Anesthetic Neurotoxicity Meets Big Data

Reasons to Be Cheerful?

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FOR more than a decade, the possibility that exposure to anesthetics may be harmful to the developing human brain has intrigued anesthesiologists and the public alike. The urgent desire to create more clarity and the need to inform parents of young children who need surgery have spawned intense research activity, including well-designed experimental studies in relevant neonatal species, as well as human epidemiologic studies in retrospective and prospective observational pediatric cohorts. In addition to these efforts, the public/private International Anesthesia Research Society/US Food and Drug Administration initiative *SMARTTots* (www.smarttots.org) and the European Society of Anaesthesiology–sponsored (Brussels, Belgium) *"EuroStar"* consortium (www.esahq.org/research/research-groups/eurostar) each coordinate research initiatives, help secure research funding, and disseminate important new results to the academic community, healthcare providers, and public arenas. Initial statements regarding the clinical consequences of anesthetic neurotoxicity concluded that there was still insufficient evidence to advise postponing surgery to a later age (http://smarttots.org/about/consensus-statement/). However, possibly fueled by emerging evidence from ongoing primate studies, the recent (2015) SmartTots advisory has a slightly more cautious tone, suggesting that the optimal timing of surgery needs to be discussed among all stakeholders (http://smarttots.org/wp-content/uploads/2015/10/ConsensusStatementV910.5.2015.pdf).

"[This study represents] an important step forward and provides us with reassuring information regarding the potential effects of brief exposure to anesthesia for minor surgery in early childhood."

In this issue of ANESTHESIOLOGY, O'Leary *et al.*[1] from Ontario, Canada, present data from a well-designed and large population-based outcome study, suggesting that children who undergo surgery before the age of 4 yr are at a very small, if any, risk of adverse developmental outcomes by the time of entering primary school (around 5 yr of age). Moreover, in this very large cohort, a previously described and reproduced relationship between the *number of surgical procedures* and anesthesia a child has received during early childhood and future neurobehavioral outcomes[2] was not confirmed. While these novel findings within a large population-based pediatric cohort are in contrast to the findings in many of the early animal studies, they align with a recent experimental study showing limited structural brain abnormalities and no behavioral changes after a brief (30 min) sevoflurane exposure with physiologic monitoring (maintained temperature, heart rate, and peripheral oxygen saturation).[3] Here, exposure times and anesthetic management reflected more closely current perioperative care for the majority of surgical procedures in children. Hence, the current study in children requires careful scrutiny to determine the significance for everyday pediatric anesthesia practice and for families and parents of young children in need of surgery.

The majority of previous experimental studies exposed neonatal animals to several hours of anesthesia, which consistently produced neurodegeneration and/or functional abnormalities. In contrast, the results of the clinical studies available so far have

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been inconclusive or even contradictory. The only multicenter controlled trial that has looked into this issue (general anesthesia *vs.* spinal [GAS]) randomized children less than 2 yr of age undergoing hernia repair to receive either general or spinal anesthesia in order to discover whether the type of anesthetic (general *vs.* regional) for a globally standardized surgical procedure results in different neurodevelopmental outcomes. The recently published interim results from the "GAS" study showed no difference between study groups in terms of neurodevelopmental outcomes at 2 yr of age,[4] suggesting that a relatively brief exposure to general anesthesia does not result in more detectable abnormalities in "early" neurodevelopmental outcomes compared to a brief exposure to a regional anesthetic. As with the current study,[1] the primary outcome of "GAS" was set at age 5 yr, and the results for that endpoint are expected in 2017.

While GAS, with a total of 722 infants randomized, was a major international effort, it can still be considered a relatively "small" randomized controlled trial that can only detect fairly large effects on neurodevelopmental outcome. Yet, the concordance of the outcomes from a small but prospective trial with those from a very large but retrospective analysis serves to confirm the results of each of the studies. To detect more subtle differences, larger studies would be needed. The advantage of very large cohort studies is their "real-life" generalizability and statistical power to detect—or negate—more subtle changes. Their main drawback, however, is that when an association is confirmed, it is almost never possible to infer causality, as a result of unmeasured remaining confounding factors. However, when a large-enough observational study does not find an effect of the exposure on the outcome, the situation is slightly different. In all observational cohort studies on this topic to date, the most important known confounder is the medical condition that dictates the need for a surgical intervention. In many cases, the presence of that condition in itself is associated with worse neurobehavioral performance and academic achievement. For example, children undergoing hernia repair more often have low birth weight, congenital central nervous system abnormalities, and perinatal hypoxia compared to children not requiring surgery,[5] and therefore, researchers must try to correct for the effect of known confounding when interpreting differences between children who were exposed to surgery and those who were not. But what does it tell us when a large study does *not* show an effect of surgery and anesthesia on early development at age 5 yr in more than 10,000 children who were younger than 2 yr of age at the time of the operation?

The study by O'Leary *et al.*[1] suggests that brief routine surgical procedures commonly performed in children under 4 yr of age most likely have minimal or no effect on early developmental outcomes by 5 yr of age. Yet, there are several perspectives that need further attention. Many epidemiologic studies on this topic, including the current study did not (or could not) adjust for the potential effects of further hospitalizations after the age of 2 to 4 yr until the outcome measure was recorded. Thus, the current study does not consider the potential effects on neurodevelopment resulting from multiple contacts with the healthcare system, such as hospitalizations or surgical procedures performed after the age of 4 yr. Within the exposed population, this means that there might be children in whom surgery, even minor and within the list of included procedures, is linked to later procedures or hospitalizations after the age of 4 yr, for which there is insufficient control. In future studies, these aspects should be considered, because it cannot be excluded that the need for surgery in young age is confounded by repeated contact with health care, including additional surgical procedures or hospitalizations after the age of 2 to 4 yr. Moreover, common medical conditions associated with in-hospital care such as neurologic or inflammatory disorders, *e.g.*, epilepsy and asthma, must also be controlled for in the two arms of exposure (control *vs.* anesthesia and surgery). However, we must realize that the effect of correcting for such confounders would be to weaken the association between the first exposure to anesthesia/surgery and the outcome.

As with similar outcome measures, early development index is influenced by many known factors such as socioeconomic status, the mother's educational level, month of birth, and sex. Such factors therefore need to be taken into account in any observational cohort when studying neurodevelopmental outcomes, but some of these data may not be available in administrative databases.

The lack of any observed effect in the youngest age interval (0 to 2 yr) in the current study,[1] while children having operation between age 2 and 4 yr displayed a slightly reduced neurodevelopmental outcome at age 5 yr, indicates that there might be unknown factors besides the potential effect of anesthetic exposure that affect the outcome measure. One could speculate that "late" surgical treatment for a condition that by itself interferes with later neurodevelopment of the child could be such a factor. An example that comes to mind is delayed language development in children with hearing problems who need drainage with ear tubes for "glue" ears. Hence, besides lack of statistical power, it is difficult to rule out the possibility that the discrepancy in neurodevelopmental outcomes between children aged less than 2 yr and those between 2 and 4 yr represents a hidden effect of delaying some types of surgery until later during early childhood.

Nonetheless, the current study by O'Leary *et al.* represents an important step forward and provides us with reassuring information regarding the potential effects of brief exposure to anesthesia for minor surgery in early childhood. Since long surgical procedures are rare in early childhood, and for many of those cases, neither regional anesthesia nor delaying surgery may be an option, only randomized trials will be able to tell us whether specific anesthetic regimes are "safer" than others. To exclude more subtle effects on neurodevelopment and academic achievement later in life, future large population-based observational studies should aim for long-term follow-up throughout childhood and adolescence.

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Competing Interests

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From Tops in "Gas" Advertising to Bottom of the Bottle: H. L. Seher, M.D., D.D.S.

In 1875 Herman L. Seher (1847 to 1897) earned his M.D. and D.D.S. from the Eclectic Medical College of Pennsylvania. His first wife died a decade later, and Dr. Seher remarried in 1888. His heavy drinking soon drove his second wife to separate from him. She moved a few houses down Philadelphia's North 11th Street from where Dr. Seher was practicing dentistry. The laughing gas services that he had advertised initially as costing 25 cents in the 1880s had risen to 50 cents (*right*) by the 1890s. By then, Dr. Seher had also begun distributing this dental trade card (*left*) featuring a boy in Asian attire. A toy depicted in the card's lower left, a wooden top, was an apt metaphor for Dr. Seher's personal life, which had begun spinning wildly out of control. After his 11-year-old daughter died, the dentist began battering his estranged wife. Not long after making bail for "habitual drunkenness and wife beating," Dr. Seher found himself clutching the feet of a safecracker who had launched himself out of one of the Seher dental office windows. Finally, in 1897, at 50 years of age, the hapless Dr. Seher died from complications of his alcoholism. This trade card is part of the WLM's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology)

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