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What Next After GAS and PANDA?

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Abstract

On April 16th and 17th, 2016, the Fifth biennial Pediatric Anesthesia & Neurodevelopment Assessment (PANDA) symposium was convened at the Morgan Stanley Children's Hospital of New York at Columbia University Medical Center. During the symposium, experts in the fields of anesthesiology, neuropsychology, and epidemiology were convened in a small group session to determine the level of confidence in the current clinical evidence and the next steps in anesthetic neurotoxicity clinical research. Among the participants in the discussion, there remained a lack of consensus on whether anesthetic exposure causes long-term neurodevelopmental deficits in children based on the current evidence. This causal relationship between anesthesia exposure and neurodevelopmental deficit is difficult to establish using observational data, and current and future clinical trials are critical for answering this question. It was however recognized that the continuum of data that is seen in studies of other toxic environmental exposures, such as lead poisoning, has not been established in the anesthetic neurotoxicity literature, specifically regarding the timing of the exposure, the dose effects, contributing perioperative conditions, or vulnerable populations. As a result, these questions may need to be addressed in observational studies in order to guide future clinical trials.

Introduction

While the existence of anesthetic neurotoxicity is well-described in animal studies, clinical studies are underway to help determine whether a similar toxic response occurs in children, and if so, under what circumstances. Updates on several of these ongoing studies have been

described elsewhere in this supplement (Pinyavat- JNA supplement). In order to determine the next steps in anesthetic neurotoxicity clinical research, experts in the fields of anesthesiology, neuropsychology, and epidemiology were convened in a small group session at the Fifth biennial Pediatric Anesthesia & Neurodevelopment Assessment (PANDA) symposium on April 16th at the Morgan Stanley Children's Hospital of New York at Columbia University Medical Center. The session was chaired by Dr. David O. Warner from the Mayo Clinic College of Medicine and Dr. Virginia Rauh, from Columbia University's Mailman School of Public Health. The purpose of this session was to determine the level of confidence in the current published clinical data, evaluate specific questions that need to be asked in future studies, and discuss whether clinical interventions need to be undertaken on a population level based on the current evidence.

Observational studies

In discussing the published data, it was recognized that while some studies have shown a difference between children exposed to anesthesia and surgery compared to unexposed children, others have found no difference.¹⁻⁵ Specifically differences have been identified in several cohorts originating from Australia and the United States, but the same is not true in many European cohorts. A number of differences exist between these studies, but one important distinction is that most studies in European cohorts have relied on academic achievement scores, which have been found to be less sensitive than other measures in studies of anesthetic neurotoxicity.⁶ The importance of using a range of outcomes has also been seen in studies of other toxic exposures, such as lead poisoning.⁷ Besides the neurodevelopmental outcomes used, within the anesthetic neurotoxicity literature there are other significant variations, including the control subjects that were chosen, the ages and doses of exposure as well as the types of anesthetic drugs used and the surgical procedures that were performed. This heterogeneity in the observational studies complicates the interpretability of the published data, but the major obstacle identified is that the causal link between anesthetic exposure and neurodevelopmental deficit cannot be adequately established solely using observational studies. Differences in neurodevelopment between children exposed and unexposed to surgery and anesthesia may be due to the surgery, the anesthesia, or the confounding due to other perioperative or clinical factors. As a result, while associations have been found, a firm link between anesthesia and neurodevelopmental deficits has yet to be confirmed in humans.

In this session, it was also recognized that the continuum of data seen in studies of other toxic environmental exposures has not been well established in the anesthetic neurotoxicity literature. At this time, there is little information with regard to the window of vulnerability, the dose effects, contributing perioperative conditions, or vulnerable populations. In order to adequately evaluate the causal relationship between anesthesia and neurodevelopment deficit, the answers to these questions will likely need to be first established with observational studies. The importance of care in interpreting published studies and designing new ones was also discussed. Biases due to the types of families that are willing to enroll in prospective and ambidirectional studies were recognized, as was the lack of sensitive neuropsychological outcomes in population based cohort studies.

While many types of studies may be performed, one potential source of observational data mentioned was the Environmental influences on Child Health Outcomes (ECHO) Program. ECHO is an initiative by the NIH to capitalize on large-scale existing prospective community cohorts, which contain biomedical data and may be used to test associations between a range of anesthesia exposures and neuropsychological, behavioral and clinical outcomes over time.

Clinical Trials

Clinical trials will be necessary to establish a causal relationship between anesthesia exposure and neurodevelopmental deficit. Currently, the one randomized controlled trial that is underway is the GAS study, which evaluates spinal anesthesia vs. sevoflurane anesthesia.⁸ The interim results at age 2 years have been published, but assessment at this age may not be adequate to evaluate what is suspected to be subtle neurodevelopmental differences.⁹ The study however is ongoing, with the 5-year neurodevelopmental outcome data expected within the next few years. A further question regarding this study was whether the short exposure to only sevoflurane as a toxic exposure in this study was of adequate dose or duration based on the pre-clinical data, which have found larger effects with longer exposures. The proposed T-Rex trials, which are in the planning stages, aim to evaluate longer exposures, using dexmedetomidine either as a mitigating agent (with remifentanyl and regional blocks) or as a comparator (to volatile-based techniques). The discussion group however recognized two fundamental challenges to the planning of clinical trials in general. First, what procedures would plausibly put children at risk? As noted above, we have not yet fully defined the characteristics of the exposure (e.g. duration of exposure, age of exposure, type of anesthetic, etc.) that would be expected to result in a deficit in a large clinical trial. Second, what are the relevant outcomes? Evidence suggests that if there is injury, it may be manifest by subtle changes in language and cognition that may not be reflected in developmental measures obtained in the first few years of life, or more broad measures such as academic achievement tests.

Overall, studies in mitigation strategies are appealing because they can be added to existing standard anesthetic regimens. The key to mitigation studies is that they have to be practically applicable for patients and able to be used across the globe. There are however several important considerations. The first is establishing if we have enough information proving the existence of neurotoxicity to justify mitigation studies and the exposure to children to an additional pharmacological agent. The second is what level of animal data is required before we can judge a mitigating agent to be potentially safe and effective in children.

Dexmedetomidine as a mitigating agent is attractive because it is already commonly used in small children, but it will be important to ensure that this and other mitigating agents are not actually causing harm. Further work will also need to be done to elucidate the appropriate dose and timing of the mitigating drug. Prior to performing mitigation studies, there was a general consensus within the group that animal data was required before enrolling patients. Data showing the safety of the mitigation strategy in rodents is needed as a minimum requirement, and preferably also primate data. Confirming safety is particularly important in agents not used in children for common clinical care.

As discussed above, confirming that neurotoxicity exists in a specific population of children prior to starting mitigation studies is critical because in a situation where there is no difference found between mitigation and control groups, it would be difficult to determine if the mitigating agent was effective in preventing neurotoxicity, or if neurotoxicity never occurred in that group of children.

Changes to Clinical Practice

If there is an association between exposure to surgery and anesthesia and long-term neurodevelopmental deficits, the question was raised regarding whether population exposure to anesthesia should be reduced prior to establishing a causal link to anesthesia? While there was not a clear answer to this question, the role of pediatric anesthesiologists was emphasized, with the thought that the benefits of surgery need to be carefully considered, and that physician anesthesiologists should be engaged and involved in the decision-making process with the surgeons.

Discussion

Different types of studies rely on each other to move science forward. Just as animal studies need clinical studies in order to establish relevance to humans, clinical studies rely on animal studies to generate new questions and direct lines of inquiry. A similar symbiotic relationship exists between clinical trials and observational studies. Given the difficulty with establishing a causal relationship between anesthesia exposure and neurodevelopmental deficit in children using observational studies, prospective clinical trials are critical. Observational studies however are also essential in order to identify the correct questions to answer in clinical trials.

Neurodevelopmental toxicity is often influenced by the age of exposure, concomitant exposures to other neurotoxicants, nutritional status, genotype, and even characteristics of the home environment, and if anesthetics are found to be neurotoxic, they are likely to also have these characteristics.⁷ This continuum of evidence has been established with other neurotoxicants, but similar data in the field of anesthetic neurotoxicity is not yet available. The GAS study will help confirm the safety of a short exposure to sevoflurane, but sevoflurane alone is typically not used in the clinical setting as delivering anesthesia in children often involves the concomitant use of IV agents or nitrous oxide. The results from the PANDA study however also echo the safety of a short anesthetic exposure for hernia repair. One limitation however is that since the families in the study come from a higher socioeconomic status than the general population, this enriched environment may reduce the severity of anesthetic effects, a hypothesis also found in research on lead toxicity.^{10,11}

Despite the limitations with these most recent studies, their results are helping to develop an idea of what a safe clinical exposure in specific children may be. The results from these and other observational studies will be important for guiding the design of future clinical trials. Given the considerable commitment of time and money involved in planning and performing well-designed multi-institutional clinical trials, the correct hypotheses need to be established, with the proper exposure groups and appropriate outcome measures.

Specifically the toxic dose, duration, or combination of anesthetic drugs will need to be identified, in addition to the impact of frequency of exposure, age of vulnerability, and existence of any vulnerable populations. As we develop a better understanding of these important questions in the preclinical and observational data, we will be able to more effectively design and implement the next wave of clinical trials.

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