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Outcomes Research in Vulnerable Pediatric Populations

Ka-Eun M. Lee, MD,
Department of Anesthesiology, Columbia University Medical Center, Columbia University College of Physicians and Surgeons, New York, NY

Thomas G. Diacovo, MD,
Departments of Pediatrics and Pharmacology, University of Pittsburgh Medical Center, Children's Hospital of Pittsburgh, Pittsburgh, PA

Johanna Calderon, PhD,
Department of Psychiatry, Harvard Medical School, Boston Children's Hospital, Boston, MA

Mary W. Byrne, PhD, DNP, MPH, FAAN,
Columbia University School of Nursing, Columbia University College of Physicians and Surgeons, New York, NY

Caleb Ing, MD, MS
Department of Anesthesiology and Epidemiology, Columbia University College of Physicians and Surgeons and Mailman School of Public Health, New York, NY

Abstract

The Pediatric Anesthesia and Neuro-Development Assessment (PANDA) study team held its biennial symposium in April 2018 to discuss issues on anesthetic neurotoxicity in the developing brain. One of the sessions invited speakers with different areas of expertise to discuss "Outcomes Research in Vulnerable Pediatric Populations." The vulnerable populations included neonates, children with congenital heart disease, children from low socioeconomic status, and children with incarcerated parents. Each speaker presented some of the ongoing research efforts in these groups as well as the challenges encountered in studying them.

Keywords

outcomes research; vulnerable pediatric populations; anesthesia; neurodevelopment; neonates; congenital heart disease; social class; prison nursery

The Sixth Pediatric Anesthesia and Neuro-Development Assessment (PANDA) symposium was convened in April 2018, with a special session dedicated to discussing "Outcomes Research in Vulnerable Pediatric Populations." The vulnerable populations included neonates, children with congenital heart disease, children from low socioeconomic status, and children with incarcerated parents. The purpose of this session was to discuss why these groups of children differ from other populations, the reasons for studying them, and

Corresponding Author: **Ka-Eun M. Lee**, **Address:** 622 West 168th Street, BH 440-N, New York, NY 10032, kl2154@cumc.columbia.edu.

highlight the unique challenges in conducting research in these groups. Dr. Sulpicio Soriano from Boston Children's Hospital moderated the session and a speaker from each of these areas was invited to share their experience and research involving this vulnerable pediatric population. The speakers included Dr. Thomas G. Diacovo from University of Pittsburgh Medical Center, Dr. Johanna Calderon from Boston Children's Hospital, Harvard Medical School, and Drs. Caleb Ing and Mary Byrne from Columbia University Medical Center.

Research in Newborn Children:

Although children represent a quarter of the world's population,[1] pediatric trials constitute only 20% of the total number of trials registered in the NIH clinical trials repository, clinicaltrials.gov. Of these pediatric trials, only about 3.4% involve neonates.[2] Thomas G. Diacovo, MD, Director of the Division of Newborn Medicine and Director of Neonatal Cardiovascular Research at the University of Pittsburgh Medical Center, addressed the lack of studies in some of our most vulnerable children and also discussed the challenges of conducting clinical drug trials in the neonatal population. For many years, there has been little incentive to study the effects of drugs in children, and as a result, the vast majority of medications have lacked adequate pediatric prescribing information.[3] In fact, over 90% of drugs commonly used in the neonatal intensive care units (NICU) throughout the United States do not have sufficient labels for dosing, safety, and efficacy. Therefore, the Food and Drug Administration (FDA) has taken several steps over the years to provide potential financial incentives to industry, including accelerated approvals and an additional 6 months of market exclusivity, to promote research in drug-labeling for children.[2] However, this legislation has yet to bear fruit for neonates. In a review of FDA databases, Laughon et al found that of the drugs that were studied in the pediatric population to obtain market exclusivity, only 7% were studied in neonates.[4] Based on a survey of 290 NICUs, almost half of the drugs studied in neonates were never used in the NICU, and therefore not clinically relevant to the neonatal population.[3,4]

The current lack of clinical trials in the pediatric population not only has a direct impact on the safety and effectiveness of medications prescribed in children, but perhaps even more importantly, has limited the availability of new drug treatments to improve survival and outcomes in children. Studies of drug safety in children are commonly not performed, particularly in neonates where >65% of drugs used in neonatal patients are administered on an off-label basis.[5] Therefore, use of these drugs is largely dependent on the professional judgement of the practitioner. The main reasons for insufficient interest in neonates are due to the fact that they are regarded as a "small market" by the pharmaceutical industry and thought to be at high risk for adverse events.

Dr. Diacovo emphasized that new approaches are necessary to make advancements in neonatal clinical research. Key principles in developing clinical trials in this population include focusing on the ultimate goal of the study, applying precision medicine, identifying target areas, and collaborating with the pharmaceutical industry and regulatory agencies. The value of a relatively new organization known as the International Neonatal Consortium (INC) was also discussed. By uniting stakeholders from research institutions, pharmaceutical industries, regulatory agencies, patient advocacy and other organizations, INC has aimed

to develop practical tools that can be incorporated into clinical trials for neonates, which will ultimately lead to more successful, efficient trials and much needed therapies. Dr. Diacovo also presented his own experience in performing a clinical trial to evaluate new therapeutic interventions in neonatal cardiac patients with systemic-to-pulmonary artery shunts. Thrombosis of this shunt in the early postoperative period can cause significant morbidity and mortality. The goal of the trial is to evaluate the use of cangrelor, an anti-platelet drug that is FDA-approved in the adult population, to reduce the risk of shunt thrombosis in the early postoperative period in neonatal cardiac patients with single ventricle physiology. As an initial step, three years of preclinical testing was performed using sophisticated microfluidic technologies and humanized animal models to generate sufficient data so that the FDA and the pharmaceutical company producing the medication would support a future clinical trial. Studying a new drug unknown to the neonatal population was accompanied by several challenges, including (i) the need of a surrogate biomarker to validate drug efficacy in real time, (ii) performing pharmacokinetic and pharmacodynamic testing using 1 ml or less of blood, and (iii) obtaining consent from parents. Currently, the phase 1 trial of the study is near completion with the next phase in progress.[6]

Neurodevelopmental Outcomes in Children with Congenital Heart Disease:

With advances in medical and surgical care, long-term survival in patients with complex congenital heart disease (CHD) has increased significantly. As a consequence, the focus has shifted from survival, to the identification and management of long-term morbidities in these patients. Neurodevelopmental impairment has been identified as one of the most common sequelae associated with complex CHD and has led to an interest in screening and diagnosis, with the possibility of therapeutic interventions to improve functional outcomes.[7] In this session, the long-term neurodevelopmental outcomes in children with CHD was discussed by Johanna Calderon, PhD, Assistant Professor of Psychiatry at the Boston Children's Hospital and Harvard Medical School.

Children with complex CHD, particularly those who had open heart surgery early in life, are at risk for deficits in higher-order neurocognitive functions such as executive functioning and social cognition. Executive function has been an area of interest because coordination of its three components - inhibitory control, working memory, and cognitive flexibility - enables higher-order mental processes, such as problem solving and completing planned goals. Deficits in executive function are found to be associated with attention-deficit hyperactivity disorder (ADHD) and attention-deficit disorder (ADD), lower academic achievement, psychiatric disorders (i.e. anxiety, depression), addiction, poor decision-making, and may lead to a lower quality of life.[8]

Complex CHD is associated with impairments in social functioning (i.e., decoding emotional facial expressions and understanding people's inner mental and emotional states).[9,10] These deficits are typically found in individuals within the autism spectrum. Indeed, the National Health Interview survey found a five-fold increased odds of autism spectrum disorder (ASD) in patients with CHD.[11]

Dr. Calderon also discussed a landmark study demonstrating the risk of executive dysfunction and social cognition impairments in adolescent patients with CHD. As a follow-up to the Boston Circulatory Arrest Study, patients who had undergone open heart surgery as infants for dextro-transposition of the great arteries continued to have difficulty with executive function and social cognition at 16 years of age.[12,13]

With more information emerging about the adverse neurodevelopmental effects of CHD, appropriate interventions to prevent and treat executive dysfunction have been explored. One intervention is the Cogmed Working Memory Training Program, a 5-week training program that specifically targets executive function and involves intensive computerized training of the working memory. It is being implemented as a home-based cost-effective intervention and its effectiveness in patients with CHD is being evaluated by Dr. Calderon in two ongoing randomized controlled trials in children and adolescents.

Poverty as a Risk Factor for Neurodevelopmental Deficit after Neurotoxic Exposures:

Questions have been raised regarding the safety of anesthetic medications in children due to findings indicating that anesthetics disrupt neurodevelopment in animal models resulting in behavioral changes later in life. A number of studies in humans have also identified associations between neurodevelopmental deficits and anesthetic exposure. Interpreting the clinical studies however are challenging because the results are less consistent than the animal studies, with associations identified in some studies but not others.

Caleb Ing, MD, MS is an Assistant Professor of Anesthesiology at Columbia University Medical Center. During this session, he discussed his use of a cohort of children enrolled in Medicaid to evaluate an association between anesthetic exposure and subsequent neurodevelopmental deficit. Medicaid/Children's Health Insurance Program (CHIP) are major sources of public financing of healthcare in the United States. In 2017, 35.7 million children were enrolled in these programs.[14] Medicaid/CHIP provide medical insurance for children of lower socioeconomic status, covering approximately 38% of all children in the United States. While criteria for enrollment varies by state, families with incomes up to at least approximately 200% of the federal poverty level are eligible in 49 of the 50 states.[15]

Cohorts of children exposed to surgery and anesthesia and enrolled in New York state Medicaid have previously been studied and found to be associated with ICD-9-coded clinical diagnoses for developmental and behavioral disorders.[16,17] Dr. Ing subsequently conducted an observational study using Medicaid data from Texas and New York to evaluate the age at exposure to anesthesia and its association with mental disorder diagnoses.[18] He found an overall increased risk of mental disorders, developmental delay, and ADHD after anesthesia exposure. The increased rates of diagnoses however were similar in all ages when exposure occurred before 5 years of age. This suggests that altering the timing of the surgical procedure at ages below 5 years may not offer significant benefit in reducing the risk of mental disorder diagnoses.

While associations have been seen in these cohorts of children enrolled in Medicaid, other recent prospective studies have not found neurodevelopmental differences in anesthetic-exposed children.[19,20] Patients enrolled in these and other prospective studies however often differ from the general population, as patients and families of higher socioeconomic status (SES) are more likely to enroll in studies. The SES of the patients evaluated in a study may be an important consideration after neurotoxic exposures. Children from higher SES families show a reduced effect on IQ after exposure to pesticides compared to children from lower SES families.[21] When compared to lower SES children with lead exposure, those from higher SES backgrounds required a higher level of lead exposure before an effect on neurodevelopmental outcomes was seen. This indicates a differential threshold of vulnerability based on SES status after lead toxicity.[22] Children of higher SES were also able to more effectively recover from a toxic lead exposure compared to lower SES children.[23] The effect of an enriched environment has also been observed in rats, where the effects of lead toxicity are decreased, and improvements in memory and cognition after exposure to sevoflurane are seen.[24–26] While higher SES has an impact in some neurotoxic exposures, and an enriched environment has been shown to be beneficial in rodent models, it is unclear whether these factors impact neurodevelopmental outcomes in children exposed to anesthesia.

There is significant heterogeneity in the results of the published clinical studies of anesthetic neurotoxicity. There are a number of potential reasons for these inconsistencies, with one potential reason being the differences in the patients in each study, including differences in SES. Given the evidence from studies of other neurotoxins, the types of patients included in a study of anesthetic neurotoxicity may be an important consideration.

Studies in Children of Incarcerated Mothers:

Children of incarcerated parents are a vulnerable population who are at risk for multiple emotional and behavioral problems, as well as social determinants that can put them at higher risk of becoming part of the criminal justice system themselves. The attachment the child forms with his or her primary caregiver during infancy and early childhood is crucial for optimal development of the child. Several states have recognized this, and as a result provide prison nurseries that permit the infant to co-reside with the incarcerated mother for a variable period of time.

Mary Byrne, PhD, DNP, MPH, FAAN is the Stone Foundation & E.D. Fish Professor of Health Care for the Underserved and Director of the Center for Children and Families at Columbia University Medical Center. During this session, she presented evidence from a series of prison nursery studies to support parenting and child development to those involved in the criminal justice system.

In one of the studies, Dr. Byrne evaluated mother-child attachment, parenting competency, and child development in those involved in mother-child prison nursery co-detention.[27] She specifically focused on the attachment achieved in the prison setting as well as how it is maintained when transitioning to the outside community. Findings from this study demonstrated that prison nurseries can be effective in providing helpful services to multiple-

risk families. However, there continues to be a need for more intense parenting support and comprehensive mental health services as well as effective alternative sentencing within the community. More research and follow-up is required in order to promote an optimal environment for this vulnerable population.

Conclusion:

This session highlighted the importance of studying vulnerable pediatric-aged populations. Neonates were identified as a largely neglected study population due to challenges in conducting research in them and a lack of appropriate incentives. Novel approaches to trial design have been necessary to overcome barriers in advancing neonatal research. In children with congenital heart disease, significant progress has been made in their medical and surgical care to improve survival. Recently, therapeutic interventions are being investigated to improve their functional outcomes as well. However, more work remains as these children present unique challenges that extend far beyond the perioperative survival period. Poverty and low SES were also recognized as potentially important considerations in studying long-term neurodevelopmental function in children as they may influence the long-term effects of neurotoxic exposures. In addition, understanding the impact of interventions in children of incarcerated parents was emphasized as these interventions may have a significant positive influence on their lives. The central theme of this session was to acknowledge that there are vulnerable pediatric populations and that the outcome of studies in these children may differ from general pediatric populations. It is therefore important that we work to not only meet the needs of healthy populations of children, but the needs of the most vulnerable children as well.

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