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Opinion

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Mind the Gap Between the Bench and the Bed: The General Anesthetics-Induced Neurotoxicity in the Real World

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From the very beginning of Morton's successful demonstration of surgical anesthesia, reversibility has been identified as one of the unique characteristics of anesthesia. However, recent studies just reveal the opposite; general anesthetics (GAs) produce long-term, if not permanent, effects in the human brain, especially in the immature brain, at clinically relevant concentrations for clinical relevant durations, so-called the neurotoxicity of GAs on immature brains.[1] The neurotoxicity has been demonstrated with all types of GAs, including volatile anesthetics, benzodiazepine, propofol, and N-methyl-d-aspartate (NMDA) antagonists.[2] Although, the underlying mechanisms have not been well-illustrated, it has been generally accepted that the neuroinflammation plays a vital role in the pathogenesis of GAs-induced neurotoxicity. Due to huge impact of this subject (animal studies showed that both fetal and early post-natal exposure to GAs caused neurotoxicity), FDA issued a change in labeling regarding the safe use of anesthetic and sedative agents[3] and suggest delaying pediatric surgerie if possible, to avoid repeated or lengthy exposure to GAs in children under the age of 3 or in pregnant women during their third trimester.

However, most of the adverse results came from animal or *in vitro* studies, while most of the human trial reveal negative results, which indicate that single exposure to GAs at early days in their life caused no neurotoxicity in children.[4-6] Even with multiple exposures, the differences are generally very small.[7]

Clearly, there is a huge difference between the animal and human studies designs. In animal studies, subjects were exposed to GAs alone, without any surgical manipulation, in order to observe the isolated effect of GAs on neurodevelopment. However, in the real world, it is unlikely for our young patients to receive GAs alone, without any surgical procedures. On the other hand, most of the surgical procedures cannot be performed without anesthesia. Therefore, young children receiving minor surgery (such as inguinal hernias, circumcisions, cystoscopies, and pyloromyotomies) were included for these clinical trials,[8] for which it is possible to perform without anesthesia or with light sedation only.

The majority of pediatric surgeries cannot be performed without anesthesia deep enough. So, it is of very limited clinical significance to compare between with and without anesthesia. As we mentioned above, all the currently available GAs have been reported to produce neurotoxicity in developing brains. Therefore, from clinical perspective, it is more reasonable for us to compare different types of GAs, such as inhaled *versus* intravenous, to identify the one with least neurotoxicity, if there is one.

Another factor needs to be considered is that the primary diseases which require surgical treatment. It is evident that different diseases produce different effects on neurodevelopment.[9] So, it is equally important to restrict the types of diseases in the future trial.

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In summary, the causal relationship between early-life exposure to GAs and neurodevelopment impairment has not been proved with human evidence, which remains one of the most intensively investigated filed in our specialty. But considering the convincing results from massive preclinical studies, it may be the time for us, the anesthesiologists, to accept the concept that anesthesia is not completely reverse and it is highly like to produce a permanent effect in developing the brain. However, we should not dwell on whether GA is neurotoxic or not. No matter how toxic it could be, most of the surgeries cannot be performed without proper anesthesia, because the untreated pain caused much more harm to children and their developing brains. Instead, it is urgent for us to find out the least toxic GA among current available GAs. Like the surgeons, who never stop performing surgery in the fear of an ugly scar, instead, they are just trying their best to make it smaller. We, anesthesiologists, should not be demanding of the neurotoxicity of GAs on developing brain while ignoring the huge benefit provided by our excellent care.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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