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Review Article

REVIEW ARTICLE

# What do recent human studies tell us about the association between anaesthesia in young children and neurodevelopmental outcomes?

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## Abstract

Anaesthetic and sedative drugs transiently disrupt normal neural activity to facilitate healthcare procedures in children, but they can also cause long-term brain injury in experimental animal models. The US Food and Drug Administration (FDA) has recently advised that repeated or lengthy exposures to anaesthetic and sedative drugs prior to 3 yr of age have the potential to harm the development of children's brains and added warnings to these drug labels. Paediatric anaesthesia toxicity could represent a significant public health issue, and concern about this potential injury in children has become an important issue for families, paediatric clinicians and healthcare regulators. Since late 2015, important new data from five major clinical studies have been published. This narrative review aims to provide a brief overview of the preclinical and clinical literature, including a comprehensive review of these recent additions to the human literature. We integrate these new data with prior studies to provide further insights into how these clinical findings can be applied to children.

**Key words:** anaesthesia neurotoxicity; neurodevelopment; paediatric surgery

Anaesthetic and sedative drugs transiently disrupt normal neural activity to facilitate medical procedures in children, but they can also cause long-term brain injury in most experimental animal models of paediatric anaesthesia exposure.[1 2] Based on a review of available evidence, the US Food and Drug Administration (FDA) recently issued (December, 2016) a safety announcement advising that repeated or lengthy exposures to anaesthetic and sedative drugs prior to 3 yr of age have the potential to harm the development of children's brains and added warnings to these drug labels.[3] Children undergo almost 3 million anaesthetics in the USA alone each year,[4 5] such that anaesthesia-related neurological injury could represent a significant public health issue. Accordingly, concern about neurotoxicity has become an important issue for families, paediatric clinicians and healthcare regulators.

Several publications have previously reviewed the aggregate animal and human data, and described the complex issues involved in interpreting this literature.[1 2 6 7] Since late 2015, important new data from five major clinical studies have been published.[8–12] The purpose of this narrative review is to provide a focused overview of the preclinical and clinical literature, with a comprehensive review of the recent additions to the human

literature, and to integrate these new data with prior studies to provide further insights into how these clinical findings can be applied to children.

## Preclinical evidence

Most experimental models have found evidence of neurotoxicity following anaesthesia exposure in infant animals,[2] but a predominant mechanistic pathway has not been identified.[1] In addition to apoptosis of neurones and glia,[13] other mechanisms implicated in the pathogenesis of paediatric anaesthesia neurotoxicity include alteration of signalling in neuroinflammatory pathways, oxygen free radical production, altered mitochondrial integrity causing acute neuronal injury[14–16] and altered neurogenesis, neurite growth, and synapse formation contributing to remodelling of neuronal circuitry and developmental dysregulation.[17] Cell age is hypothesized to be a central factor for anaesthesia neurotoxicity, and those parts of the brain undergoing neurogenesis may be particularly vulnerable to the deleterious effects of anaesthesia.[18] Because of regional heterogeneity of continued neurodevelopment throughout childhood,[19] there is also the potential for regional heterogeneity in vulnerability to neurotoxic effects that could change with age.[20] This raises the possibility that the phenotype of anaesthesia-related neurotoxicity may depend on the age of exposure, and that neurotoxic effects could occur outside of periods of peak brain development in early childhood.[21] Not unexpectedly, a range of neurological deficits after anaesthesia exposure have been described using experimental models, including cognitive deficits and delayed learning, impaired memory formation and retention, and altered motor and behavioural development.

Experimental animal models have the important advantage of studying the effects of anaesthesia in the absence of surgery. However, translation of these models to humans can be difficult due to differences in brain development trajectories, developmental age at exposure, neuronal structure, and equipotency of anaesthetic drugs administered to animals of different lifespans and species. Non-human primate models of anaesthesia neurotoxicity mitigate many of these issues, are regarded as being most translatable to humans, and have provided histological and functional evidence supporting the plausibility and potential significance of anaesthesia neurotoxicity in humans.[22–24] Two recently published non-human primate studies that examined the effects of exposure to volatile anaesthetics on behavioural development are especially notable.[25 26] Raper and colleagues[25] found that infant rhesus macaques exposed repeatedly to sevoflurane (three exposures of 4 h each) had increased anxiety-related behaviours at 6 months of age compared with unexposed controls. Consistent with these results, Coleman and colleagues[26] found that infant macaques exposed repeatedly to isoflurane (three exposures of 5 h each) had motor reflex deficits at one month of age compared with unexposed controls, and exhibited increased anxiety in response to novel social environments at 12 months of age. There was evidence of changes in some assessed parameters for a separate group of macaques receiving a single 5 h exposure to isoflurane, but these did not reach statistical significance.[26] Both of these studies support the concept that repeated exposure to general anaesthesia can have long-term behavioural consequences in primates, although both employed durations of anaesthesia exceeding those typically seen in most children.

## Clinical evidence

### Prior literature

Several observational clinical studies published prior to 2016 investigated the association between childhood exposure to general anaesthesia for surgical procedures and neurodevelopmental outcomes. These results have been summarized in several reviews.[27–30] In general, those studies that have investigated associations between select neurodevelopment or academic outcomes and multiple exposures to procedures requiring general anaesthesia (in children aged less than 2–4 yr) find significant associations.[31–34] Studies that examined single exposures or did not distinguish between single and multiple exposures are less consistent; some found impairments in a range of domains[35–40] whereas others did not find evidence of adverse outcomes.[41–45] Although these findings are often characterized as 'conflicting,' these retrospective observational studies use a multiplicity of study designs and outcomes, which are usually repurposed (i.e. primary data collection was not performed for the purpose of examining anaesthetic effects) and dictated by the types of available data sources. Thus, it is difficult (and perhaps unwise) to attempt evidence synthesis using this heterogeneous group of both 'positive' and 'negative' studies. For example, and also as noted by others,[46] some outcomes (e.g. academic achievement) lack sensitivity to detect or accurately describe phenotypes of anaesthesia neurotoxicity. Of these earlier studies, only the repurposed Western Australia Pregnancy (Raine) Cohort used direct neurodevelopmental assessments, finding that children who underwent general anaesthesia before 3 yr of age were more likely to have select deficits in language and cognition (abstract reasoning) compared with unexposed children.[37 46]

Given the existing heterogeneity in findings, the following five new major clinical studies published since late 2015 are important additions to the literature.[8–12]

### GAS study

The interim results of the GAS (General Anaesthesia compared to Spinal anaesthesia) study were published in late 2015.[8] Although primary outcome data [intelligence quotient (IQ) at 5 yr] will not be reported until 2018, this is a landmark study in the investigation of anaesthesia neurotoxicity as it represents the first, and thus far only, randomized clinical trial in the field. This multicentre equivalence randomized controlled trial conducted across 26 countries compared the effect of awake-regional *vs* sevoflurane anaesthesia on neurodevelopmental outcomes for 722 infants who were less than 60 weeks post-conceptual age at the time of inguinal hernia repair. Prespecified interim neurodevelopmental outcomes were assessed at 2 yr of age using the Bayley Scales of Infant and Toddler Development III,[47] which has good psychometric properties and is frequently considered the gold standard for neurodevelopment assessment.[48] For cognitive composite score, there was no difference between groups ($98.6 \pm 14.2$ *vs* $98.2 \pm 14.7$ in awake-regional and general anaesthesia groups, respectively) using a per-protocol analysis. While there were some instances of cross-over between groups and loss to follow up, this finding was quite robust in several sensitivity analyses, and the overall conduct and reporting of the trial were exemplary. As acknowledged by the authors, more subtle deficits may not be reliably assessed due to instability of developmental trajectories in young children and the potential for intra-individual variability when testing.[49] In addition, the Bayley-III conducted at younger