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Anesthetic induced neurotoxicity in children

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Numerous studies have questioned the safety of anesthetics on the developing brain given that many data support anesthetic neurotoxicity in infants [1-3]. In this issue of the *Korean Journal of Anesthesiology* [4], we discuss studies that found that co-administration of apocynin, an NADPH oxidase inhibitor, prevents long-term memory loss in neonatal mice exposed to sevoflurane by preserving glutamatergic neurons in the basolateral amygdala.

Rodent-based studies have shown that agents that affect NMDA and GABA receptors, like most of the anesthetics currently in use, produce profound apoptotic and neurodegenerative changes in the developing brain. These effects are associated with long-term deficits in learning and behavior, and may be mitigated by pharmacological agents and behavioral means.

Several studies in non-human primates at the National Center of Toxicological Research (NCTR) [5-10] also show adverse cognitive effects related to anesthesia. These studies used an operant test battery, a tool that has not yet been used or validated by other investigators.

Human studies to date are confined to retrospective cohort studies of existing databases. Results are mixed; however, the strongest of these studies consistently show that multiple exposures, not a single exposure, are associated with adverse cognitive effects.

Three comprehensive studies are currently underway using a prospective comprehensive battery of neurocognitive tests:

GAS: The GAS study is the only randomized clinical trial currently funded to study this adverse effect. It compares the neurocognitive performance of 5-year-old patients who underwent hernia repair under either spinal or general anesthesia as infants. Last year, results showed no association between the incidence of adverse neurodevelopmental effects at two years of age and less than one hour of sevoflurane anesthesia in infancy [11]. However, the GAS trial's prespecified primary outcome of global cognitive function at 5 years of age is still pending.

PANDA: An ambidirectional study of children exposed to general anesthesia for hernia repair matched to siblings who were not exposed. PANDA also uses a prospective comprehensive battery of neurocognitive tests. Results of the PANDA study indicate that there was no statistically significant difference in the full-scale IQ score between siblings at 8–15 years, with and without a single anesthesia exposure before the age of 3 years [12].

Further studies will more fully elucidate the neurocognitive risks of repeated exposure, prolonged exposure, and other effects in vulnerable subgroups such as premature infants.

MASK: The MASK study is also ambidirectional but differs in that it measures comprehensive outcomes at two separate ages, includes children with single and multiple exposures, and includes the operant test battery as a means of extrapolating existing non-human primate findings to children. The study is likely to report results soon.

Regardless of mechanism, multiple studies have now shown an association between anesthetic procedures and adverse neurodevelopmental outcomes. Anesthesia is one potential mechanism to explain this apparent association; there are several others.

The results of this research highlight the importance of continuing advancements in pediatric anesthesia in terms of patient safety, outcome and comfort.

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