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Review

Anaesthesia and the developing brain

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Abstract:

Increasing concern about the effect of anaesthesia on the infant and young child is raised by health care practitioners as well as the public immature neurons exposed to anaesthesia may lead to apoptosis and long-term neurobehavioural deficits in animals.. The majority of anaesthetic agents work by influencing GABA or NMDA receptors and may induce animal neuro apoptosis. The search for neuroprotective strategies to reverse or counter act the effect of anaesthesia, so far, has not been very successful. Dexmedetomidine is an α-2 adrenoreceptor and may have neuroprotective effects. The available human studies have failed to prove any long-term neurobehavioural deficiencies caused by anaesthetic exposure. Large international prospective studies are currently on the way that may change the practice of paediatric and obstetric anaesthesiologists in the future.

Introduction

For more than 150 years of anaesthesia practice it was believed that once the anaesthetic has worn off, the brain returns to the same state as it was before.[1] With emerging evidence in animal studies of long-term neurobehavioural deficits after anaesthesia exposure, including extensive neuroapoptosis,[1] the question often comes up from the parents, parents to be and surgical colleagues: could the anaesthetic agents cause any long term neurological development deficits? What is the evidence? How can we prevent this from happening or is this reversible?

To answer these questions we have to know how the brain develops and how anaesthetic drugs influence the brain. Understanding that, we may be able to make better choices in terms of timing elective surgery in pregnancy as well as in the neonate or young child. And if surgery is prudent what anaesthetic drug(s) are safer?

Brain development in the human

The development of the human nervous system consists of consecutive steps: neurogenesis starts in the foetus with differentiation and neuronal migration followed by establishment of synaptic connections (i.e. synaptogenesis) that continues post nataly.[2,3] At birth most neurons have migrated to their final location in the brain.[2] The formation of synapses is dependent on electrochemical activity involving the activation of calcium channels.[3] Neurogenesis and synaptogenesis are activity dependent; "neurons that fire together, wire together"[2] The peak period of myelination occurs during the first two years after birth, during which period the brain structures drastically change their biochemical composition.[4] The brain's ability to learn, remember, forget, recover from injury and reorganise is called cerebral plasticity.[2] The developing brain has the greatest potential for recovery because of an overproduction of neurons in the foetus and overproduction of synapses after birth.[2] Cerebral plasticity not only helps the brain to recover from injury, but may also lead to abnormal adaptation and therefore abnormal structural changes.[2] Adverse experiences (e.g., repetitive pain during early brain development) can modify neuronal activity patterns and may permanently alter the functional wiring of immature neurons.[5] This may lead to behavioural and emotional problems in childhood, altered pain responses, anxiety, depression or suicidal tendencies.[2] Apoptosis is also a part of normal growth and development,[6] and about 1 % of mammalian brain neurons that are dysfunctional are normally pruned in this process to maintain normal functioning pathways.[7] Brain development is not a uniform process, but consists of spurs of increased development followed by periods of less brain development occurring in different areas of the brain. Neurogenesis and neuronal migration accelerate and reach a peak during and after the second trimester of pregnancy.[3]

Mechanism of action of anaesthetics on the brain

The majority of anaesthetic agents work by two basic mechanisms in the brain: an increase in inhibition via GABA receptors (e.g., benzodiazepines, barbiturates, propofol, etomidate, isoflurane, enflurane, and halothane),[8] and a decrease in excitation through NMDA receptors (e.g., ketamine, nitrous oxide (N_2O), and xenon).[9,10] The exception to these mechanisms is dexmedetomidine. The drug is a potent α-2 adrenoceptor agonist that has eight times higher affinity for the α-2 adrenoceptor than clonidine. Dexmedetomidine has sedative, analgesic and anxiolytic properties.[11] Recent findings indicate that drugs that act by either stimulation of GABA receptors or inhibition of NMDA receptors, induce widespread neuronal apoptosis in immature rat brain when administered during synaptogenesis.[12] Apoptosis is increased if neurons are exposed to a combination of GABA agonists and NMDA antagonists.[7] Neuronal exposure to anaesthetics during a critical neurodevelopmental period triggers an unknown chain of events causing translocation of BCL2-associated X protein (Bax) to mitochondria, followed by mitochondrial membrane disruption and permeability, resulting in leakage of cytochrome c into the cytosol.[7]

The evidence

Animal studies

In analysing the literature, it is important to keep a few details about the animal model in consideration. The lifespan of the rodent is about three years, and synaptogenesis occurs mainly after birth.[3] Therefore, the neuron lifespan of the rodent is a maximum of 3 years in comparison with the human neuron lifespan that may be over 100 years.[6] It is important to recognise that the anaesthetic exposure of a rat is equivalent to a much longer exposure in humans. An anaesthetic exposure of six hours in the pregnant rat, extrapolated to the human, may be over 48 hours of anaesthesia exposure in the pregnant human, and thus may only be relevant in intensive care sedation settings.[3]

Evidence in the animal models indicates long-term neuro-development deficiencies after anaesthesia exposure. The infant rat exposed to commonly used anaesthetics (midazolam, N_2O and isoflurane) in clinically relevant dosages, caused widespread apoptotic neurodegeneration in the brain as well as persistent memory/learning impairments.[13] These data have been reproduced in other species and had similar results.[6] A study in monkeys reported persistent neurocognitive deficits several years after 24 hrs of exposure to ketamine.[6] The volatile anaesthetics, isoflurane and sevoflurane and intravenous agents, propofol, ketamine, midazolam, diazepam and thiopentone have all induced neuronal apoptosis in some situations in rodents.[14] A hypothesis for the mechanism of neuronal injury is based on the synaptic neurotransmission suppression that causes neuronal death; if this proves to be true, anaesthetics may induce apoptosis irrespective of the agent used.[14]

Human studies

There are no prospective studies, and may never be, evaluating neurocognitive function in children after neonatal exposure to anaesthetics. Several retrospective studies have been published since 2007. A study published by the Mayo Clinic in 2009, that assessed the impact of obstetric anaesthesia on learning disabilities in children younger than five years, concluded that there was no evidence of harm following Caesarean and vaginal delivery.[15] A feasibility pilot study, published by a group from The Netherlands in the same year, assessed the neurobehavioural development after a single anaesthesia exposure before age 6 years, by using a questionnaire at age 1 – 14 years. The authors concluded that, with the size of the study, there is no "indisputable evidence" against the use of anaesthesia in the young.[16] The same year, another study came out about the association between anaesthetic exposure before age 4 years and the development of reading, written language and math learning disabilities. The authors concluded that multiple exposures to anaesthesia may contribute to learning disabilities, but added that perhaps the need for anaesthesia maybe a marker for other unidentified factors contributing to learning disabilities.[17] A study that examined twins, with one child exposed to anaesthesia and the other not, concluded that there was no evidence for a causal relationship between anaesthesia administration and learning-related outcomes. They concluded that early anaesthesia is a marker of an individual's vulnerability for later learning problems, regardless of their exposure to anaesthesia.[18]

Surgery during pregnancy

Historically, the 2nd trimester was considered the safest period during pregnancy for surgery and anaesthesia.[3] The focus has been on the first trimester, due to concerns for teratogenicity during embryogenesis, and the 3rd trimester, due to concerns of premature labour.[3] However, recently, the safety of surgery and anaesthesia during the 2nd trimester has been questioned because of foetal neuro-development during this period.[3]

The underlying mechanism of the potential, intrauterine anaesthetic drug-induced, neurological changes during pregnancy is not fully understood.[3] It seems that since GABA is a trophic factor for the developing brain, use of GABA stimulating agents during critical brain development periods can lead to neural connectivity injury.[3] Reduced synaptic activity and neuroapoptosis in the developing brain can be triggered even by a short exposure to commonly used anaesthetics like propofol, ketamine, nitrous oxide, isoflurane, sevoflurane, barbiturates and benzodiazepines.[14] Combinations of anaesthetic drugs can increase the severity of neuroapoptosis.[14]

However, it is very difficult to translate animal studies to humans. In contrast with the rodent, where rapid brain growth (synaptogenesis) takes place after birth, in the humans, the process starts in mid gestation and continues for a number of years after birth.[3]

Surgery in the child

Recent clinical studies suggest that major disability is unlikely with brief exposure in an older child.[14] It is known that anaesthesia induced neurotoxicity is a real phenomenon in the young rodent.[14] Infants are rarely exposed to anaesthesia in isolation.[14] There are many other factors that could lead to neurotoxicity; e.g., untreated pain induces significant long-term harmful consequenses.[14] In addition, hypercarbia has been associated with neuronal apoptosis in neonatal animals.[14] There are many confounding factors that influence the results of human studies. Children who require more interventions/anaesthetics usually have significant chronic illnesses that may, per se, contribute to learning disabilities.[14] Another factor is that the majority of the studies did not comment on subtle neurobehavioural deficiencies. Environmental influences, e.g., lag in psychosocial stimulation, resulted in lower intelligence quotients and memory scores and more behavioural difficulties in children.[2]

Neuroprotective strategies

If all anaesthetic agents may be detrimental to neurobehavioural development in the unborn or young, are there any strategies/medications to reverse or counteract the effects?

Erythropoietin, antidepressants, lithium, etc., are all modalities that may enhance recovery after cerebral injury.[1, 2] Melatonin is worth mentioning. Melatonin was found to reduce anaesthesia-induced neuronal apoptosis in rats in a dose-dependent way. It was previously shown that melatonin counteracts the mitochondrial biochemical changes by anaesthetics that lead to apoptosis. Melatonin causes an up-regulation of the anti-apoptotic protein and a decrease in anaesthesia-induced cytochrome c release into the cytoplasm. Also melatonin causes a decrease in anaesthesia-induced activation of caspase-3, an important step in the activation of DNAses and the formation

of the apoptotic bodies.[19] Another nonspecific neuroprotective effect of melatonin may be the ability to decrease the requirement of anaesthesia by inducing sleep and attenuating analgesia.[1] Hypothermia demonstrated neuroprotective effects in several neonatal studies with hypoxic-ischaemic encephalopathy and improved neurologic outcome.[2] Hypothermia has its own harmful effects on newborns and this is well described in the literature (e.g., impairment of transition from intrauterine to extrauterine circulatory pathways by increasing pulmonary vascular resistance).[20]

Because dexmedetomidine is neither a GABAergic nor NMDA antagonist, it has been hypothesised that it is free of developmental anaesthetic toxicity. Dexmedetomidine improves the neurocognitive deficit induced by a subanaesthetic dose of isoflurane, by reducing neuronal apoptosis in a dose-dependent way. This was reversed by blocking the α-2 adrenoceptor, indicating that the protective effect is mediated by this receptor.[1] Unfortunately, at present, there is no convincing data to propagate the use of any of these agents in the human, with or after anaesthesia exposure.[1,6]

The future

With so many questions and so few answers, several international research groups are currently conducting research to help us better understand this very important concern:

- *GAS study:* international, multi-site, randomised controlled study that is investigating if the long-term effects of spinal- and general anaesthesia result in the same neurodevelopment outcomes.
- *PANDA study* (Pediatric Anaesthesia Neuro Development Assessment Study): multicentre USA group; their focus is to compare the neurodevelopment of children exposed to anaesthesia and those not exposed to anaesthesia.
- *Oregan University group:* Ansgar Brambrink, with a multidisciplinary group, is investigating the long-term functional and morphologic consequences of single vs. triple anaesthesia exposure of infant non-human primates.
- *NCTR* (National Center for Toxicological Research): a group in the USA, is conducting non-clinical studies, in rodents and nonhuman primates, to assess mechanisms, long-term deficits and strategies to prevent/decrease neurotoxicity with clinically-relevant anaesthesia.
- *MASK study:* Mayo Clinic with the NCTR, the study compares performance of children with no anaesthetic exposure to those with single or multiple exposures.

SmartTots (Strategies for Mitigating Anaesthesia-Related neuroToxicity in Tots) is a collaborative effort between the US Food and Drug Administration (FDA) and the International Anaesthesia Research Society (IARS) to coordinate and fund some of the above research programs.

Conclusion

Research in animal studies indicates that anaesthetic exposure of the immature brain causes long-term anatomical and neurobehavioural deficits. The limited data available from prenatal animal studies indicate that the brain is vulnerable to the maternal exposure of anaesthesia, especially from the second trimester onwards. All anaesthetic agents may be harmful and have an additive effect. No agent or modality was proved to counteract or neutralise the anaesthetic effect on the brain. Human studies are limited and are lacking evidence of detrimental effect on the neonatal and foetal brain. Currently, there is not sufficient evidence to warrant a change in paediatric anaesthesia practice, postponing necessary procedures, or withholding necessary analgesics, sedatives or anaesthetics from pregnant as well as neonatal and young patients. This is unethical and may lead to significant harm. Multicentre, international studies are underway and hopefully will delineate the risk of anaesthesia exposure in the foetus and newborn.

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