Anaesthetic considerations for surgery in newborns

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ABSTRACT

Almost 30 years ago, the American Academy of Pediatrics Committee on Fetus and Newborn coauthored a policy statement strongly advocating for the use of anaesthesia in all neonates stating 'local or systemic pharmacologic agents now available permit relatively safe administration of anesthesia or analgesia to neonates undergoing surgical procedures and that such administration is indicated according to the usual guidelines for the administration of anesthesia to high-risk, potentially unstable patients'. With current techniques and advanced monitoring, preterm and full-term infants routinely undergo surgical procedures under general anaesthesia to repair congenital defects that were lethal in years past. Recent research in immature animal models, however, has shown evidence of enhanced neuroapoptosis and other signs of neurotoxicity with all of the currently used anaesthetic agents. There is also increasing concern about the potential adverse effects of perioperative hypotension and hypocapnia on neurocognitive development in infants. This review outlines the most recent animal and human evidence regarding the effects of general anaesthesia and anaesthetic-related haemodynamic changes on the developing brain of newborns.

MORBIDITY AND MORTALITY OF ANAESTHESIA IN NEWBORNS

Every year, thousands of preterm and newborn infants undergo general anaesthesia for a variety of surgical procedures and imaging studies. The landmark studies of Anand and Hickey demonstrated almost 30 years ago that general anaesthesia in infants ameliorates the surgical stress response and decreases morbidity and mortality perioperatively.[1] Though the rate of paediatric deaths attributable to anaesthesia has declined by more than two-thirds since the first study in the 1960s (currently estimated to be 0.65–0.98/10 000), perioperative morbidity and mortality remains disproportionally high in neonates.[2–6] A compilation of the single institution and multi-institutional perioperative mortality studies to date has revealed that neonates (<30 days of age) have 6 times the mortality rate of infants 1 month to 1 year of age and almost 25 times the mortality of children from 1 year of age to 18 years. In one study in the USA, the risk of mortality for infants undergoing a surgical procedure was 69 times greater for neonates than children >10 years.[4] This higher mortality has been attributed largely to the degree of preoperative illness, the complexity of the surgeries (eg, cardiac surgery) and infant physiology.

ANAESTHESIA-RELATED NEUROTOXICITY

Animal studies

Recent epidemiological studies in infants have suggested an association between general anaesthesia exposure and later learning deficits. This association has been clearly shown after cardiac surgery in infants but more recent studies suggest that there may be increased risks of neurocognitive deficits and neurobehavioural abnormalities in otherwise healthy infants and toddlers.[7 8] These concerns have been driven by animal studies that suggest long-term deficits in memory and learning in infant animals after anaesthesia exposure. Two types of anaesthetic agents have been implicated in fetal and neonatal animals as the cause of accelerated neuronal cell death (apoptosis): N-methyl-D-aspartate (NMDA) antagonists (eg, ketamine, nitrous oxide) and gamma amino butyric acid (GABA) agonists (eg, midazolam, propofol and inhaled anaesthetics such as sevoflurane or isoflurane). A seminal study in 1999 demonstrated widespread neuroapoptosis following combined exposure to the GABA agonists midazolam and isoflurane and the NMDA antagonist nitrous oxide in rat pups.[9] Subsequently, accelerated apoptosis was found after exposure to most general anaesthetic and sedative agents including benzodiazepines, nitrous oxide, halothane, isoflurane, sevoflurane, thiopental, propofol and ketamine in immature animals of a variety of species including rodents, piglets, nematodes and non-human primates[10] (table 1). Though neuroapoptosis is part of the normal pruning process of redundant neurons during mammalian development as the brain differentiates into specific functions, the neuroapoptosis seen in the animal experiments was excessive and led to developmental impairments when the animals matured.[11] The changes noted after administration of NMDA and GABA agents were greatest after longer exposures, and accelerated apoptosis was usually only seen after several hours of exposure. The effects were greatest in young animals (<7 days in rats and during late gestation and the neonatal period in primates), a time that has been specifically associated with rapid brain growth.[12]

Apoptosis is not the only abnormality seen after exposure to anaesthetic and sedative agents in infant animals. Other effects include alterations in dendritic spines,[13] effects on neurogenesis,[14] decreases in trophic factors,[15] impairment of astroglial development (changes in the actin cytoskeleton)[16] and degeneration of the mitochondria.[17] A summary of the preclinical data on neurotoxicity in infant animals can be found in table 2. Long-term neurodevelopmental effects especially in learning and memory and altered behaviour have been found in many animal studies, the most concerning of which are those that have demonstrated long-term altered behaviour and impaired learning in non-human primates.[18] Conversely, there are examples where accelerated neuroapoptosis is not associated with neurobehavioural deficits and studies in rodents where the neurobehavioural effects were

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Table 1 Anaesthetic agents implicated in increased neuroapoptosis

GABA agonists	NMDA antagonists
Benzodiazepines	Ketamine
Midazolam	
Lorazepam	
Propofol	Nitrous oxide
Etomidate	
Fluorinated volatile anaesthetics	
Isoflurane	
Sevoflurane	
Halothane	
Desflurane	
Barbiturates	
Thiopental	
Pentobarbital	
Methohexital	

GABA, gamma amino butyric acid; NMDA, N-methyl-D-aspartate.

Table 2 Neurological changes noted in infant animals following anaesthetic exposure

Type of injury	Animal species
Neuroapoptosis	Rodents, non-human primates, nematodes
Alterations in dendritic spines	Rodents
Altered neurogenesis	Rodents
Impaired astroglial development	Rodent astroglial cultures
Mitochondrial degeneration	Rodents
Decreases in trophic factors	Rodent primary neurons
Cognitive deficits	Non-human primates
Memory and learning	Rodents, non-human primates

mitigated by enriching the physical environment after exposure.[19]

The translation of these animal studies to specific effects in human infants is not clear. Since the neurotoxic effects are seen in a large number of species, it is reasonable to expect an effect in humans if a sufficient dose is given for a sufficient period of time at the age of highest susceptibility. However, the human brain is far more complex than the rodent or non-human primate brain and is greatly affected by the environment and genetic make-up of the child. Studies of brain injury in neonates have shown that the outcome is significantly affected by the timing and nature of the injury and whether it is diffuse or focal. In addition, the physiological impact of anaesthesia (ie, respiratory and cardiovascular effects) on experimental animals is generally not monitored during these studies and it is not clear whether cerebral effects of hypoxia, hypotension and hypoglycaemia may also impact subsequent neurodevelopment. The animal experiments to date have involved relatively large doses of anaesthetic agents per body weight (although in many cases the minimum doses needed to keep the animals anaesthetised) and have exposed the animals for prolonged periods. It is unknown whether exposing an animal with a natural life span of 2 years to a prolonged period of anaesthesia is comparable to the same length of time in a human with a natural life span of 80 years.

There exists some data suggesting a protective role for α-2 agonists (specifically dexmedetomidine). While this is controversial, it forms the basis for a number of active animal and clinical studies and could represent a future direction in anaesthesia practice. Other potential neuroprotective strategies involve agents such as xenon, melatonin and β-estradiol.[20]

Human studies

Though it is not clear when or if human infants would be potentially vulnerable to these types of effects, human infants undergo their most rapid brain growth between 28 weeks gestational age and 24 months of age. Most of the epidemiological cohort studies to date have examined children exposed to anaesthesia at <4 years of age. Some have shown an association between exposure to anaesthesia at an early age and subsequent adverse neurodevelopmental outcomes and others including twin and sibling studies have not.

One of the first studies to demonstrate an increase in learning disabilities in children receiving anaesthesia at a young age was reported in 2009 by Robert Wilder and his colleagues at the Mayo Clinic using an epidemiological cohort of approximately 5000 children from Rochester, Minnesota, who were followed from birth through their school age years.[7] They found no increase in learning disabilities in children who underwent one general anaesthetic but reported an association with increased learning disabilities in children who underwent two or more anaesthetics before the age of 4 years (figure 1). Similar findings were seen in a study examining Medicare records in New York.[21] In the subsequent 7 years, there have been numerous cohort studies examining the association between exposure to anaesthesia in early childhood and neurodevelopmental outcome. Many have found an increased risk of poor neurodevelopmental outcome following anaesthesia though several that examined overall educational achievement have not.[10] Most notable of these is the study of Bartels *et al*[22] that examined monozygotic twin pairs from the Netherlands and revealed that the intellectual attainments were similar between the anaesthesia-exposed and non-exposed twins of twin pairs. Although many of the findings in these cohort studies have been in line with the findings in preclinical data (ie, effects on learning, memory and cognition), these effects could also be related to the effects of surgery, underlying pathology, perioperative risk factors or other comorbidities and only demonstrate correlation, not *causation*. For this reason, most recent epidemiological neurotoxicity studies directly address, and attempt to control for, comorbid illness (eg, congenital heart disease) and socioeconomic factors (eg, maternal education) that are likely to impact neurobehavioural outcomes. Two recent population-

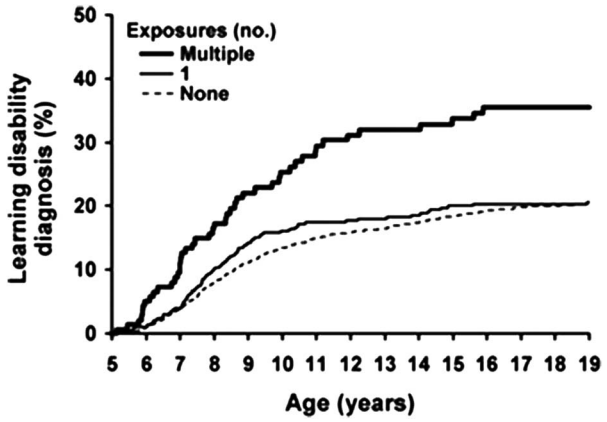

Figure 1 Graph from Wilder *et al*[7] illustrating the increased risk of learning disabilities in children with 2 or more anaesthesia exposures at <4 years.

based Canadian cohort studies examined the association between surgery in young children and a test of readiness for school (Early Development Index—EDI) and found a weak association between early anaesthesia exposure and poorer EDI. This association persisted when adjusted for age, gestational age at birth and socioeconomic factors but the increased risk was only apparent in children who were exposed to anaesthesia at >2 years of age and there was no association with exposure to multiple anaesthetics.[23] The authors speculated that this discordant data suggest that the associations seen in previous studies might be related to unknown confounders.

Within the last year, the largest cohort study to use detailed neurodevelopmental testing, the Pediatric Anesthesia and Neurodevelopmental Assessment study was published. This study of 105 sibling pairs from four different paediatric institutions compared a group of children 8–15 years of age who underwent hernia repair before 3 years of age with their closely spaced (<36 months) siblings on a number of neurodevelopmental tests with full scale IQ as the primary outcome.[24] There were no differences in performance and verbal subscales of the IQ and no differences in tests of motor speed, processing speed, visuospatial, language, attention and executive function or differences in behaviour. Anaesthesia duration ranged from 20 to 240 min with a median duration of 80 min.

There has been only one randomised controlled study that has examined the effects of different types of anaesthetic regimens and neurodevelopmental outcome. This multi-institutional study involving 722 infants from three continents randomised infants to receive either awake-regional anaesthesia or general anaesthesia for inguinal hernia repair. The primary outcome is the Wechsler Preschool and Primary Scale of Intelligence—Third Edition Full Scale IQ at 5 years of age. Though the results of the primary outcome will not be available until 2018, the secondary outcome of the Bayley-III at 2 years of age was recently published.[25] No differences were found in the two groups in the composite cognitive score adjusted for gestational age at birth. The median duration of anaesthesia was 54 min in the general anaesthesia group so this study provides preliminary evidence that exposure to a short duration of general anaesthesia does not cause significant neurobehavioural effects. A summary of the above-described studies can be found in table 3.

THE EFFECT OF ANAESTHESIA-RELATED RESPIRATORY AND HAEMODYNAMIC FACTORS ON NEURODEVELOPMENT

In recent years, there has also been increasing concern that haemodynamic and metabolic changes during the perioperative period may be detrimental to neurocognitive development. Anaesthesia is akin to a medically induced coma, and some of the recent studies examining the effects of blood pressure (BP) and carbon dioxide tension on neurocognitive outcomes in neonates may also apply to neonatal anaesthesia.

Hypotension and cerebral autoregulation in neonates

The normative values for blood pressure vary greatly depending on an infant's postmenstrual age. For full-term infants, blood pressure is generally lower on the first day of life (systolic BP=62.6 mm Hg) and increases by approximately 9% by 36 hours of age. By the end of the first week of life, the normal blood pressure for awake term infants is 71.8/50.5 mm Hg for girls and 72.7/51.1 mm Hg for boys.[26 27] Blood pressure levels increase steadily until 6 weeks of age and then remain fairly stable until 1 year of age. In the neonatal literature, hypotension is generally defined as a decrease in mean arterial blood pressure below the 5th or 10th percentile for gestational and postnatal age. The consensus statement of the Joint Working Group of the British Association of Perinatal Medicine in 1992 recommended that mean arterial pressure (MAP) should not be allowed to drop below the infant's gestational age in weeks (approximately the 10th percentile for age).[28] Others have suggested that an absolute lower limit for mean blood pressure of 30 mm Hg should be used to define hypotension in infants <30 weeks postmenstrual age.[29]

Most experts believe that maintaining mean arterial blood pressure within the limits of cerebral autoregulation is optimal for cerebral protection. For infants with open fontanelles,

Table 3 Recent studies correlating early anaesthetic exposure to neurocognitive development in humans*

Year	Study	Population	Findings	Adjustments for known confounders
2009	Wilder *et al* (Mayo Clinic)	Epidemiological cohort of 5000 children	▶ No difference in learning disabilities with one anaesthetic. ▶ Increased risk with ≥2 anaesthetics	No adjustment for comorbidities Subanalysis excluding ASA PS >3 did not change conclusion
2009	Bartels (Netherlands)	Monozygotic twin pairs	Similar intellectual attainment between twins	Most comorbidities addressed by evaluating monozygotic twins Twins <32 weeks EGA excluded
2016	Graham *et al* (Canada)	Canadian cohort	▶ Weak association between anaesthesia exposure and lower EDI but only for children exposed at >2 years ▶ No difference in EDI with multiple anaesthetics	Excluded children with developmental disabilities. Johns Hopkins Resource Utilization Bands (before GA and follow-up analysis) as covariates in mixed logistic regression models to account for severity of comorbid illness
2016	PANDA study (multicentre)	Healthy sibling pairs from multiple institutions undergoing hernia repair <3 years of age	▶ No differences in performance and verbal subscales of IQ ▶ No differences in tests of motor and processing speed, visuospatial ability, language, attention, executive function ▶ No differences in behaviour	Inclusion criteria included ASA PS 1 and 2 and EGA ≥36 weeks to exclude the confounding effect of comorbid illness
2016	GAS study (multicentre, international)	Infants undergoing inguinal hernia repair randomised to GA or regional anaesthesia (spinal or caudal block)	▶ Primary outcome at 5 years *pending* ▶ Secondary outcome at 2 years shows no difference in the composite cognitive score adjusted for gestational age at birth	Allowed infants born premature (but at least 26 weeks EGA) Excluded those with 'existing risk factors for neurological injury', including but not limited to congenital heart disease requiring surgery or pharmacotherapy, prior neurological injury and mechanical ventilation immediately before surgery

*This selection of papers represents notable papers in this field and is not intended to be exhaustive of all data.
ASA PS, American Society of Anesthesiologists Physical Status; EDI, Early Development Index; EGA, estimated gestational age; GA, general anaesthesia; PANDA, Pediatric Anesthesia and Neurodevelopmental Assessment.

cerebral perfusion pressures will vary directly with arterial blood pressures below and above the limits of cerebral autoregulation. Unfortunately, the lower limits of autoregulation in neonates are not precisely known. A study of infants undergoing sevoflurane anaesthesia showed that infants <6 months of age demonstrated a lower limit of autoregulation at 38 mm Hg, a 20% decrease from baseline MAP in the awake state.[30] In contrast, in infants older than 6 months, the lower limit of autoregulation did not occur until blood pressure had decreased 40%. These studies suggest that young infants likely have less cerebral autoregulatory reserve and may be at risk of inadequate cerebral perfusion during anaesthesia. Inadequate perfusion from hypotension can lead to partial ischaemia and can damage the watershed areas between major cerebral blood vessels. Most general, anaesthetics are associated with some degree of hypotension that is ameliorated by surgical stimulation. Anaesthesia induction can at times be associated with prolonged periods with minimal painful stimulation during placement of intravenous lines, neuraxial blocks and surgical preparation which may lead to protracted periods of hypotension.

General anaesthesia in adults is generally thought to decrease cerebral metabolic rate and therefore decrease oxygen demand. For infants, though, this may not be true. Common anaesthetic agents such as the volatile and intravenous anaesthetics are GABA receptor agonists, which are inhibitory in the mature brain but may be excitatory during brain development.[31] GABA excitation can be critical to normal neural development by enhancing synaptogenesis and other neurogenic actions. The switch from an excitatory effect to an inhibitory effect begins around the 15th postnatal week in term infants and is not complete until about 1 year of age.

A case series by McCann *et al*[32] in 2014 shed light on concerns regarding perioperative hypotension as a cause of postoperative encephalopathy. They reported on six infants who were <48 weeks postmenstrual age and developed postoperative encephalopathy consistent with intraoperative cerebral hypoperfusion. Intraoperative records revealed that most of the measured systolic blood pressure values during the procedure were <60 mm Hg. Four infants also exhibited prolonged periods of mild hypocapnia (<35 mm Hg). All infants developed new-onset seizures within 25 hours of the administration of the anaesthetic, with a predominant cerebral pathology of supratentorial watershed infarction in the border zone between the anterior, middle and posterior cerebral arteries. Follow-up of these infants found that one died, one had profound developmental delays, one had minor motor delays, two were normal and one was lost to follow-up. The authors emphasised the importance of avoiding intraoperative hypotension in vulnerable infants.

Hypocapnia and brain perfusion

The partial pressure of arterial carbon dioxide ($PaCO_2$) is an important modulator of cerebral blood flow (CBF) due to its effect on cerebral arteries. Hypocapnia causes cerebral vasoconstriction and decreased CBF and recent studies in the neonatal intensive care unit confirm the growing evidence for hypocapnia-induced brain ischaemia.[33] In a single-centre retrospective review of clinical and blood gas data in the first four postnatal days in very low birth weight neonates, infants with a maximal $PaCO_2$ value <39 had a 27% incidence of severe intraventricular haemorrhage (IVH) and those with both maximal $PaCO_2$ values >60 mm Hg and minimal $PaCO_2$ values <39 mm Hg had a 38% incidence of severe IVH. This compares with infants whose minimal and maximal $PaCO_2$ measurements were in the 'optimal' range between 39 and 60 mm Hg and had only a 3% incidence of severe IVH.[34] In a randomised trial of whole-body cooling in encephalopathic infants >36 weeks gestational age, both minimum $PaCO_2$ and cumulative $PaCO_2$ <35 mm Hg were associated with poorer outcomes.[35] In addition, hypocapnia defined as $PaCO_2$ <35 mm Hg was associated with periventricular leukomalacia in preterm infants.[36] Though capnography is a standard anaesthesia monitor, end-tidal CO_2 measurements may not correlate well with $PaCO_2$ in infants with severe lung disease or very low birth weight and capillary blood gas or arterial measurements may be necessary to prevent prolonged hypocapnia.

CONCLUSIONS

In light of the multiple animal studies in various species over the last 15 years that have shown evidence of neurotoxicity, the US Food and Drug Administration (FDA) recently released a Drug Safety Communication warning that 'repeated or lengthy use of general anesthetic or sedation drugs during surgeries or procedures in children younger than three years of age or in pregnant women during the final trimester may affect development of children's brains'. The FDA defined lengthy as >3 hours of exposure. This warning will be added to a total of 11 anaesthetic and sedative agents including all of the currently used anaesthetic agents and the benzodiazepines, midazolam and lorazepam.[37] Paediatric anaesthesiologists are committed to finding the safest ways to anesthetise and sedate vulnerable infants and have been working closely with SmartTots (http://smarttots.org), the public private partnership between the FDA and the International Anesthesia Research Society 'to coordinate and fund research with the goal of ensuring safe surgery for the millions of infants and young children who undergo anesthesia and/or sedation each year'. Until more data emerge to guide practice, it is incumbent upon all paediatric specialists to ensure that exposure to general anaesthesia is as brief as possible and that the risks and benefits are carefully weighed for all imaging studies and surgical procedures in infants.

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Notes