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Preclinical and clinical paediatric anaesthesia research

Daniil P Aksenov,
NorthShore University HealthSystem, Evanston, IL 60201, USA

Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

David A Gascoigne,
Department of Radiology, NorthShore University HealthSystem, Evanston, IL 60201, USA

Steven B Greenberg,
Department of Anesthesiology, NorthShore University HealthSystem, Evanston, IL 60201, USA

Mohammed M Minhaj
Department of Anesthesiology, NorthShore University HealthSystem, Evanston, IL 60201, USA

Concerns about the long-term consequences of anaesthesia exposure before age 4 years were brought to the attention of researchers and clinicians by some notable retrospective studies, which reported learning and behavioural deficits in adolescence that were significantly correlated to early anaesthesia exposure.[1,2] These clinical findings instigated a large amount of preclinical work that has consistently provided converging evidence for learning deficiency due to early anaesthesia exposure in a dose-dependent and duration-dependent manner.[3] However, when attempts have been made to apply these results to prospective clinical studies, similar deficits are not reported, potentially due to a disjunction in methodological continuity.

Several high-profile clinical studies have reported minimal to no consequences of early anaesthesia exposure in children and infants (ie, the general anaesthesia and awake-regional anaesthesia in infancy study [GAS],[4,5] The Mayo Anesthesia Safety in Kids [MASK] study,[6] and the Pediatric Anesthesia Neurodevelopment Assessment [PANDA] project).[7] For example, the GAS study was unique in its evaluation of the consequences of neonatal anaesthesia as it used a randomised, controlled study design—a quality of investigative rigour that, at the time, had not been seen in clinical research on early anaesthesia exposure. The researchers reported no significant difference in the Full-Scale Intelligence Quotient (FSIQ) of anaesthesia-exposed children compared with control children at ages 2 and 5 years.[4,5] These findings were discussed in a subsequent paper, in which the authors placed these important findings in the context of previous preclinical work and concluded that, although a single, brief exposure to general anaesthesia seems to be safe, there is a need to investigate long-term effects of extended anaesthesia exposure in patients.[8]

daksenov@northshore.org .

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The discrepancy between the primary outcome measures of preclinical and clinical research is notable. In the MASK and GAS studies, the primary outcome measure was FSIQ score, derived from the age-appropriate version of the Wechsler Scale of intelligence—which was also a main component of the assessments administered in the PANDA study. However, these tests are based on verbal comprehension skills and working memory abilities that have already been developed. Although these measures are of interest to the research community, it is not known at what rate the associated skills were acquired. By contrast, preclinical studies have not been able to conduct cognitive performance tests on animal subjects. Instead, they have used both active and passive assessments, such as the Morris water maze and classical conditioning models, to show a slowed rate of learning. Unfortunately, comparable rate-of-learning tests have not yet been administered to patients. Therefore, clinical and preclinical studies involving early anaesthesia exposure do not have directly comparable outcome measures.

Another important difference between the clinical and preclinical tests is their relative level of cognitive difficulty. In preclinical studies, even healthy individuals can take days to learn novel tasks, depending on the intensity and nature of stimuli. Therefore, the tests represent a difficult task for animal subjects to learn, as only gradual improvements in measures of learning are typically seen. Conversely, although human FSIQ tests might require substantial attention from a patient for the duration of the test, the tasks involved in the assessment are learned immediately with the guidance of an administrator. This simplicity is by design, so FSIQ tests can be completed in a relatively short period of time. Thus, both the basis and the demand placed on the participant of clinical measures compared with preclinical measures are substantially different.

To improve current clinical approaches to early anaesthesia exposure, future strategies should include assessments capable of investigating the rate of learning of children. Active learning could be investigated by a novel task that requires active processing, such as a complex maze.[9,10] Passive learning could be evaluated by the participant watching an unfamiliar video, then being tasked with accurately discriminating which words and objects were presented. In contrast to FSIQ-based measures, these possible alternatives can be re-administered for multiple trials across days to show gradual improvements in performance scores (depending on difficulty and participant age).

There is often a separation in the approach and outcome measures of clinical versus preclinical research, particularly in early anaesthesia exposure research. Clinical research would benefit from supplementing current work with alternatives to FSIQ tests and enabling valid comparisons with existing preclinical literature. These additions would investigate passive and active types of learning, which can also be applied to longer durations of anaesthesia. With continued collaboration between clinical and preclinical researchers, we expect novel studies to make immense progress in early anaesthesia exposure research in the near future.

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