Editorial

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Website: www.ijaweb.org

DOI: 10.4103/0019-5049.115572

Quick response code

Safety first, safety at early age: The quagmire of neurotoxicity in paediatric anaesthesia

Millions of surgeries and procedures are performed world-wide in children and sedatives and anaesthetic agents have sometimes been used with impunity in these cases. The modern anaesthetic agents have good safety profiles as far as the immediate goals of anaesthesia and post-operative period are concerned. Increasingly, concerns have cropped up on their long-term adverse effects on the neural structure and neurocognitive function, more so in neonates and infants. Much of the evidence is based on animal studies (preclinical) and few retrospective human clinical studies; human prospective clinical studies are few.

What is known is that the anaesthetics exert their effects by action on multiple receptors and ion channels in the central nervous system. Intravenous agents are more potent than the inhalational agents but have similar effects on the various receptors and channels involved in anaesthesia. It is also known that anaesthetics induce neuroapoptosis, an active programmed cell death.[1] It could involve promotion of the physiological apoptosis or induction of pathological apoptosis. Spurt in brain growth or synaptogenesis occurs in early postnatal period in the majority of experimental animals and in humans, it starts in mid- gestation and extends for few years into childhood. The risk of damage to neuronal tissue is therefore, maximum during this period. Inhibitions of brain-derived neurotrophic factor (BDNF) signalling pathways by agents with N-methyl-D-aspartate glutamate (NMDA) receptor antagonism, or γ-amino-butyric acid (GABA) type. Receptor agonism or both (ethanol) are associated with extensive neuronal apoptosis in animal models.[1,2] BDNF is essential for growth, differentiation and survival of neuronal tissue. Other proposed neural effects of these agents include alteration in dendritic spine architecture.[3]

Simultaneous with the evidence of harmful effects of anaesthetics in preclinical studies, it has also been found that neurodegeneration and apoptosis are prevented/countered by agents such as lithium, dexmedetomidine and xenon.[4-8] Dexmedetomidine and xenon are known to reduce isoflurane induced neuronal apoptosis in neonatal rats.[6-8] Xenon was found to retain its apoptotic effects while diminishing isoflurane-induced cellular death.[8]

Studies since 1980's, *in vitro* and *in vivo*, have shown conflicting effects of anaesthetic and sedative agents in experimental animals. Benzodiazepines, nitrous oxide, halothane, enflurane, isoflurane, sevoflurane, propofol, ketamine and others have been studied, some possibly precipitating and some reducing neuronal degeneration.[1] The dose of the agent, duration of exposure and use of multiple agents may all increase the risk.[9] Propofol used in subanaesthetic doses has been shown to induce neuronal apoptosis.[10] Midazolam, nitrous oxide, isoflurane combination is used commonly in paediatric anaesthesia; these drugs have been found to promote BDNF activated neuroapoptosis in rats.[1,10,11]

Retrospective studies in *humans* indicated that learning disability was likely with multiple postnatal anaesthetic exposures at an early age.[12] The results and correlations of some older studies need not influence the current practice as halothane is almost phased out in the majority of countries and use of nitrous oxide has also become less frequent. The criteria used to describe learning disability in such studies may not reflect specific neuronal injury and to extrapolate the results of animal studies to humans may not be the optimum approach. Structurally, the threshold for apoptotic changes leading to actual injury may

How to cite this article: Bhaskar SB. Safety first, safety at early age: The quagmire of neurotoxicity in paediatric anaesthesia. Indian J Anaesth 2013;57:221-2.

be higher in humans as compared to animals. The animal models used in studies were subject to various drugs and largely disregarded the noxious stimuli, obtained during surgeries in humans. No confounding conditions such as sepsis, hypoglycaemia, hypotension, stress of anaesthesia and surgery and other critical states existed in animal models, which otherwise could contribute to or precipitate neuronal changes in humans under anaesthesia/sedation.

Large, prospective, human multicentric studies are underway in paediatric patients undergoing hernia surgeries, a common surgery in the paediatric population. Paediatric anaesthesia and neurodevelopment assessment (PANDA) project is designed to compare children exposed to general anaesthesia (before 36 months of age) with their siblings who are not, with regard to neurodevelopment and cognitive functions between 8 and 15 years of age.[13] General anaesthesia spinal (GAS) study is another on-going randomized controlled trial, aimed to investigate the long-term effects of spinal and general anaesthesia in new-born and tested for developmental outcomes at 2 years of age and neurodevelopmental and intelligence outcomes at 5 years. If similar scores are obtained in two groups, the preclinical evidences may need to be revisited and future studies redesigned. Similarly, Mayo Safety in Kids (MASK) Study is a population-based cohort study of long-term cognitive development in children with no anaesthetic exposure to those with single or multiple exposures before 3 years of age.

As human studies are difficult to conduct and interpret, it is better to be careful in managing anaesthesia in younger patients, at least until 4 years of age, based on the present retrospective human data. Prolonged exposure to sedatives and anaesthetic agents or use of multiple drugs should be avoided. Advances in anaesthetic pharmacology and monitoring have allowed complicated surgeries to be conducted safely in paediatric patients. The benefit of surgery must be weighed with the potential for neuronal and behavioural adverse effects of the anaesthetic agents. Current safe practices of modern anaesthesia however should not be the casualty till sound evidence emerges, necessitating specific recommendations for or against the use of agents.

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