ARTICLE OF THE MONTH

[Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia: The Mayo Anesthesia Safety in Kids (MASK) Study]

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Welcome to the February 2019 installment of the SNACC Article of the Month. This month our contributors wrote an insightful commentary on the Mayo Anesthesia Safety in Kids (MASK) study, published in 2018. In this study Warner *et al.* analyze the hypothesis that exposure to multiple anesthesia-requiring procedures before the age of three is associated with adverse neurodevelopmental outcomes. Our expert commentators this month are Gregory Chinn MD, PhD and Jeffrey Sall, MD, PhD. Dr. Chinn is a recent graduate of the UCSF Anesthesia research track residency. He is currently a T32 fellow in the UCSF Anesthesia Department and is studying the effects of early life anesthesia exposure on cognitive development under the mentorship of Dr. Sall. Dr. Sall is a professor of anesthesia at UCSF whose research focuses on the effects of anesthetics on brain development.

As always, we encourage our readers to give us their feedback on the SNACC **Twitter** feed or on **Facebook**.

~ Oana Maties, MD; Adrian Pichurko, MD; Nina Schloemerkemper, MD

Commentary

Gregory Chinn, MD, PhD; Jeffrey Sall, MD, PhD

The Mayo Anesthesia Safety in Kids (MASK) study (Warner *et al.*, 2018) was a large matched cohort study designed to answer the question whether multiple, but not single exposures, to anesthesia before the age of three results in adverse neurodevelopmental outcomes.

The impetus for this study follows a decade and a half of preclinical studies, starting with the discovery that perinatal rats exposed to a mixture of isoflurane, midazolam and nitrous oxide experienced massive neuroapoptosis and life-long cognitive deficits (Jevtovic-Todorovic *et al.*, 2003). While initially met with skepticism over the human implications, concern grew as these results were reproduced in a multitude of preclinical studies, including non-human primates (review Walters and Paule 2017). Based on these studies, most anesthetic agents have been implicated, including volatile anesthetics, nitrous oxide, propofol, etomidate, benzodiazepines and ketamine. At the same time, researchers using epidemiological approaches found concerning trends among human subjects who were exposed to anesthetics early in life, finding correlations with worse standardized test scores, grades and incidence of behavioral diagnoses. In fact, some of the strongest epidemiologic evidence came from this same research group studying children from the Rochester, Minnesota area (Flick *et al.*, 2011).

As a result of these preclinical trials, the FDA and International Anesthesia Research Society (IARS) launched a public-private partnership with the goal of understanding the risks of anesthetics in young children and to provide safe care for all children undergoing anesthesia. In 2016, the FDA took the added step of issuing a warning for commonly used anesthetics based on the overwhelming preclinical results.

While these laboratory results were alarming, the clinician researchers did not have a phenotype to characterize. As others have noted, this is the reverse of most biomedical research, where a human disease state requires a reductionist approach to understand the basic mechanisms of disease (Orser *et al.*, 2018; Vutskits, 2018). This poses a particular challenge to designing human studies as there are very important differences in those who require anesthesia (usually for surgery) and those who are unexposed control subjects. Consequently, the human studies have focused on comparing relatively healthy children who needed minor surgeries (inguinal hernias, hypospadias, myringotomy tubes, etc.) while eliminating those with congenital abnormalities, neurologic impairments which could confound interpretation. Before the MASK study, there have been two large prospective human trials−the GAS and PANDA studies. Neither of these studies showed gross impairment in cognition after single short anesthetic exposures before the age of three (Davidson *et al.*, 2016; Sun *et al.*, 2016).

This brings us to the MASK trial, which asked an important question about the effect of the cumulative dose of anesthetic. There is evidence from animal studies as well as correlations in the epidemiologic literature that longer or multiple exposures may be worse than a short or single exposure.

The MASK study recruited 997 children from Olmsted County, Minnesota from 1994-2007 using a propensity-guides approach to minimize recruitment bias. These subjects were prospectively tested with a battery of neuropsychological tests at ages 8-12 or 15-20. The primary outcome was the full-scale intelligence quotient from the Wechsler Abbreviated Scale of Intelligence (WASI). Secondary outcomes included standardized tests for different memory domains, language, motor skills and behavior as reported by parents.

The study's enrolled subjects (998) were similar to those not enrolled (2,2122), although the parents' education in the enrolled group was higher. Among those enrolled, 411 were unexposed, 380 were singly exposed and 206 had multiple exposures. The characteristics of these groups were likewise similar, and a reflection of their propensity-guided approach. Parental education was among those factors which was statistically significant. This and several other factors were weighted accordingly in the primary statistical analysis.

The primary outcome, the weighted WASI score, was not different between single vs multiple exposures with singly exposed subjects scoring 0.5 points (95% CI, -2.8 to 1.9) lower and multiple exposed subjects scoring 1.3 points (95% CI, -3.8 to 1.2) lower than unexposed subjects. The analysis of secondary outcomes found a difference in fine motor ability and processing speed in multiply exposed subjects but not singly exposed subjects. Parents also reported more problems with reading, attention and behavior for subjects that were multiply exposed compared to singly exposed.

This study is a well-designed, rigorously matched cohort study. It is interesting that while previous studies by this same group suggested that multiple exposures would result in a significant cognitive deficit, this study provides evidence that IQ is not substantially affected. While it is possible that it was underpowered to find a statistical difference in the primary outcome, it is unlikely that 1-2 points lower on an IQ test is a significant deficit, especially considering +/- 15 points represent one standard deviation.

It is still possible that there is a cumulative toxic effect of anesthesia. This study attempts to address this by comparing multiply exposed group to singly exposed subjects but there is a huge range in average total exposure time (295min. +/- 354). This suggests that the average is skewed from a few very long procedures, while most exposures were substantially shorter. For comparison, the average length of exposure for the singly exposed group was 61min. +/- 51.

In the context of the other prospective human studies, this adds to a growing sigh of relief that brief, even multiple exposures of anesthesia in otherwise healthy children do not significantly affect intellectual ability as measured by IQ. There may be some effects on behavior, processing speed and fine motor ability, but these should be viewed with some level of caution since they were secondary analyses. The MASK study represents a well-designed clinical study and will be helpful in counseling concerned parents of children requiring anesthesia.

The overarching question of defining a clear clinical phenotype from anesthetic toxicity has been advanced by this study and will still remain an important driver of research. While we have now seen that short anesthetics in healthy humans are likely safe, it will be important to look at those particularly vulnerable populations such as critically ill neonates, those with congenital abnormalities, those with very long exposures and those having suffered neurologic insults. These will be difficult groups to study, but may help further define the important outcomes to evaluate. The results of the current trial are reassuring for the vast majority of patients that experience a short or limited exposure to anesthesia.

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