 5, Nov 2008
20. Summary of the national Halothane Study: Possible association between halothane anesthesia and postoperative hepatic necrosis JAMA 1996; 197:775–88

Appendix: Coinvestigators of the PANDA Research Network

Robert I. Block, Ph.D. (Associate Professor, Department of Anesthesiology, University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa); Jayant K. Deshpande, M.D., M.P.H. (Professor, Departments of Anesthesiology and Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee); Steven C. Hall, M.D. (Arthur C. King Professor of Pediatric Anesthesia, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois); Andreas Loepke, M.D., Ph.D., F.A.A.P. (Associate Professor, Departments of Anesthesiology and Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio); Lynne Maxwell, M.D. (Associate Professor, Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania); Francis X. McGowan, Jr., M.D. (Professor, Department of Anesthesia, Children’s Hospital Boston, Boston, Massachusetts); Tonya Miller, M.D. (Instructor, Department of Anesthesia, Children’s Hospital Boston); Santhanam Suresh, M.D. (Professor, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine); Ronald S. Litman, D.O., F.A.A.P. (Associate Professor, Departments of Anesthesiology and Pediatrics, University of Pennsylvania).