European Society of Anaesthesiology Task Force on Nitrous Oxide: a narrative review of its role in clinical practice

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GAS, PANDA, and MASK

No Evidence of Clinical Anesthetic Neurotoxicity!

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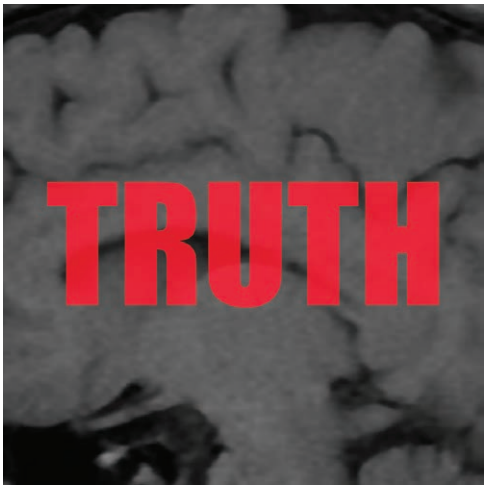
Two decades ago, the possibility that anesthetics could harm the developing brain was identified in rodents.[1] This work has been replicated in multiple species, including subhuman primates, raising serious concern in the anesthesia community and leading to a U.S. Food and Drug Administration warning on the use of anesthetic agents in young children.[2,3] Heated discussions have divided healthcare providers and policy makers on the risks *versus* benefits of general anesthesia and surgery in pediatric populations.[4,5] The major reason for this long-standing debate is that some human cohort studies have found an association between early exposure to anesthesia and subsequent neurodevelopmental alterations, while others have not.[6] Recently, the only prospective clinical trial addressing whether anesthetics contribute to long-term neurodevelopmental delays in children was published in *Lancet*, and the news is good.[7] This multisite randomized controlled trial compared regional and general anesthesia for their effects on neurodevelopmental outcome and apnea in infants. This study, commonly known as the general anesthesia spinal (GAS) trial, included more than 700 children undergoing inguinal hernia repair during early life who were randomized to either sevoflurane-based general or awake-spinal anesthesia.[7,8] Both the primary and secondary outcomes of the study demonstrated no association between 1 h of sevoflurane anesthesia in early life and cognitive composite scores at the age 2 yr or full-scale intelligence quotient from the Wechsler Preschool and Primary Scale of Intelligence test at the age of 5 yr when compared to spinal anesthesia.[7,8] This clinical trial is consistent with the results of two other recent human studies, Pediatric Anesthesia Neurodevelopment Assessment (PANDA) and Mayo Anesthesia Safety in Kids (MASK), providing strong evidence that a short exposure to general anesthesia at a young age does not result in detectable alterations in neurodevelopmental outcome.[9,10]



"The comfortable truth is…the likelihood that developmental anesthesia neurotoxicity may not exist in routine surgical procedures that occur in early life."

This is an important update, as most infants undergoing anesthesia and surgery have exposures to anesthetics that are comparable in length to those of infants in the GAS, PANDA, and MASK studies.[11] Thus, as parents and physicians, we can assume that the findings of these studies are relevant to a wide range of infants having general anesthesia for short elective surgical procedures. What remains unknown is whether longer exposures to anesthetics have an effect on long-term cognitive performance. These surgical procedures are relatively rare and may be associated with underlying disease processes such that any adverse outcome identified in the course of such studies may merely be a marker of a phenotype predisposed to neurotoxicity.[11]

One is left wondering whether the Food and Drug Administration warning on the use of anesthetics in young children should be eliminated due to the lack of reasonable clinical evidence that general anesthetics or sedatives are associated with adverse neurocognitive outcomes in humans or whether delay of surgical procedures for fear of the unknown is justified.[12] While the Food and Drug Administration amended the initial 2016 warning on the use of anesthetics and sedatives in young children to suggest that they may be associated with adverse neurocognitive outcomes when used for 3 h or more, the warning is based on preclinical studies that may have little validity in humans.[7,8] Being practicing anesthesiologists and parents, we have spent many restless nights wondering what the better

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anesthetic option would be for a minor surgical intervention in a little person: a general anesthetic or the potential stress of an awake regional procedure with no sedation, no mom or dad, and instead a pediatric anesthesiologist providing sucrose on a pacifier to calm you. As anesthesiologists also involved in basic science research, we recognize that laboratory research to understand a well-defined clinical problem differs from clinical research to find a problem identified in the laboratory. While the former allows one to dive into potential mechanisms of the clinical problem, the latter seeks a potentially nonexistent clinical problem, that is unlikely to lead to meaningful changes in clinical practice but may lead to other unanticipated outcomes.[13,14]

The comfortable truth is that we are currently facing the likelihood that developmental anesthesia neurotoxicity may not exist in routine surgical procedures that occur in early life. Unfortunately, we are unlikely to be able to prove or disprove this nonexistence. With that said, the accompanying *Lancet* editorial on the GAS study[15] suggests that research in the perioperative domain is still needed as it is plausible that there may be high-risk patients such as those with baseline cognitive or other coexisting disabilities[16] or specific genetic or epigenetic backgrounds that increase the risk of exposure to anesthetics. Perhaps most importantly, we are only beginning to understand the effects of anesthetics on surgery-induced neuroinflammation and perioperative stress and how these may affect neurodevelopment. Future translational research should guide us to explore these areas that, in turn, would better inform planning of human clinical trials.[14] However, the uncomfortable unknown is whether we will be able to convince funding resources to promote investigations into these questions at the current stage of clinical (non)evidence.

Beyond demonstrating equivalence between two anesthesia techniques, the GAS study did have another very important indirect contribution to the practice of pediatric anesthesiology. It helped to bring together a large number of dedicated pediatric anesthesiologists to think about optimal perioperative care in children and led to an understanding that perioperative care to this young fragile patient population should be delivered by specifically trained healthcare personnel. As a result, questions such as "What is the adequate level of anesthesia in neonates and infants?" and "What is the optimal blood pressure?" are now actively discussed in the pediatric anesthesia community. Answers from science that is fueled by these discussions may ultimately result in changes in clinical practice that will benefit all pediatric patients.

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Competing Interests

Dr. Vutskits is an Editor of Anesthesiology. He served as consultant for Primex (Zug, Switzerland) and Regeneron Pharmaceuticals (Tarrytown, New York). Dr. Culley is an Executive Editor of Anesthesiology. She serves as a Director and Secretary for the American Board of Anesthesiology, Chair of the Academic Anesthesiology Committee for the American Society of Anesthesiology, an *Ex Officio* Member of the Anesthesiology Review Committee for the Accreditation Council for Graduate Medical Education, and a member of the Committee on Continuing Certification for American Board of Medical Specialties.

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