Effect of Anesthesia on the Developing Brain

One of the fundamental premises of general anesthesia is that it produces a state of unconsciousness and unresponsiveness that is reversible implying that the brain remains neurophysiologically the same before and after anesthesia. Some of the experimental data obtained over last several decades question this implication (1-5). Multiple general anesthetic agents have been shown to affect the development of the immature animal brain by induction of neuronal apoptosis and disturbance of the normal cerebral development (6). These findings originated from studies conducted primarily in rodents and nonhuman primates. Human observational studies have both confirmed and rejected associations between exposure to general anesthesia in young children and subsequent impaired neurodevelopment (7-9).

Approximately 6 million children receive anesthesia annually in the US alone, almost one half of these include children of less than 3 years of age (10). Given the large number of neonates and infants that undergo surgery and anesthesia, the implications of these data are apparent. Although the relevance of these findings to humans is a subject of heated debate, the unequivocal demonstration of neuronal death in animals exposed to clinically relevant concentrations of anesthetics has provoked significant concern amongst anesthesia care providers, regulatory agencies and naturally families of the patients.

In December 2016, the US FDA issued a Drug Safety Communication (DSC) warning that general anesthesia and sedation drugs used in children less than 3 years of age or in pregnant women in their third trimester who were undergoing anesthesia for more than 3 hours or repeated use of anesthetics "may affect the development of children's brains" (11). This warning has resulted in a labeling change to all common anesthetic drugs binding to GABA and NMDA receptors, including volatile anesthetic agents, propofol, ketamine, barbiturates, and benzodiazepines.

Despite this, several large well controlled studies of brief, single exposures for relatively minor procedures have been reassuring (9). GAS study published in Lancet that evaluated effects of GA vs awake spinal anesthesia in infants on their neurodevelopmental outcomes at 2 and 5 years provided strong evidence of equivalence between the outcomes (12, 13). In addition, the PANDA study published in JAMA included sibling pairs with only 1 sibling exposed to anesthesia before age 3 (14). This study also failed to find any difference between siblings on extensive battery of neurocognitive testing at age 8–15 years. Both studies have important implications for the field of anesthetic neurotoxicity. They imply that a single, relatively brief exposure to anesthesia is not associated with an increased incidence of neurobehavioral adverse effects.

Many researchers feel that the focus of this field of investigation should shift to prolonged or repeated exposures to anesthesia, or to the effect of anesthesia on vulnerable brains such as the fetus, congenital heart disease infants, or infants with other complex neonatal surgical conditions. These long-term adverse neurodevelopmental effects, however, remain difficult to interpret because of confounding by indication with otherwise healthy young children rarely needing to undergo lengthy or repeated procedures under general anesthesia.

Obvious ethical considerations limit the conductance of experiments in human neonates. The use of animal models is still considered feasible. In order to identify reasonable neurocognitive outcomes, vulnerable periods in brain development need further identification, as do neurotoxic and neuroprotective interventions.

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