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Neurodegeneration and pediatric anesthesia: the case is still open

Neurodegeneración y anestesia pediátrica. El debate continúa

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In December of 2016, the US Food and Drug Administration (FDA) officially released a warning (https://goo.gl/5HHx53) requiring that labels of general anesthetics and sedation drugs be modified, to better inform the public of the potential deleterious effects on the developing human brain. The warning alerts the public that "repeated or lengthy use of general anesthetics and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during the third trimester may affect the development of the children's brain". The FDA goes on to say that based on conclusive animal studies and suggestive clinical research, all parents, patients, and healthcare providers should make a concerted effort to balance the absolute need and risk of procedures requiring sedation or general anesthesia.

Although the FDA has diligently reviewed the data available through advisory committee meetings in 3 separate occasions (2007, 2011, and 2014), the core of the scientific evidence remains relatively unchanged. For example, the basic science investigations continue to discover new molecular mechanisms by which general anesthetics potentially disrupt normal brain development.[1,2] Animal models convincingly illustrate a definitive change at the micro and macro neuroanatomical level of animals exposed to general anesthetics for clinically relevant periods of time.[3,4] But most importantly, how about humans? The body of evidence from human studies continues to show conflicting results. As of 2017, it is not clear yet whether a single prolonged or multiple exposures to general anesthetics constitute an independent predictor of neurodevelopmental outcome in patients exposed anesthetic drugs.

At the center of the controversy of the human data is the study design between various reports. It is understandable that physiological and ethical limitations in studies involving anesthesia in humans preclude an unbiased approach demonstrating with certainty a cause–effect relationship. Despite study design limitations, some progress has been made. One such example is the study by Davidson et al, published in 2016. Working in collaboration with an international group and using a randomization strategy, the authors studied the effect of general anesthesia and neurodevelopmental outcomes in infancy. In this study, Davidson recruited a total of 722 infants around 28 hospitals in 7 countries, who were randomized to receive either general anesthesia with sevoflurane or awake regional anesthesia for inguinal herniorrhaphy. The authors report that there were no differences [mean (standard deviation) 98.6 (14.2) vs 98.2 (14.7)] in the cognitive composite score of the Bayley Scales of Infant and Toddler Development III assessed at 2 years of age between general and regional anesthesia. The most

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important conclusion of this trial is that short anesthetic exposure (<60 minutes) is most likely not associated to significant neurocognitive dysfunction in children that are otherwise relatively healthy undergoing hernia repair.[5] Although this is certainly comforting for this group of patients, and a good resource when counseling families, these results only apply to a confined group of patients. Unfortunately, a large proportion of children during infancy and early childhood require repeated surgeries and are exposed to multiple sedation and general anesthesia drugs. On the polar opposite spectrum of healthy children, the study by Diaz, et al, report the effect of cumulative exposure to volatile anesthetics on the intelligence quotient (IQ) between 4 and 5 years of age after surgery and anesthesia. In this study, the authors retrospectively reviewed the volatile anesthetic exposure of infants with variants of the Hypoplastic Left Heart Syndrome undergoing surgical repair and evaluated their cognitive function by analyzing the postoperative IQ (full-scale, verbal, performance and processing speed). Diaz et al[6] report by linear regression a significant association between volatile anesthetic exposure expressed as minimal alveolar concentration (MAC-hours) and poorer performance in all IQ post-operative testing. The authors concluded that increased cumulative MAC-hours are positively associated to worse neurodevelopmental outcomes measured by IQ scales.

Both of these studies describe critical elements of the overall discussion on whether general anesthetics pose a significant risk of neurocognitive dysfunction after surgery. However, these studies are not without significant limitations. On the first instance, the results by Davidson et al should be analyzed with caution, because the incidence of significant developmental delay at 2 years of age was low in both groups and may have mislead the conclusion that no difference between the 2 general and regional anesthesia techniques truly exist. A full evaluation of the neurocognitive status at 5 years of age would have been ideal; however, these data are not available from this study. From these data, it is not clear if definitive differences in long-term developmental outcome do really exist attributable to general anesthesia, because neuro evaluation at 2 years of age is not sensitive enough predict long-term outcomes. In the second study, a detailed analysis of the data reported by Diaz et al, in Figure 1 of the manuscript, demonstrates the correlation of volatile anesthetic exposure and full-scale IQ and verbal IQ, with coefficients of correlation of 0.07 and 0.09, respectively. The correlation coefficients between volatile anesthetic exposure and performance IQ and processing speed were not reported and the *P* values of this model were 0.07 and 0.36, respectively. It appears from these data that the strength of the association and correlation are not particularly strong, and one could argue are not statistically significant. It would have been interesting to analyze the IQ results by quartiles of volatile anesthetic exposure, as it seems that most patients were distributed in less than 10 MAC-hours and very few around 20 to 30 MAC-hours, potentially affecting the regression model. Regrettably, the conclusions on the basis of these results are also limited.

Although there may be good news in that short anesthetics do not increase the risk neurocognitive deficiency and perhaps children with severe heart disease do have worse neurodevelopmental outcomes directly related to increased exposure, this is not yet apparent from the data available. As correctly stated by the FDA and in absence of full conclusive evidence that general anesthetics result in abnormal brain development, a careful analysis of the pros and cons on every procedure in children involving anesthesia should engage parents and caregivers who have the patient's best interest. In the meantime, we should continue to support all efforts to identify novel strategies that could potentially be neuroprotective starting at the basic science level, involving animal models and finally at human trials.

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Conflict of interest

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