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Impact of anaesthetics and surgery on neurodevelopment: an update

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Editor's key points

- Robust evidence from neonatal non-primate animal models indicates increased programmed brain cell death after exposure to general anaesthesia.
- Emerging evidence from primate models confirms developmentally defined anaesthetic-induced neurotoxicity with associated neurocognitive deficits.
- Currently available retrospective clinical data are inconclusive, and the results of prospective studies are pending, making drastic changes to current paediatric anaesthesia practice premature.

Summary. Accumulating preclinical and clinical evidence suggests the possibility of neurotoxicity from neonatal exposure to general anaesthetics. Here, we review the weight of the evidence from both human and animal studies and discuss the putative mechanisms of injury and options for protective strategies. Our review identified 55 rodent studies, seven primate studies, and nine clinical studies of interest. While the preclinical data consistently demonstrate robust apoptosis in the nervous system after anaesthetic exposure, only a few studies have performed cognitive follow-up. Nonetheless, the emerging evidence that the primate brain is vulnerable to anaesthetic-induced apoptosis is of concern. The impact of surgery on anaesthetic-induced brain injury has not been adequately addressed yet. The clinical data, comprising largely retrospective cohort database analyses, are inconclusive, in part due to confounding variables inherent in these observational epidemiological approaches. This places even greater emphasis on prospective approaches to this problem, such as the ongoing GAS trial and PANDA study.

Keywords: brain, anaesthesia, molecular effects; nerve, damage (postoperative); nerve, neurotransmitters; nerve, regeneration

In this systematic review, we will update previous reviews of this topic published in the *BJA*[1–3] by describing the current weight of preclinical evidence for anaesthetic-induced neurodegeneration in the neonatal brain, along with a discussion of putative mechanisms of injury and potential adverse effects of surgery on neurodevelopment. Then, we review the clinical literature and ongoing prospective investigations that should shed further light on the potential harm of anaesthesia, surgery, or both in the neonatal period.

Preclinical studies in rodents and primates have shown that anaesthesia is neurotoxic to the developing brain after exposure in the neonatal period.[1 4–13] This neurotoxicity manifests as a pathological increase in apoptosis (programmed cell death), although other effects such as impaired neurogenesis and neuroinflammation likely also contribute. These studies randomized healthy neonatal animals to anaesthetic exposure or not; hence, a causal relationship has been established between the anaesthetic and neonatal brain injury. Furthermore, such neurotoxicity has been observed with exposure to drugs with similar mechanisms of action such as antiepileptic medications[14] and ethanol.[15] Significant concern has arisen that present medical therapies could expose neonates to neurotoxicity.

Furthermore, in some animal studies, the anaesthetic injury is associated with impaired cognition that persists into adulthood. In primates, 24 h of ketamine exposure leads to apoptosis[8] and cognitive impairment up to 3.5 yr after the insult.[10] Several rodent studies also support this assertion of prolonged cognitive compromise associated with apoptosis after anaesthetic exposure.[1 4 7 11 16] Thus, the brain injury adversely affects neurodevelopment and leads to long-term impairment in cognition, at least in animals.

The difficulties of replicating these studies in humans include the ethical obstacle of being unable to randomize neonates to having an anaesthetic or not; it is unacceptable to perform surgery without any anaesthetic and it is unacceptable to give a neonate anaesthesia for no reason.[1 11] Both these options would likely provoke greater harm than current practice.[1 11] Therefore, current clinical studies have been limited to an observational cohort design, with the incumbent issues of confounding factors. These accumulating clinical data cannot exclude a clinically important effect of neonatal and paediatric anaesthesia and surgery on cognition in later life.[17–26] While these studies have used heterogeneous retrospective approaches (with varying degrees of

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confounding effects), they provide sufficient preliminary evidence to cause concern in clinicians and parents alike.

Search strategy methods

To provide an update on the weight of preclinical and clinical evidence of harm of anaesthetics and surgery on neurodevelopment, we performed literature searches for preclinical and clinical data. J.H. performed the search for preclinical data using the search terms: an(a)esth*, neuroapoptosis, neuronal cell death, develop* brain, and neurodevelop*. The results included *in vivo* studies identified in Tables 1 (rodents) and 2 (primates). Two piglet studies were identified but were not tabulated. This search was designed to highlight the scope of the preclinical literature pertaining to anaesthetic-induced neurodegeneration in the developing brain. This search revealed an initial 4379 titles that were reviewed for relevance. Fifty-five rodent, two piglet, and seven primate studies were identified. The search for clinical data was conducted by R.D.S. using the search terms: cognitive or behavioral disorder and anaesth* with the following limits: published in the last 10 yr, humans, English, infant: birth—23 months. To be included in the systematic review, some attempt to compare an anaesthetic exposed group with a non-exposed control group was required. However, we did include studies that used population controls, even if exposure status was not defined in this population. We only included studies of anaesthesia, not intensive care sedation, and only included studies from non-cardiac non-neurological surgery in term births. Our search revealed 3727 hits and the titles were then searched for relevant studies. The reference list of relevant studies and recent reviews were also hand searched for additional studies. Our formal search results are displayed in Table 3.

Preclinical evidence for anaesthetic-induced neurodegeneration: rodent studies

After the seminal work of Jevtovic-Todorovic and colleagues[4] and Ikonomidou and colleagues,[13] numerous studies have now demonstrated that exposure of neonatal rodents to anaesthetics induces apoptosis in the developing brain (Table 1). This injury is most readily observed in the first 2 weeks of life in rodents when synaptogenesis peaks. The exact clinical correlate for this injury is unknown. Many factors influence the translation of these findings to humans, one being that synaptogenesis extends for many years post-partum in humans, suggesting that the window of vulnerability in humans may be longer.[27] Most rodent studies have also used relatively long exposures to anaesthetics, although isoflurane has been shown to induce apoptosis after exposure for just 1 h at concentrations of <1 MAC.[28] While ketamine and other *N*-methyl-D-aspartate (NMDA) antagonist drugs were initially implicated,[13] different combinations of agents have also been shown to induce apoptosis such as midazolam–nitrous oxide–isoflurane,[4] nitrous oxide–isoflurane,[29] or combinations of ketamine and thiopental or propofol.[30] Similarly, benzodiazepine drugs, such as midazolam,[31] have been shown to be toxic.

Perhaps of most significance to modern neonatal clinical practice is that all volatile anaesthetics, and propofol,[32] have been shown to induce the injury.[7 33–35] The apoptosis is widespread among central nervous system loci, with cortical, thalamic, basal ganglia, and hippocampal injury prominent; the injury is also present in the spinal cord.[4 6 7 36] Significant effects on neurogenesis have also been noted, with suppressed proliferation of neural progenitors observed for 5 days after isoflurane exposure to 7-day-old rat pups.[37] This is paralleled by effects of isoflurane[38] (but not propofol)[39] on neuronal growth in *in vitro* culture, suggesting direct effects on these progenitor cells. Neurogenesis is important for both cognitive function and particularly brain repair; therefore, the inhibitory effects of isoflurane on neurogenesis likely play an important part in the development of impaired cognition in rodents.

When long-term follow-up of neonatal anaesthetic exposure have been performed, the majority of studies have identified some cognitive impairment persisiting into adulthood. This relatively consistent finding is of particular interest, given the wide range of different tests used. Rodent studies suggest that general anaesthetics do not induce long-term motor impairment or altered nociceptive processing[6] but do impair memory function, likely through injury in both the hippocampus and frontal cortex.[4 6 7] Another study noted that anaesthetic exposure leads to behaviours that may be akin to autism;[34] this is particularly interesting as many clinical studies have focused on behavioural abnormalities rather than overt cognition. Of course, sophisticated cognitive function is difficult to test in rodents, limiting our knowledge about the exact effect on cognitive and other neurobehavioural domains. Rodent studies are also difficult to interpret due to the limited ability to control and monitor the physiology of the animal during anaesthesia. Indeed, in some of the studies, some of the newborn rodents die during anaesthesia implying that physiological control is not comparable with that in humans.

Spinal anaesthesia also exerts some neurotoxic effects (recently reviewed by Walker and Yaksh)[40] with ketamine again implicated. Intrathecal ketamine induced-apoptosis in the spinal cord was associated with abnormal gait and altered nociceptive processing.[41] Further information is needed on the effects of local anaesthetics, although recent data do not indicate harm.[36] Similarly, morphine and clonidine do not induce apoptosis when administered intrathecally to rats.[42]

In utero exposure to isoflurane also leads to apoptosis in the rat fetal hippocampus and retrosplenial cortex.[43] In a separate study, exposure to 1.4% isoflurane for 4 h during 1 day of pregnancy led to abnormal spatial memory acquisition and reduced anxiety in rats in adulthood.[44] Hence, there is evidence that the rodent fetus, like the neonates, is vulnerable to developmental neurotoxicity.

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