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Anesthetic exposure in perinatal period: should we still be concerned?

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Keypoints

a) Anesthetic exposure in early neonatal period in animals have demonstrated significant changes in neuronal development. Perinatal exposure are not well described in animals as well as human beings.

b) The retrospective studies detailed show minimal changes in motor and social activities in children exposed to anesthesia in perinatal period without change in Intelligence. These studies are inconclusive about any such neurotoxicity following perinatal exposure.

c) Regional anesthesia in children of any age group will be advisable to reduce such exposure but needs proper practise and equipment.

Abstract

In the last decade perinatal medicine has batteried up primarily over the growing concern of safety of anesthesia in infants and children. Increasing data in rodents and primates have proved beyond doubt that anesthesia causes neurotoxicity in developing brain and causes long term neurobehavioural abnormalities. However, clinical data regarding the risks of abnormal neuronal cell death in the fetal brain after maternal anesthetic exposure during pregnancy are still minimal.

Keywords: Anesthesia, general, inhalational, intravenous, developmental disabilities

Introduction

Growth and development of the mammalian central nervous system (CNS) involve complex cellular processes such as neurogenesis, differentiation, migration of cells to their final destination, synaptogenesis with connection formation, and axonal myelination.

In humans, synaptogenesis starts during the third trimester of gestation and rapid brain growth continues for up to 2 to 3 yr after birth.

Apoptosis or cell suicide serves to remove neurons from pathological insults such as ischemia, hypoxia or after withdrawal from neurotropic factors. GABA and NMDA receptors are directly involved in cell proliferation, migration, cell survival, and dendritic maturation. The GABA and NMDA receptors are indirectly involved in the balance of activity and, thus, the generation of trophic factors that drive differentiation, growth, and apoptosis. Almost all the anesthetics were found to proactivate apoptosis by multiple mechanisms.

In the human brain, there are significant regional differences in the timing for peak synaptogenesis. The last region to peak in synaptogenesis is in the prefrontal cortex, which occurs at age 2–3 yr. Different regions execute different functions and hence damage to them at specific periods canchange the functionality as adult. The vulnerability period for anaesthetic induced neurotoxicity might be up to 36 months of age in the developing human brain.

Advances in medicine and attempts to save premature and very ill infants have resulted in prolonged, deep se-

dation, and repeated anesthesia during an extremely complex and delicate period of human development. Exposure to these agents makes the vulnerable group to undergo more changes in the brain and in turn leading to cognitive dysfunctions. This review focuses on impact of anesthesia during gestational period on the cognitive development.

Mechanism of neurotoxicity

Multiple mechanisms have been studied in animals and nonhuman primates. Most proposed and analysed mechanisms are NMDA inhibition and GABA excitation. Relative inactivity caused by anesthesia results in a loss of trophic factors, which in turn triggers apoptosis. Suppression of neurotrophic synaptic signalling, pro-inflammatory effects of anaesthesia, anaesthetics-induced decrease in neutrotrophic factors, and anaesthetics-induced activation of inositol 1,4,5-trisphosphate (IP3) receptors have all evolved as reasons for neurotoxicity.

Neonatal neurons may be dependent upon NMDA receptor stimulation; withdrawal or inhibition of NMDA receptor stimulation therefore triggers apoptosis. Propofol and inhalational anesthetics cause changes in dendritic spine morphology. Altered neurogenesis and abnormal re-entry into the cell cycle impaired mitochondrial function has also been observed.[1]

Nonobstetric surgery in pregnant patients

The frequency with which pregnancies are complicated by the need for surgical procedures ranges from0.75%-2.0%, commonest surgeries being Appendicectomy, Cholecystectomy, Adnexal diseases. Although general anesthetics have been used safely for su rgery in adults for decades [2], their use in pregnancy is becoming a more concerning issue due to their potential effects on the immature or developing brain. Anesthetic administration during pregnancy would lead to a significant amount of general anesthetic exposure to the fetus and its long-term effects on human fetal brain development remain unclear.

Fetal surgery

Fetus exhibits pituitary adrenal, sympatho adrenal and circulatory stress responses to noxious stimuli as early as 18 weeks of gestation. These are largely mediated in the spinalcord, brain stem or basal ganglia rather than the cortex. Most fetal surgeries in humans are performed during mid-gestation, it is important and urgent to know if the anesthetics used cause damage to the developing brain and subsequent postnatal memory problems and learning disabilities.[3]

Volatile anesthetics remain the primary agent of choice for fetal anesthesia during open fetal surgery. Higher concentrations of volatile anesthetic agent to provide uterine atony during fetal surgeries [4] cause reductions in the maternal and thereby fetal perfusion. Anesthetic gas concentration in the fetus is dependent on both the maternal inspired agent concentration and the duration of anesthetic agent administration to the mother.

Surgery induces significant pain that might exacerbate the excitotoxic injury of hypoxia–ischaemia by augmenting neuronal activity. Also directly altering neuronal function, [5] inflammatory changes might provoke further degeneration, including activation of the extrinsic apoptotic cascade leading to further neuronal death. Pain experienced before 32 weeks post conceptual age has been identified as a factor in growth impairment, as well as reduced white and gray matter maturation. [6] Pain-related stress has been correlated with cortical thinning at seven to eight years of age in preterm children without any history of severe brain injury in the neonatal period and without significant cognitive, sensory, or motor impairments. [7]

Neonatal ICU and preterm newborns

During the first two weeks of admission to the NICU (neonatal intensive care unit), neonates experience an average of 14 painful procedures per day with the majority occurring during the first few days of life. Increased numbers of skin-breaking procedures have been recently associated with lower scores on mental and psychomotor indices. [8] Functional brain MRIs of former preterm

neonates showed increased activation of sensory areas in response to pain compared to former full term, non-hospitalized controls. [9]

Significant number of confounding variables like sepsis, prematurity perse, chromosomal abnormalities in addition to anesthetic is associated with increased risk of poor neurobehavioural outcomes. [10] The precise role of anesthesia in these complex cases is very difficult to tease out from among the multitude of variables. But yet together all these factors entail cumulative neurodegeneration and would increase the chances of long term neurobehavioural disturbances.

Preclinical studies

Multiple animal studies have been conducted over the past decade and ongoing trials have published their pilot study data on this issue. The search for evidence for anesthesia-related effects on neurocognitive outcome in this patient population is further complicated by the lack of information on the anesthetic management or the sedative treatment in the intensive care unit.

In fetal macaque brain exposure to isoflurane caused severe white matter involvement due to oligodendrocyte injury than in neonate. [11,12] Guinea pig embryos demonstrated a drastic enhancement of apoptosis following administration of nitrous oxide, midazolam and isoflurane in utero at 35-40 days of gestation but not when exposed to fentanyl. [13] Pregnant rats administered isoflurane on gestational day 14 (G14) had birthed pups that subsequently showed significant deficits in spatial working memory as adults due to involvement of Hippocampus. [14,15]

Few studies are in odds to the above mentioned, data in rats show a reduction in neuronal cell death when pregnant rats were anesthetised with isoflurane for 6 hours and improvement in their spatial memory as adolescents. Also they suggested that preconditioning of rat primary cortical neurons abolished the neurotoxicity induced by a subsequent exposure to isoflurane. [16, 17]

Following exposure 2.5% sevoflurane anaesthesia to mice on day 14 of gestation for 2 h there was immediate increase of neuroapoptosis in fetal mouse brain tissues and subsequent learning and memory impairment in offspring mice. [18] These studies also showed that sevoflurane exposure impaired progenitor cell proliferation and reduce neuronal nitric oxide synthase (nNOS) level. [19] In the hippocampus which determines spatial learning, nNOS is known to play an important role in learning and memory.

In rhesus macaque brain, fetus is more vulnerable to neurodegeneration than neonate follwing ketamine, a finding similar to isoflurane. [20] This signifies that anaesthesia induced neuroapoptosis in primate brain gives rise to lasting neurocognitive disabilities, the nature of disabilities will vary as a function of time of exposure. [21] After analysis in prenatal (G122) and neonatal (PND 5) rhesus monkeys to exposure of 24h ketamine, the topographic differences in neurodegeneration was attributed to duration of exposure, ketamine plasma levels and developmental stage at the time of exposure. [22] Another significant finding in this study is that 3h exposure did-not have significant neurotoxicity which amounts to-normal pediatric general anaethesia.

In prenatal rats (G18), exposure to subanesthetic doses of propofol induced impaired learning and memory to the juvenile offspring. Propofol when given in fetal and neonatal rhesus monkeys has produced overall apoptotic profile 2.4 and 3.8 times more than drug naïve brain. [20,23] Propofol and isoflurane had a tendency to affect temporal, parietal cortices mostly in fetus whereas rostral brain in the neonates. But Ketamine showed evenly and lightly distributed degeneration distributed in various divisions of cerebral cortex without any predilection to specific areas. [21] Neonatal NHP brain exposed to anesthesia for same duration using isoflurane or propofol, the toxic impact of isoflurane is approximately four times greater than that of propofol. [23]

Creeley et al have stated that all their studies focusing on neuroapoptosis in fetal or newborn period, regardless whether the apoptogenic agent is alcohol, ketamine, propofol, or isoflurane, have documented dense degene-

ration of a specific population of neurons in the cerebellum.[21, 23-25]

Opioid administration during pregnancy caused delay in embryonic development, preterm labor, fetus death, chromo-somal anomalies, neural tube defects and reduced birth weight. [26-30] These children had several behavioral abnormalities including hyperactivity, lower Mental Development index, and lower motor development index. [26,27,29] Multiple studies in animals have shown that opiods do affect the normal synaptogenesis, proliferation, differentiation and survival of neuroblasts, when given prenatal and also postnatally.[31-33]

Several other evidences state that the problem happens only due to chronic exposure and during the early phases of growth spurt. [34,35] If administered immediately prior to painful interventions, studies in rats have shown a neuroprotective role for morphine. [36] Many studies have shown deleterious neuromodulatory effects of opiates, but upcoming research has demonstrated that morphine may have protective effects in specific conditions of pain and stress. Administration of opiods producing neurotoxicity therefore depends on the dose, duration and timing of exposure.

Human studies

The difficulty in the interpretation of the clinical studies that have been completed to date is due to the retrospective nature of the studies, the lack of precise information in terms of age, agent, duration, dose of anaesthetics, specific agents used. The trials have used variable outcome measures for neurocognitive function which lack specificity and standardization.

An epidemiologic study based on a birth cohort from Olmstead County in Minnesota found that children exposed to general anesthesia for caesarean section deliveries are not more likely to develop learning disabilities than those born of vaginal deliveries. [37] A separate study, using this same database found that there was no impact of neuroaxial labor analgesia on the incidence of childhood learning disabilities. [38] But the important limitation of the cohort study is techniques used to provide neuraxial analgesia for labor and deliveries during the study period differ from contemporary practice.

Interestingly, the incidence of early neurological abnormalities after cesarean delivery did not differ between neonates exposed to general anesthesia, including thiopental and nitrous oxide, or to maternal epidural analgesia using lidocaine. [39] In a study of 159 Japanese full-term infants, those that were exposed to nitrous oxide during the last stages of delivery had statistically significant increase in neurologic sequelae like weaker habituation to sound, stronger muscular tension, fewer smiles and resistance to cuddling at postnatal day 5 compared with infants that were not exposed to anesthesia without long term followup. [40]

Propofol sedation for 48 h in a pregnant patient with intracerebral hemorrhage did not lead to any measurable adverse effects in the newborn after emergency cesarean delivery. [41] In a small, 4-year follow-up after prenatal exposure to anesthetics for dental procedures, [42] children had decreased intelligence scores compared with unexposed controls, but demonstrated similar performance on tests of their vocabulary.

The NEOPAIN trial (Neurologic Outcome and Preemptive Analgesia in Neonates) [43] concluded that there was no difference in IQ, self-sufficiency, motivation or school-related performance between the placebo and morphine treated groups. Morphine related adverse effects were not found in the CANTAB trial which has followed the preterm children upto 8-9 yrs in their subsequent reports. [44,45]

Another small study found that anaesthesia and surgery in premature neonates was associated with impaired mental development index and reduced brain volumes and increased white matter injury on magnetic resonance imaging at 2 yr of age. [46] These studies highlight some anomalies in certain social and motor activities but do not demonstrate marked changes in IQ or academic performance. However, given the complex nature of neonatal critical care and subsequent development, the

true long-term impact of therapy may be difficult to quantify.

About the future

In the recent years, human stem cells-derived models, especially human embryonic neural stem cells, have become a new avenue of research for detecting early-life anaesthetics-induced neurotoxicity and developing potential protection/prevention strategies against such neuronal injury. [47] These cells have provided a potentially invaluable tool for investigating the developmental effects of anaesthetics in human tissues, and yet avoiding the ethical issues around *in vivo* research in human infants and children.

Recent studies suggested that inhibition of excessive NMDA-mediated excitatory pathway, prevention of reactive oxygen species accumulation, and improvement of peri-anaesthesia neuroinflammation can all ameliorate anaesthetics-associated cognitive impairment in animal models. Emphasis has been laid on the dose, duration, and the period of exposure for neurodegeneration based on the recent studies. [48,49,50]

The neurobehavioral development is multifactorial, and that anaesthesia exposure is likely just one of many important influences, some of which may be far greater than the anaesthesia exposure. Zheng et al (29) suggested that environmental enrichment like social interaction and novel stimulation ameliorated the effects of sevoflurane induced neurotoxicity. Probably this positivity can be extrapolated into humans and methods of environmental enrichment need to be identified and practised in unavoidable circumstances of anesthetic exposure.

Conclusion

We have to continue our efforts to provide improved care that will not have long-term devastating effects on the patients' cognitive and behavioral well-being. Thus, we must improve our understanding of the mechanisms that underlie the neurotoxicity of GAs so that preventive strategies could be developed especially in cases when life-threatening conditions make frequent anesthesia exposures a necessity that cannot be avoided. If children are society's future, we owe them the opportunity to answer this question appropriately.

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