# Anesthetic-induced developmental neurotoxicity: causes, prospective studies and possible interventions

Anesthetic-induced developmental neurotoxicity (AIDN) is the term used to describe adverse neurological events occurring in pediatric patients who are exposed to general anesthetic before synaptogenesis in the brain. Animal studies have shown behavioural and developmental changes when exposed to sevoflurane and isoflurane.

**Mechanism of AIDN:** The agents lead to damage in the hippocampus and amygdala which leads to learning and memory disturbances subsequently. The γ-aminobutyric acid (GABA)-ergic and glutaminergic neurons have been found to undergo apoptosis due to exposure. Experimental studies have shown that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation occurs due to inhalational anesthetics, which leads to superoxide overproduction, mitochondrial dysfunction and apoptosis. Other proposed mechanisms are altered expression of ligand-gated ion channels and disturbance to intracellular calcium homeostasis. The concentration of agent used, type of agent and duration of exposure are also factors that are considered responsible for AIDN.[1] Although single exposure for a small duration might be safe, children requiring multiple anesthetic exposures could theoretically manifest with developmental issues in their adult life.

**Studies addressing AIDN:** There are very few prospective studies which investigated development of AIDN in pediatric patients exposed to inhalational anesthetics in early years of life. In the Pediatric Anesthesia Neuro Development Assessment (PANDA) study by Sun et al.,[2] the authors studied single exposure to general anesthesia (GA) during inguinal hernia surgery in the exposed sibling *versus* no anesthesia exposure in the unexposed sibling before 36 months of age in 105 sibling pairs. The exposure to inhalational anesthetic was 20–240 minutes. On assessing neurocognitive and behavior outcomes with retrospectively documented anesthesia exposure data, authors found no statistically significant differences in intelligence quotient scores in later childhood.

In general anesthesia and awake-regional anesthesia in infancy (GAS) trial by Davidson et al.,[3] they randomized infants to receive awake-regional anesthesia *versus* GA for inguinal herniorraphy. The authors found no increase in the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake regional anesthesia after 1 hour of sevoflurane anesthesia. Mayo Anesthesia Safety in Kids (MASK) study is an ongoing research which is investigating the effect of multiple anesthetics before 3 years of age on neurocognitive performance.[4] Results are still awaited. Glatz et al.[5] conducted a cohort study among children born in Sweden between January 1973 and December 1993. They investigated the association of anesthesia and surgery before 4 years of age with long-term academic and cognitive performance based on school grades achieved at age of 16 years and intelligence quotient test scores at military conscription. They analysed the children for performance between April 2013 to October 2015. On analysis they found that exposure to anesthesia and surgery before 4 years of age has a small association with academic performance or cognitive performance in adolescence on a population level.

**Pharmacological interventions for preventing AIDN:** Several drugs like lithium, melatonin, 7-nitroindazole, L-carnitine, dexmedetomidine and xenon have been tried and have been found to reduce AIDN but the mechanism of its efficacy was not understood properly.[6] Two new experimental drugs which could be used to treat or reverse AIDN are Ciproxifan and Apocynin. Ciproxifan is an $H_3$-receptor antagonist having imidaxole moiety acts by increasing the release of dopamine and norepinephrine in prefrontal cortex and acetylcholine in hippocampus, prefrontal and entorhinal cortex.[7] In an experimental study, Ding et al.[8] administered 1–3 mg/kg of ciproxifan IV to mice 24 hours after exposure to isoflurane for 2 hours. They found that the cognitive impairment reversed 30 minutes after administration of ciproxifan.

Apocynin (4′-hydroxy-3′-methoxyacetophenone or acetovanillone) is the biologically active substance extracted from the roots of Picrorhiza kurroa which is a plant found in Alpine-Himalayan Region. Apocynin is a selective inhibitor of the phagocyte NADPH oxidase Nox2 that can be applied orally and is remarkably effective at low dose.[9] Sun et al.[10] used intraperitoneal apocynin 50 mg/kg prior to neonatal sevoflurane exposure in 6-day-old mice 30 minutes before sevoflurane exposure. At 11–13 weeks of age, the exposed mice were subjected to contextual fear conditioning test. They found that apocynin not only prevented learning deficits but also preserved c-Fos-expressing glutamatergic neurons in the basolateral amygdala. Simonyi et al.[11] have described the neuroprotective effects of apocynin in conditions like stroke, Alzheimer's disease, Parkinson's disease and several psychiatric disorders. The antioxidant properties of apocynin have been used by investigators in patients

with prostate cancer, nephrolithiasis, diabetic nephropathy, rheumatoid arthritis and cardiovascular diseases.[12-14] The proposed mechanism of action is by reducing superoxide levels and by preventing further mitochondrial dysfunction.

**The future direction:** Both ciproxifan and apocynin needs to be evaluated further to know whether it can be used safely in humans either for preventing or for treating AIDN. The drugs look promising in animal studies. Children coming for multiple anaesthetics are the one who are theoretically susceptible for AIDN. Although the data shows a small association between exposure to anaesthetic agents and adverse neurocognitive outcomes; the duration of exposure, concentration of agent should be addressed. More than one exposure should be avoided unless the surgical intervention is emergent or urgent.

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*doi: 10.4103/2045-9912.215754*
*How to cite this article: Nair AS, Pulipaka K, Rayani BK (2017) Anesthetic-induced developmental neurotoxicity: causes, prospective studies and possible interventions. Med Gas Res 7(3):224-225.*
**Plagiarism check:** *Checked twice by iThenticate.*
**Peer review:** *Externally peer reviewed.*

**Open peer reviewer:** *Lei Huang, Loma Linda University, USA.*

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