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Long term neurotoxicity by general anesthetics in infants

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ABSTRACT

Development of neurotoxicity in infants and children who had been exposed to general anesthetics has garnered attention in recent times and sparked vigorous debates. The effects range from learning disability, cognitive defects to development of neurodegenerative diseases like Alzheimer's disease in later life. Theories to explain these changes are calcium dysregulation leading to apoptosis, altered neurogenesis, accumulation of degenerative proteins like β amyloid and many others. A large volume of literature has accumulated in the form of animal and human studies which have implicated general anesthetic drugs like ketamine, propofol, volatile agents, and benzodiazepines in the development of neurodegenerative conditions in later life. These studies being retrospective are associated with a good deal of methodological flaws. Hence a direct cause effect relationship is yet to be firmly established. In the present scenario, it would be prudent for the anaesthesiologists, to be aware of the possible existence of such an association. In the meantime, further research and evidence in this arena is demanded.

Keywords: Neurotoxicity; General anesthesia; Infants; Pediatrics; Children; Ketamine; Cognitive disorders

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INTRODUCTION

Pediatric anesthesia has evolved gradually over the years and has become a new anesthesia sub-specialty in modern times. However, the rapid strides in refinement of anesthetic drugs and techniques recently have translated into an exponential increase in the number of children undergoing surgical, diagnostic and therapeutic procedures.

The risk and safety concerns in anesthesia practice have always troubled the anesthesia fraternity.[1] Remarkably safe general anesthesia is administered to millions of padiatric patients annually. However, burgeoning laboratory and clinical evidence have shifted the focus and raised significant concerns over the possible long term behavioral and cognitive consequences of apparently uncomplicated general anesthetic in otherwise healthy children. This includes neurodegenerative modifications which might result in onset and progression of Alzheimer's disease (AD) by increasing β-amyloid production and aggregation.[2,3] The underlying molecular and cellular mechanisms resulting in neurotoxicity remains yet to be laid threadbare, but the accumulated evidence have already raised reservations regarding the safety of general anesthesia in children and infants and generated debates amongst the medical fraternity. The issue is of highest concern in developing nations as majority of clinical practice is empirically based on logics and experience of attending anaesthesiologist especially in private sector. The innovations, improvisations and challenges in pediatric anesthesia throughout the globe has propelled the advancements in pediatric anesthetic techniques as well as enhanced our understanding of the impact general anesthetics have on infant and pediatric population.[4,5] The current review article aims to amalgamate the available literature concerning the neurotoxic realm of anesthesia and its effects especially on the developing brains of infants and children.

PRECLINICAL EVIDENCES OF NEUROTOXICITY IN DEVELOPING BRAIN

Available evidence does points towards harmful effect of the anesthetic drugs on developing brain which we commonly use in our daily practice. N-methyl–D–aspartate glutamate receptor (NMDAR) antagonism leads to apoptosis in developing rat brain was first observed by Ikonomidou et al.[3] Subsequent investigations revealed the same pattern of apoptosis on exposing the developing rat brain to anesthetic

agents acting on NMDAR antagonist[2] and gamma amino butyric acid type A receptor (GABAR) antagonists.[6] Ketamine induces neuronal degeneration in rats and primates when they are exposed to high and repeated doses and for prolonged period of time.[7-9] Propofol and isoflurane demonstrated identical dose dependant effects.[6,10,11] Midazolam, diazepam and thiopentone have been implicated in neuronal injuries in rodents.[6,12,13] Recently, newer drugs and adjuvants have also become available in anesthesia practice but it will take a long time before their safety can be established with randomized controlled trials.[14]

A significant observation which came to light was that neurotoxicity caused was maximum when exposure was during the period of peak synaptogenesis in the experimental models (rats and non human primates) manifesting as apoptosis and necrosis.[8,15] Neurogenesis and development of dendritic spine architecture, which are critically important processes of synapse formation are also known to be distorted by anesthetics.[16,17] Volatile anesthetics have also been implicated of reducing the generation of tissue plasminogen activator (tPA) which converts pro Brain Derived Natriuretic to mature BDNF. Accumulation of pro BDNF triggers cellular death by binding to p75NTR receptor (a cell death receptor).[17] Apoptosis of developing neurons is a tightly controlled step which can be significantly distorted using anesthetics. GABAergic drugs stimulate the $GABA_A$ receptors. Sustained blockade of NMDA receptors produces a compensatory increase in the receptor expression. Calcium influx following withdrawal of the blockade can lead to necrotic and apoptotic cell death which appears to be the general underlying mechanism.[8] The total injury is also enhanced by transient suppression of neurogenesis and alteration in the development of neuronal circuitry. Though, the mechanisms of how these changes cause cognitive defects in later life are not clear, they are more relevant in the immature brain. However, the safe doses or duration of anesthetics to avoid these changes were not defined in these investigations. The role of pharmacogenetics acquires significant dimensions here so as to evaluate the close association of anesthesia and various impacts it has on developing brain.[18]

ANESTHETIC INDUCED NEUROTOXICITY: ANATOMICAL CONSIDERATIONS

Animal evidences have pointed out that the hippocampus (region associated with memory and learning) is the most vulnerable region which gets affected and this manifests as deficits in memory, attention, learning and motor functions. Significant regional differences exist in the developing human brain regarding the timing of peak synaptogenesis. The primary sensorimotor cortex is the first to develop at around birth. This is followed by parietal and temporal association cortex (important in language and spatial attention) where synaptogenesis peaks at around 9 months. The prefrontal cortex, important in executive, integrative and modulatory brain function is the last to undergo accelerated synaptogenesis at 36 months of age.[19] Since synaptogenesis occurs at a rapid phase between birth to 36 months of age, this roughly indicates that the developing human brain is more vulnerable to anesthetic induced neurotoxicity in the said time period.[20-22]

CLINICAL CORRELATION IN HUMANS

Experts have refuted the theories of anesthetic induced neurotoxicity on grounds that neuronal damage and its sequelae in rodent models could be due to causes other than anesthetic drugs. Also neurodevelopmental time course in mammalian species varies, and hence timing and duration of exposure cannot be generalized. Still, extrapolation of these data over the developing human brain raised serious concerns regarding the possible neurocognitive impairment in infants and children following anesthesia administration. The physiological variation in the infant brain makes it increasingly prone to anesthetic induced toxicity. Neuronal growth is higher in infants with intense synaptogenesis occurring in most cortical regions. This period of critical growth is between third trimester of pregnancy and first few months of postnatal life with the most marked changes occurring between birth and six months of age.[23] Synapses are later pruned to make behaviorally relevant neuronal connections. Apoptosis causes neuronal pruning and anesthesia can alter the normal pattern of this pruning.[24] These concerns prompted the Food and Drug Agency (FDA) to convene a scientific advisory committee to formulate recommendations. They suggested deferring truly elective surgery later than 6 months of age. However, this committee was unable to provide a concrete consensus which could be the basis of formulating certain guidelines as data from clinical studies was limited. The formulation of guidelines needs a biopsychosocial perspective also besides clinical evidence and literature as the younger age group is not able to communicate, convey or express their feelings.[25]

ANESTHETIC EXPOSURE AND NEUROCOGNITIVE BEHAVIOR: LITERARY EVIDENCE

Quite a few retrospective cohort studies were undertaken to address the issue of association of anesthetic exposure in childhood and neuronal impairment in later life. Kalkman et al[26] studied 314 children who had undergone general anesthesia for urological procedures under 6 years. Neurobehavioral development was assessed using Child Behaviour Checklist (CBCL). However, association between behavioral disturbances and anesthesia exposure could not be ascertained. The investigators acknowledged the study to be underpowered and also the limitations of CBCL as an insensitive tool to detect neurodevelopmental disability.

Another study involving twins concluded that anesthesia exposure does not cause learning disability before the age of 3 years.[27] This study was also limited by inadequate sample size, absence of subgroup analysis and also the number of anesthetic exposures was not stated.[28] An analysis by DiMaggio et al[29] studying the incidence of behavioral and developmental disorders in children who had undergone hernia repair before the age of 3 years revealed a twofold higher frequency of behavioral and developmental disorders compared to control cohorts. However, unmeasured cofounders were present along with the known ones of the pathology and surgical procedures.

Sprung and colleagues surveyed the impact of obstetric anesthesia on the learning disabilities of children up to 5 years of age.[30] They found no difference in the risk in children born through caesarean section and those delivered vaginally. An interesting observation of the study was that the children who were born through caesarean section under regional anesthesia had a lesser risk of learning disability as compared to other modes. Here also the authors acknowledged the existence of confounding factors and the possibility of subtle disabilities being missed. Wilder et al[31] retrospectively reviewed the records of children who had undergone surgeries prior to 4 years of age and found that association exists between two or more anesthetic exposures before the age of 4 years and increased risk of learning disabilities. However, the limiting factors of the study included the confounding influences of the higher severity of illness, the greater need for surgeries and the corresponding greater levels of learning disabilities. Moreover, the study could have missed subtle neurocognitive dysfunctions and also the effect of exposure during neonatal period could not be excluded.

The Flick's group[32] evaluated a database containing health records (anesthetic and surgical histories) and linked them with school performance data. They found an association of two or more episodes of anesthesia with development of subsequent learning disability. They also revealed the association between exposure and diagnosis of learning disabilities and the need for an individualized educational plan based on learning disabilities. However, they could not find any relationship between exposures and need for individualized educational plan based on behavioral and emotional issues. Even though the burden of illness was controlled it was not possible to completely isolate the need for surgery or the consequences of anesthesia.

Hansen and coworkers[33] retrieved data from the Danish National Hospital Registry about infants who had undergone inguinal hernia repair in infancy and evaluated their performances in ninth grade. They could not find evidence of relatively brief anesthetic exposure leading to reduced academic performance at 15-16 years. This analysis was limited by large sample size and coarse outcome measures. Also the medical records of the randomly selected controls were not reviewed.

Ing et al[34] studied a cohort of 2868 children who had undergone surgery and were exposed to anesthesia prior to 3 years of age as compared to children who did not have any exposure. Upon evaluating at 10 years of age, they were found to have disability in language and cognition even with a single exposure but there was no association of anesthetic exposure with behavioral problems or motor function deficits. The weakness of this study was that the history was based on parent's diary on regular follow up. Moreover, the sensitivity and comprehensiveness of the neurocognitive measures seemed to be very high. The biggest hindrances in accepting the findings of these retrospective studies to provide convincing evidences of long lasting effects of anesthetics on CNS are their methodological limitations. They also do not provide information regarding the risk factors like age of exposure, agent used or their dosages. In spite of these limitations, these studies provide weak evidences that a single exposure in childhood is not associated with substantial learning disability in later life.

ANESTHESIA INDUCED NEUROTOXICITY: FUTURE TRENDS

Studies relevant to anesthesia induced neurotoxicity have been retrospective in nature and hence allowed identification of association without establishing causality. The effects of anesthesia cannot be disassociated from factors associated with anesthesia such as surgical trauma and pathology. Humoral and inflammatory stress, metabolic, hemodynamic and respiratory events are all confounding factors which might influence the outcomes of these investigations. Children may suffer from sepsis, prematurity, chromosomal aberrations and less paternal interaction which might be associated with developmental delay and greater need for surgery.

A strong need is felt to do a qualitative research before we can enhance our knowledge in this field of pediatric anesthesia.[35] To overcome these limitations, the necessity of prospective studies was felt. Currently two large scale studies are being undertaken to address the concern of anesthetic neurotoxicity. The General Anaesthesia Study (GAS)[36] is a randomized controlled trial involving 29 centers from across the world. The primary objective of the study is to compare the effects of regional versus general anesthesia on neurodevelopmental outcome and apnoea on children undergoing inguinal hernia repair. With a follow up period of 5 years (evaluation of children at 2 years using Bayley Scales for Infant Development-III and evaluation at 5 years using Wechsler Preschool and Primary Scale of intelligence and additional neuropsychological tests within NEPSY–II),the study is expected to complete by 2015/2016.

The PANDA (Paediatric Anaesthesia and Neurodevelopment Assesment) study is another multicentre initiative that proposes to use a bidirectional epidemiological approach to identify a cohort exposed to general anesthesia for inguinal hernia repair before 36 months of age. The study proposes

to negate the effects of genetic and environmental factors affecting cognitive performances. A pilot study which demonstrated the feasibility of such an approach has already been completed.[37]

Studying of primary cultures of neonatal human neurons is difficult due to limited access to human neuronal tissues. Stem cell technology has helped to recreate the process of neurogenesis from in vitro human cells and investigate anesthetic induced neurotoxicity in humans. Advantages of this technique includes providing unlimited number of neuronal stem cells and other cell lineage, high levels of screening regarding the dose, duration and frequency of exposure, allowing dissection of the cells at various developmental stages, investigating the potential preventive strategies and reducing the need for animals for studies.[38] Ethanol has been found to cause phenotypic changes, stem cell proliferation and loss of trophic astrocytes.[39] Isoflurane in low concentration (0.6%) increased proliferation of stem cells, at clinical concentration (1.2%) had no effect and again increased proliferation when administered at high doses (2.4%)[40] Ketamine also increases stem cell proliferation after 6 hours of exposure.[41] Short exposure of high dose of isoflurane had no effect on stem cell cultures whereas long duration exposure altered neuronal differentiation and promoted glial differentiation.[42] These changes are attributed to alteration in calcium regulation caused by activation of inositol-1,4,5 triphosphate (InsP3R) and/or ryanodine receptors (RYR). Pretreatment of the stem cell culture with InsP3R or RYR antagonist (xestospongin-C and dantrolene) prevented the effects of isoflurane on differentiation and can be viewed as future protective strategies.[40]

General anesthetics have been acknowledged for their neuroprotective roles in conditions like traumatic brain injuries, brain infarction (hypoxia or ischaemia related), ischaemic injuries to heart, lung, kidneys or liver by their effect of ischaemic preconditioning and also protecting against endotoxin mediated cell damage. Their protective effects are also mediated through InsP3R and RYR by modulation of calcium channel opening. However, the studies on neuroprotection are limited by lack of reliable degenerative markers and complexities of cognitive function tests. Nevertheless the fundamental difference which could be elucidated between neuroprotection caused by general anesthetics and neurocognitive disability caused by the same exist in the duration of exposure inspite of the action on similar receptors. Longer duration of exposure leads to neurodegeneration whereas shorter duration of exposure was associated with neuroprotective effects due to differential regulation of calcium release.[42] However concerns regarding anesthetic induced neurotoxicity opened a new and unexplored frontier and set vigorous debates into motion. Thus, in face of the available existing literature, general anesthesia appears to be a dual edged sword though not conclusively proven by scientific evidences.

ANESTHETIC NEUROTOXICITY: YET UNRAVELED QUERIES

Anesthesia related neurotoxicity is a complex issue which still needs to be unraveled completely. Is the evidence depicted in animal studies clinically relevant in human infants and can it be extrapolated on them is still controversial. Our understanding of the risk factors and the particular age up to which anesthetic toxicity is high is still limited and the exact age upto which surgery should be delayed is yet not concretely spelled out. In the absence of convincing data it is not possible to comment whether a particular agent or technique is better as compared to others. The dosage of drugs also needs to be addressed. Whereas weak evidence exists regarding dose effects in certain studies, limiting the dose can lead to complications of light anesthesia and awareness. Even though preclinical studies on protective strategies have been carried out, human trials have not yet been conducted.

CONCLUSION

Various facets regarding the issue of anesthesia induced neurotoxicity in infants are still under investigation and they would require further scientific evaluation and validation before a firm framework is created to establish sound guidelines. The age of vulnerability, the dosage of exposure, the duration of exposure, particularly risky procedures and anesthetic techniques still remain too vague to be pin pointed except that the neurotoxicity increases with higher frequency of exposure. It would be prudent for us to accept that available evidence is at best, preliminary and inconclusive. Firm guidelines on this issue based on stringently controlled prospective studies are the order of the day. However the anaesthesiologists must be aware of this subject on which a good deal of research is nowadays underway and understand the limitations of its evidence. They should be able to counsel the anxious parents seeking answers or alternatives to delay surgical procedures or investigations which require anesthesia provided that the delay does not increase the risk. Surgeries like inguinal hernia or circumscision can be conducted under regional anesthesia as it seems to be free from the risk of neuro toxicity.[43] Moreover local anesthetics and narcotic drugs seem to be free from neurotoxic apprehensions.[43] In their editorial, McGowan and Davis have recommended that "until the risk of neurocognitive injury is understood, pediatric specialties, in conjunction with anesthesiologists and pediatricians, should identify surgical procedures that can be delayed until older ages without incurring additional risk".[44] Additionally, it should also be borne in mind that it is grossly unethical to subject an infant to surgical or investigative procedures without the protection of sedation, analgesia or anesthesia. Thus essential invasive procedures must not be unnecessarily delayed in front of a currently ill defined risk.

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