Perioperative central nervous system injury in neonates

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Editor’s key points
- Anaesthetic-induced developmental neurotoxicity exists in animal models, raising the possibility of similar effects in humans.
- Clinical evidence for developmental anaesthetic neurotoxicity is inconclusive, and will be difficult to obtain.
- Neonatal anaesthesia is also complicated by physiological and pathological derangements that can contribute to neurological injury.

Summary. Anaesthetic-induced developmental neurotoxicity (AIDN) has been clearly established in laboratory animal models. The possibility of neurotoxicity during uneventful anaesthetic procedures in human neonates or infants has led to serious questions about the safety of paediatric anaesthesia. However, the applicability of animal data to clinical anaesthesia practice remains uncertain. The spectre of cerebral injury due to cerebral hypoperfusion, metabolic derangements, coexisting disease, and surgery itself further muddles the picture. Given the potential magnitude of the public health importance of this issue, the clinician should be cognisant of the literature and ongoing investigations on AIDN, and raise awareness of the risks of both surgery and anaesthesia.

Keywords: anaesthesia, paediatric; brain injury; paediatric; surgery

The neonatal brain appears uniquely susceptible to both ischaemic and neurotoxic damage during general anaesthesia. Given the immature nature of neonatal organ systems, this patient group is highly sensitive to the cardiovascular and respiratory-depressant effects of anaesthetic drugs. In the recent past, withholding volatile and narcotic anaesthetic drugs was prevalent in neonatal anaesthetic practice because of the perceived haemodynamic stability afforded by the sympathetic response to the surgical manipulations. This has been the standard of care for many years. However, advances in the understanding of developmental neurobiology confirmed that the neonatal central nervous system (CNS) is capable of sensing pain. Neonates undergoing surgery mount a stress response, and deep levels of anaesthesia appeared to blunt stress hormones during neonatal cardiac surgery. These reports promoted a fundamental change in the practice of neonatal anaesthesia by advocating for the routine use of anaesthetic and analgesic drugs.

The neurotoxic potential of general anaesthetics has been well documented in the laboratory, but its clinical relevance to humans has not been definitively established at this time. As a result, these observations question the relative safety of anaesthesia in paediatric patients. It can be argued that the most important goal of general anaesthesia for neonates is maintaining homeostasis during the surgery. The difficulties of achieving this homeostasis are magnified in neonates because of the impediments of obtaining meaningful measurements during capnography and non-invasive arterial pressure monitoring during general anaesthesia. The urgent and emergent nature of most procedures in this age group leaves some infants in suboptimal condition for general anaesthesia, which can predispose them to haemodynamic instability during surgery. Furthermore, the traditional goals of general anaesthesia such as amnesia, analgesia, and muscle relaxation might not be relevant for neonates undergoing surgery. Should the concern of anaesthetic-induced developmental neurotoxicity (AIDN) warrant paediatric anaesthesia to come back full circle and resume the practice of withholding anaesthetic drugs during surgery and painful procedures? In this review, we will discuss relevance of these issues in the context of the management of general anaesthesia in the paediatric patients.

Anaesthetic-induced developmental neurotoxicity

Preclinical studies in fetal and neonatal laboratory animals clearly link commonly used anaesthetic drugs to accelerated neuroapoptosis and neurobehavioural deficits. These anaesthetics are primarily N-methyl-D-aspartate (NMDA) antagonists and γ-aminobutyric acid (GABA) agonists. Anaesthetic exposure can cause additional effects on neurones including an increase in dendritic spine density and abnormal neurogenesis. The only anaesthetics that do not induce neuroapoptosis and alleviate AIDN are dexmedetomidine and possibly xenon. Most preclinical studies on AIDN were conducted in the absence of concurrent noxious stimulation, which does not account for the interaction of anaesthesia and surgery/painful procedures. Recent reports of neonatal rats receiving ketamine or isoflurane during the...
application of noxious stimuli resulted in contrasting results with ketamine alleviating and isoflurane increasing neuro-
apoptosis.\textsuperscript{16} \textsuperscript{17} Taken together, these preclinical observations demonstrate causality between anaesthetic exposure during a vulnerable developmental period with synaptic modelling and plasticity.

Whether human neonates are susceptible to the neuro-
apoptotic effects of general anaesthetics remains a subject of debate. Synaptogenesis occurs from the last trimester of gestation to about 3 yr after birth.\textsuperscript{18} \textsuperscript{19} However, neuroinformatic analysis using neuroscience, evolutionary science, statistical modelling, and computer science specify the peak period of susceptibility to AIDN to be between 17 and 20 weeks gestation.\textsuperscript{20} \textsuperscript{21} Ethanol is both an NMDA receptor antagonist and GABA receptor agonist and an established neurotoxin in preclinical studies. Epidemiological work suggests that fetal alcohol syndrome is associated with alcohol exposure as early as the 18th and 20th week after conception.\textsuperscript{22} \textsuperscript{23} The comparable period of vulnerability to AIDN is still unknown in humans.

**General anaesthesia and the paediatric surgery patient**

There is ample epidemiological evidence to support an association between paediatric surgery and poor neurodevelopmental outcomes in humans. However, most of these are retrospective studies where it is difficult to eliminate the obvious confounders of underlying pathology and surgery. The Victorian Infant Collaborative Study group reported that procedures in infants <27 weeks postconception who underwent surgery, including patent ducts arteriosus ligation, inguinal herniorrhaphy, gastrointestinal procedures, neurosurgery, and tracheostomy, were associated with blindness, cerebral palsy, deafness, and neurocognitive scores <3 so below the mean.\textsuperscript{24} Surgically managed premature neonates with necrotizing enterocolitis have a higher incidence of cerebral palsy and lower neurocognitive scores than those treated medically.\textsuperscript{25} \textsuperscript{30} However, a study on premature infants with tracheoesophageal fistula repaired at birth did not have different IQ scores from their normal cohort.\textsuperscript{31} \textsuperscript{32}

There are several studies examining the neurobehavioural outcomes of patients born with congenital heart disease. Prospective neuroimaging of these infants before their cardiac surgery revealed a high incidence of abnormal magnetic resonance imaging and computed tomography findings including stroke and periventricular white matter damage.\textsuperscript{33} \textsuperscript{35} Not surprisingly, several outcome studies in neonates undergoing cardiac surgery have shown an increased incidence of cerebral palsy, lower IQ scores, speech and language impairment, and motor dysfunction.\textsuperscript{36} \textsuperscript{42} A longitudinal, prospective trial comparing circulatory arrest with low-flow cardiopulmonary bypass revealed that the mean scores for most outcomes were within normal limits. However, the neurodevelopmental status of the whole patient cohort was below the general population in terms of academic achievement, fine motor function, visual spatial skills, working memory, hypothesis generating and testing, sustained attention, and higher-order language skills.\textsuperscript{34} \textsuperscript{36}

There has been a spate of epidemiological studies to determine if general anaesthesia is associated with learning disabilities. A retrospective cohort study from Olmsted County, Minnesota, concluded that children who were exposed to two or more general anaesthetics had significantly more learning disabilities.\textsuperscript{43} \textsuperscript{44} The duration of exposure was also positively linked with the cumulative risk of learning disabilities. A New York State Medicaid billing database identified 383 patients who underwent inguinal herniorrhaphy before age 1.\textsuperscript{45} These patients were found to have a nearly two-fold increase in developmental and behavioural issues when compared with a gender and birth weight-matched control group. A follow-up study from the same database identified sibling pairs and found no association between general anaesthesia and poorer neurobehavioural outcomes.\textsuperscript{46} A positive trend towards abnormal neurobehavioural development was found in children from the Netherlands who underwent surgery before 24 months of age for urological procedures compared with older children.\textsuperscript{47} A recent retrospective report from Australia demonstrated that even a single exposure to anaesthesia in a cohort of patients undergoing surgery developed long-term deficits in language and cognitive function.\textsuperscript{48} A similar retrospective analysis of children demonstrated that the time of anaesthesia and surgery as infants had a negative correlation with academic achievement tests scores.\textsuperscript{49}

There are several well-designed epidemiological studies that show no association between general anaesthetic exposure at a young age and academic performance. In Denmark, infants who had undergone inguinal herniorrhaphy compared with a matched cohort had no significant differences in academic performance between the exposed and non-exposed children.\textsuperscript{50} This was similar to the finding of the Olmsted county cohort in which there was no increase in learning disabilities in children who had only a single general anaesthetic before the age of 4 yr.\textsuperscript{43} An identical twin study of 1143 pairs from the Netherlands also reported no difference in cognitive problems and educational achievements in the twin pairs that were discordant in their exposure to general anaesthesia.\textsuperscript{51}

The epidemiology data in the positive studies are provocative but only demonstrate an association between early anaesthesia/surgery and neurodevelopmental deficiencies. These retrospective reports cannot and should not confirm causation between early exposure to anaesthesia and surgery and subsequent neurological outcomes. It is plausible that the underlying pathology and also the stress of surgery and prolonged hospitalization impact the neurodevelopment of these patients and that cumulative exposure to general anaesthesia might be more harmful than a single short exposure. These studies also point out the need for well-controlled prospective randomized trials to determine whether there is an association between general anaesthesia and poorer developmental outcomes.
Table 1  Intraoperative variables that affect cerebral perfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Arterial pressure</td>
<td>Blood pressure in the arteries</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide</td>
<td>CO₂ in the partial pressure system</td>
</tr>
<tr>
<td>Inspired oxygen concentration</td>
<td>Oxygen concentration in the inspired air</td>
</tr>
<tr>
<td>Glucose</td>
<td>Blood glucose concentration</td>
</tr>
<tr>
<td>Temperature</td>
<td>Core body temperature</td>
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CNS injury during general anaesthesia

The risk of intraoperative cerebral hypoperfusion leading to CNS injury during routine general anaesthesia for neonates is unknown. Cerebral perfusion can be decreased by intraoperative hypotension, hypoglycaemia, hyperoxia, and hypocapnia, all of which can occur during a routine general anaesthetic (Table 1). Hypoglycaemia and hypoxaemia independently can lead to cerebral ischaemic changes and intraoperative hyperthermia can increase the cerebral metabolic rate, which can injure the brain in a low perfusion state.

Intraoperative hypotension

Management of intraoperative arterial pressure in infants is not only hampered by inconclusive parameters, but also by the measurement method. The measured non-invasive arterial pressure values are dependent upon the type of non-invasive arterial pressure monitor and the circumference of the infant’s extremity. Furthermore, in healthy neonates undergoing non-invasive arterial pressure measurements of their four limbs, one study demonstrated wide variability of the mean arterial pressures (MAP) with 8% of the neonates undergoing non-invasive arterial pressure measurements of their four limbs, one study demonstrated wide variability of the mean arterial pressures (MAP) with 8% of the neonates having a 20 mm Hg lower MAP in their legs compared with their arms and 16% of the neonates demonstrating the same difference between their upper arms.

There are no clear definitions of hypotension even for non-anaesthetized premature and term infants. In 2006, the American Academy of Pediatrics stated in their summary proceedings that ‘there is no consensus regarding the actual definition of hypotension in the neonate or how best to raise perceived low blood pressure’. Normative values for arterial pressure in the awake state have been established for both premature and term infants. Hypotension in non-anaesthetized neonates is usually defined as below the 5th percentile for gestational and postnatal age. However, there is also evidence that correction of hypotension with vasopressors or plasma expanders can actually increase the incidence of adverse neurological events.

The acceptable arterial pressure for an individual undergoing anaesthesia is generally less than his or her baseline arterial pressure. The definition of hypotension under anaesthesia is a MAP of 20% less than baseline. A recent survey of members from the Society of Pediatric Anesthesia and the Association of Paediatric Anaesthetists designated an acceptable systolic threshold for neonates as 45.5 (8.5) and 49.6 (8.4) mm Hg, respectively, for the two societies. As for a qualitative definition, a change from systolic arterial pressure baseline of 20–30% was indicative of intraoperative hypotension for 70% of the responders, a decrease of 40% for 6%. Other investigators have sought to define hypotension based on end-organ perfusion, especially cerebral perfusion pressure. The lower limit of cerebral autoregulation may be a MAP of 29 mm Hg in non-anaesthetized preterm infants, but at least one study revealed that some preterm infants (24–34 weeks postmenstrual age) demonstrate intact cerebral autoregulation as low as 23 mm Hg MAP.

Hypocapnia

Cerebral perfusion is also sensitive to changes in partial arterial pressure of carbon dioxide ($P_{\text{aCO}_2}$). Similar to cerebral blood flow and metabolism, $CO_2$ vasoreactivity might be higher in healthy children than in adults under propofol and volatile anaesthetics. Non-invasive measures of carbon dioxide in the neonate are challenging. Transcutaneous $CO_2$ sensors are accurate but can lead to thermal injury on delicate skin. End-tidal capnography can be inaccurate because of leakage around the tracheal tube. Some studies have found poor correlation between proximally measured $ECO_2$ and $P_{\text{aCO}_2}$ even in patients without pulmonary disease. Furthermore, there are also no standard definitions for degrees of hypocapnia. Some authors have suggested definitions of hypocapnia to include: mild to moderate, $ECO_2$ 4.0–4.7 kPa; moderate to severe, $ECO_2$ between 3.3 and 4.0 kPa; and severe, $ECO_2$ < 3.3 kPa. Deliberate moderate to severe
hypocapnia during anaesthesia was used in the past during anaesthesia to reduce the requirements for sedative, anaesthetic, and neuromuscular agents, and mild hypocapnia is still used as an adjunct to minimize spontaneous ventilation by some practitioners. Hypocapnia was also used in ventilated neonates to improve oxygenation in babies with persistent pulmonary hypertension and diaphragmatic hernias, but has been found to increase pulmonary barotrauma and lead to an increase in mortality. In addition, inadvertent periods of moderate to severe hypocapnia during anaesthesia are common, especially during anaesthetic induction; its effect on cerebral perfusion in healthy newborns is unknown. In contrast, in term neonates with prior hypoxic-ischaemic encephalopathy, exposure to hypocapnic conditions worsens neurocognitive outcomes at 18–22 months and also increases immediate mortality.82 Preterm infants with hypocapnia also have a higher incidence of intraventricular haemorrhage and periventricular leukomalacia.84 Although there is a clear association between hypocapnic conditions in infants with hypoxic-ischaemic encephalography and worse neurological outcome, it is unclear whether the hypocapnia is causative or merely a marker for identifying sicker infants who are in a low cardiac output state. However, near-infrared spectroscopy in premature infants with normal baseline cranial ultrasound reveals that hypocapnia leads to a decrease in cerebral oxygen levels presumably from decreased cerebral perfusion.85

Oxygen

The effect of excess oxygen administration in infants receiving general anaesthesia is unknown. It is common practice to transport sick neonates with higher fractional inspired oxygen than is needed to saturate their blood to create an ‘oxygen reserve’ in an event of disruption of ventilation or oxygen supply. The universal practice of preoxygenating patients with 100% oxygen before tracheal intubations might further complicate this issue. The effect of this brief period of hyperoxegenation is unknown. There are several preclinical reports showing that hyperoxia leads to inflammation and necrosis/apoptosis in the brain and other organs.86 87 Furthermore, hyperoxia after an asphyxiatic injury causes a reduction in perivascular production of nitric oxide and reduced cerebral perfusion.88 It is believed that hyperoxia in these animals uncouples endothelial nitric oxide synthase leading to reduced nitric oxide and increased oxygen radical production resulting in a worsening cerebral injury.

It is important to keep in mind that at least 5% of infants born in the USA are resuscitated at birth.89 A recent meta-analysis in newborn infants revealed a 30% reduction in mortality when resuscitation was carried out with 21% instead of 100% O₂.90 Presumably, these infants are at risk for having sustained birth asphyxia and needing surgery in the neonatal period. Although there are not enough human data to change recommendations about preoxygenating neonates before tracheal intubation, the possible harmful effects of this practice need to be examined.

Glucose

Hyperglycaemia can be deleterious to adult animals that undergo a period of cerebral asphyxia. However, there is evidence in perinatal animal models that normoglycaemia or hyperglycaemia during asphyxia might be beneficial.91–93 The reasons for this are unclear but could relate to the rapid utilization of lactate by the neonatal brain and a more rapid efflux of lactate from the brain, which in turn might limit cerebral damage from high lactate levels. Hyperglycaemia is associated with a slight decrease in perfusion as measured by near-infrared spectroscopy. However, the clinical implications of this observation are unclear.94 Long-term neurodevelopmental follow-up studies in children who underwent cardiac surgery as infants do not show an association between serum glucose levels and neurodevelopmental outcomes.95–97 Studies in newborn primates show that prolonged, severe hypoglycaemia or mild hypocapnia accompanied with mild hypoxia–ischaemia cause cerebral injury.28 99 This pattern of cerebral injury occurs in the upper cortical areas, in particular the parieto-occipital regions and the hippocampus, caudate, and white matter. Human studies of neonates with isolated hypoglycaemia have shown a wider spectrum of injuries such as deep nuclear grey matter and cortical infarction. In fact, it is difficult to differentiate a hypoglycaemic cerebral injury from a hypoxic-ischaemic injury in human neonates.

In the past, it was felt that general anaesthesia confers some cerebral protection to humans because it lowers cerebral metabolic rate and thus the need for energy substrates. This may not be the case with neonates. Sevoflurane has been implicated in eliciting seizures in neonates, children, and adults.100 Propofol has also been shown to produce tonic clonic seizures in neonates.101 102 Both anaesthetics are GABAergic agents. While GABA acts as an inhibitory transmitter in the mature brain, it has been found in many preclinical studies to be excitatory during early stages of brain development.103 104 GABAergic agents activate GABAA receptors that produce chloride efflux, leading to cell depolarization and neuronal excitation, and leads to seizure activity in the whole animal. As a consequence, GABA remains excitatory until GABA receptors adopt the normal inhibitory mode when the mature chloride transporter KCC2 is expressed, which actively transports chloride out of the cell.105 This switch begins around postnatal week 15 in term infants but it is not complete until about 1 yr of age. Thus, it is important to maintain an adequate level of both perfusion and glucose delivery to neonates undergoing general anaesthesia.

Temperature control

It is axiomatic in paediatric anaesthesia to maintain body temperature during general anaesthesia. The energy expended by the infant to rewarm might be depleted. However, there is extensive literature demonstrating that mild hypothermia (core temperature 32–34°C) is
neuroprotective in the setting of prior hypoxic-ischaemic injury in neonates leading to less mortality and less neurocognitive deficits at 18 months of age. There is also evidence from these same randomized controlled trials that hyperthermic infants fare worse than normothermic infants in terms of mortality and neurocognitive outcomes. The literature is sparse prospectively examining the effects of hyperthermia on neonates undergoing surgery and anaesthesia. However, even a moderate elevation in maternal temperature before delivery increases the risk of hypoxic-ischaemic injury to the newborn.

The costs of maintaining moderate hypothermia in neonates with hypoxic-ischaemic injury include an increased need for arterial pressure support, more bradycardia, and coagulation abnormalities, all of which would be problematic in the operating theatre. There are not enough scientific data to recommend mild hypothermia for neonates undergoing surgery, but the literature suggests that neonates with hyperthermia are at risk for cerebral injury, especially during a low perfusion state.

**Declaration of interest**

None declared.

**Funding**

This work was supported by the National Institute of Health grant 1-R01 HD06 1136-01A1 (M.E.M.) and the Boston Children’s Hospital Endowed Chair in Pediatric Neuroanesthesia (S.G.S.).

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