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Editorial

Anesthetic-induced neurotoxicity of the neonate: time for clinical guidelines?

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By now most pediatric anesthetists will be aware of the issue of possible neurotoxic effects of general anesthetics on the developing brain. The subject is regularly discussed in editorials, reviews, and conference meetings. It is also being raised in the lay press. Parents are understandably concerned about the effects of any drugs on their newborn or unborn child. Is it time to go further and develop clinical guidelines based on the available evidence? Some recommendations have indeed already been made. In 2007, the Federal Drug Administration (FDA) anesthetic and Life Support Drugs Advisory Committee released minutes suggesting that surgery that was truly elective should be postponed until after 6 months of age. This was based on concerns about the neurotoxic effects of anesthetics on neonatal animals (1). An editorial in 2008 built on these remarks stated: 'Until the risk of neurocognitive injury is understood, pediatric surgical specialties, in conjunction with anesthesiologists and pediatricians, should identify surgical procedures that can be delayed until older ages *without incurring additional risk*'(2). Are these recommendations sufficient, or should more concrete clinical guidelines be developed?

The above recommendations suggest surgery be delayed provided it is either elective, or the delay incurs no added risk. A key question in implementing this recommendation is how long should surgery be delayed. Also, it only applies to the relatively uncommon scenario of the truly elective case that can be postponed indefinitely. It is already recognized that anesthesia in the neonate is technically challenging, and that neonatal anesthesia poses greater risk than anesthesia in older children. This is for many reasons apart from neurotoxicity (3,4). In consequence, truly elective surgery tends not to be performed in infants; infants have surgery or anesthesia because they need it, and therefore, any delay usually incurs some risk. For clinical guidelines to have any practical value, they must address the scenarios where delay is unavoidable or delay has some risk. To develop guidelines for these cases, additional questions must be answered: what is the actual risk of general anesthetic exposure, which infants are most at risk, and which anesthetic techniques have least risk? Additionally, are there any safe and effective protective agents that can be used? If these questions can be answered, the degree of risk of exposure in a particular infant can be balanced with the risk of delay, and alternate anesthetic techniques or protective strategies can be suggested.

Thus, the five key questions that must be answered to develop practically useful clinical guidelines are:

1. What is the degree of risk in terms of likelihood and magnitude?
2. At what age does the risk of exposure become negligible?
3. Apart from age, what other patient factors influence risk?
4. To what extent can different anesthetic techniques, agents, and dose influence risk?
5. Are there protective agents that can be used?

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Given the animal and human data, how close are we to getting answers?

Preclinical studies of anaesthetic-induced neurotoxicity in the developing brain

In the decade, since the discovery that N-methyl-D-Aspartate (NMDA) antagonists induced apoptotic neurodegeneration in the neonatal rodent brain (5), numerous studies have repeated this finding (6,7). A similar injury has been observed in the monkey brain with ketamine treatment, albeit only after a longer exposure than seen in the rodent and only in the neonatal and preterm time period (8). Whether or not monkeys are similarly vulnerable to other drugs such as the volatile anesthetics is a focus of ongoing research, and this will prove a critical step in the investigation into this field. The volatile anesthetics, isoflurane (9) and sevoflurane, (10) and intravenous agents, propofol (11), ketamine (12), midazolam (12), diazepam (13) and thiopentone (14), have all induced this injury in some situations in rodents. This effect does not appear dependent on disruption of systemic physiology (6,7,9,15,16), and this direct brain injury occurs in a dose-dependent manner with longer duration, larger concentrations, and combinations of agents all producing greater injury (9,15). Anesthetic administration to neonatal rodents is associated with long-term impairments in cognitive function with impaired learning and memory later in life (9,10,16), but available evidence suggests that motor and nociceptive systems are not affected (17).

These studies show a remarkable class effect of anesthetics in producing this injury. However, the exact mechanism of injury is still to be determined. Although preliminary evidence suggests that the $GABA_A$ receptor is not responsible for the anesthetic injury (16) [perhaps in keeping with an excitatory rather than inhibitory role of this receptor in the young (18)], the induction of apoptosis by a wide range of anesthetics still suggests that the mechanisms of anesthesia and neurotoxicity may overlap (6). In this regard, the NMDA receptor remains a prime suspect for the toxicity, although other targets such as potassium channels and intracellular effectors may also prove to be involved (6).

The preeminent hypothesis for the mechanism of injury is related to the depression of synaptic neurotransmission (9,19), with consequent suppression of neurotrophic signaling and death of the postsynaptic neuron. If true, this mechanism has critical importance as it suggests that anesthesia may induce the apoptosis regardless of agent involved. While electrophysiological evidence of reduced synaptic activity has been known for many years, anesthesia predominantly relates to a postsynaptic phenomenon (20). However, a recent study has demonstrated that in the anesthetized state, reduced tissue plasminogen activator (tPA) release from the presynaptic terminal in the presence of isoflurane prevents the tPA-dependent conversion of pro-Brain Derived Neurotrophic Factor (pro-BDNF) to its mature form, BDNF, in the synaptic cleft (21). BDNF would usually act to maintain neuronal survival, however if pro-BDNF is not converted to BDNF, the increased levels of pro-BDNF instead triggers cellular apoptosis by binding to a type of cell death receptor termed the p75NTR receptor. Thus, suppression of neural activity triggers apoptosis by preventing the presynaptic release of tPA that would activate BDNF neurotrophic signaling to maintain cell survival. The neurotoxic effects of anesthetics also appear to go beyond apoptosis with other forms of injury, delayed neurogenesis and altered neuronal dendritic spine development, recently detected in young animals (22). These injuries are associated with the development of cognitive deficits in other animal models, therefore, the window of vulnerability for anesthetic toxicity maybe much wider than previously anticipated.

Reduced synaptic activity is a central tenet in anesthesia, so what could be done to minimize or reverse this injury? Pharmacological manipulation of the BDNF pathway with TAT-P5 to prevent signaling through the p75NTR receptor has been suggested (21). Several other interesting approaches have been advocated. Ma et al. (15) recently showed that xenon reduces the injury induced by isoflurane demonstrating prominent cortical protection (which appears the most vulnerable brain region in the primate); however, as yet functional studies assessing whether this translates as improved cognition in later life have not been performed. In a second study, xenon was associated with a minor degree of apoptosis but still provided significant neuroprotection against isoflurane injury (23). We have also shown that dexmedetomidine reduces the isoflurane

injury in a dose-dependent manner and improves the neurocognitive deficit induced by isoflurane (16). Dexmedetomidine did not produce toxicity even when given at a dose that is 75 times the hypnotic dose in neonatal rats. Other neuroprotective strategies include the use of melatonin (24), lithium (25), carnitine (26), and erythropoietin (27). Whether these latter strategies or xenon can induce functional protection and prevent the long-term deficits induced by isoflurane remains to be tested. Interestingly, many of these drugs activate similar cell survival signaling cascades including the extracellular-regulated kinase and protein kinase B/AKT pathways; therefore, there is both the opportunity to look for synergism with combination strategies and to develop drugs working through alternate mechanisms. In summary, there are promising protective agents but these are still in early preclinical stages of assessment; not enough evidence to warrant inclusion in any guidelines.

What about other anesthetic techniques? There is very little data examining the effect of regional anesthesia or opioids on the development of the central nervous system. In theory, if toxicity is related to activity then regional anesthesia should not affect the cortex, as apart from sleep, the cortical activity is not diminished. Regional anesthesia may, however, significantly reduce activity in the spinal cord. Thus, from an understanding of the mechanisms of toxicity, it is reasonable to suggest that regional anesthesia would not induce the same degree of neurotoxicty in the cortex; however, there remains a nagging worry about possible toxicity to the spinal cord (17). Investigation of whether opioids also induce apoptotic injury is important, given the prevalence of opioid-based sedation in the neonatal intensive care unit as well as the perioperative use of opioids for analgesia.

In the clinical situation, infants are rarely exposed to anesthesia in isolation. There are many other factors that could interact with any neurotoxicty. These include the influence of surgical stimulation, pain or inflammation (6). Extensive evidence suggests that inadequate anesthesia or untreated pain induce significant long-term detrimental effects (6,28). Hypercarbia has also been associated with neuronal apoptosis in neonatal animals (29). Therefore, the effects of hypercarbia superimposed on anesthesia need attention especially with the increasing incidence of laparoscopic surgery in the neonate. Most preclinical studies have not assessed the potential effect of these factors, that coincide with anesthesia in the clinical setting, on outcomes. These differences between the preclinical models and the clinical setting further inhibits direct translation of preclinical data to clinical anesthesia and hence to clinical guidelines.

In summary, the preclinical data suggest changes are seen after most commonly used general anesthetics. There is some evidence for some long-term effect, some dose effect, and a window of vulnerability. However, many of these data are still confined to rodent studies, and the translation of dose and timing to humans is too imprecise to form a basis for any guidelines on magnitude of risk, time of risk, or who is at risk. Similarly, there is also some evidence to suggest some agents could be better than others and that some agents may be protective; but still there is insufficient evidence to form the basis of any clinical guidelines for choice of agent.

Clinical studies of anaesthetic-induced neurotoxicity in the neonate and young child

Loepke and Soriano (30) recently reviewed the evidence linking exposure to anesthetics and neurocognitive function in children. They considered a variety of studies that have followed children after surgery and concluded 'anecdotal data point toward the possibility for neurological impairment after neonatal surgery and anesthesia'. Since publication of that review, five further important and relevant cohort studies have been published. While the impact of surgery continues to confound the association between anesthesia and outcome, these studies do provide valuable information.

Wilder et al. (31) probed medical records retrospectively, looking at surgeries performed before 4 years old and found evidence for an association between having two or more anesthetics before the age of 4 and increased risk of learning disabilities. This risk of learning difficulties increased with the number of anesthetics. At first sight, this may appear to be a dose response for anesthesia; however, it may also be explained by the confounding influences. Children with significant illness and chronic conditions are more likely to need surgery, the greater the

illness, the more surgeries they require and perhaps the greater the learning disability. Some may be reassured that no evidence was found for any association between a single exposure and any learning disability. However, first, the outcome measure may still have missed subtle neurocognitive deficits [as have been revealed for adult postoperative cognitive dysfunction (32)] and secondly, the study cannot exclude an effect seen with exposure in the neonatal period (where preclinical data may suggest the effect is most likely).

In a small retrospective pilot study, Kalkman *et al.* (33) explored the feasibility of studying neurobehavioral development in children who had been exposed to anesthesia for urological surgery. Not surprisingly, in their small sample they found no strong evidence for an association between anesthesia and outcome and concluded a larger study, requiring at least 2000 children, could be feasible.

In a large Dutch twin study, Bartells *et al.* (34) recently demonstrated no evidence for an association between exposure to anesthesia before age 3 and later educational achievement However, like the study by Wilder *et al*., they may have missed a more subtle effect and an effect seen only in subgroups such as neonates.

Di Maggio *et al*. (35) surveyed the incidence of behavioral and developmental disorders in children who had hernia repair under 3 years of age compared to a control cohort of children. In contrast to the other studies, children who had hernia repair were twice as likely to develop a behavioral and developmental disorder. However, as the authors concede, unmeasured confounders hinder definite conclusions from this work with the known confounders of the pathology and surgical procedure still present.

Sprung et al. (36) assessed the impact of obstetric anesthesia on learning disabilities in children up to 5 years of age. They found no evidence for a difference in risk of learning difficulties between those delivered by cesarean delivery with general anesthesia compared to vaginal delivery, but unexpectedly, they did find that children born by cesarean delivery with regional anesthesia had a lower risk of learning disability compared to other modes of delivery. Although this may provide some reassurance that brief exposure to general anesthesia is not associated with learning disability, the authors acknowledge that there are many possible confounding factors and that like other studies, more subtle disability may be missed.

The retrospective cohort design of these epidemiological studies is confounded by known and unknown factors, and by the influence of the pathology and possibly the surgery itself. In spite of the limitations, recent clinical studies do provide some weak evidence to suggest a single exposure in children is not associated with substantial learning disability. However, they do not provide much evidence to help identify risk in terms of age of exposure, agent used, or dose given. Critically, they do not exclude injury in subgroups such as neonates.

Should we provide clinical guidelines?

From the above can we produce more concrete clinical guidelines?

1. *Is there any risk in humans?* We know anesthesia-induced neurotoxicty is a real phenomenon in young rodents. We know some children having surgery have a poor outcome, but we still do not know for sure if this is actually anything at all to do with the anesthesia. Thus, we can start by saying we have not ruled out neurotoxicity being clinically relevant in humans.
2. *What is the magnitude of risk? What factors increase the risk and up to what age should surgery be delayed?* Recent clinical studies suggest major disability is unlikely with brief exposure in an older child. If any major effect was to be seen, it would have to be in a subpopulation (such as the neonate), or with longer than brief exposure, but we have insufficient evidence to further define any at-risk subgroups. There is no clinical evidence to guide us on the risk of subtle disability. To date, preclinical studies are also largely unhelpful in identifying the children at greatest risk. Like clinical studies, there is some evidence to suggest that younger ages may be more at risk and the longer the exposure may increase the risk, but the issues of translation between the animal studies and children are too poorly defined to make firm clinical guidelines. As we are unsure of the age when exposure is relevant, we cannot provide any firm recommendation on how long surgery should be delayed.

3. *Is one agent or technique better?* While there is preclinical data to suggest this may indeed be so, no clinical data have emerged to support this. At best, if all else is equal, then we could recommend using agents that have not been found to produce neurotoxicity in preclinical studies. However, given the lack of clinical evidence, the treating anesthetist would have to be sure that the choice of agent has no added risk in any other aspect of the child's anesthetic. If the experience with the other agents is limited, it is hard to be so assured.
4. *Should we limit the dose?* There is some evidence for a dose effect in preclinical studies, but as mentioned before, translating animal data is difficult. There is considerable evidence that pain is associated with poor outcome (6,28). Similarly, inadequate anesthetic dosing may increase the chance of complications of light anesthesia. Lastly, there is some, albeit mixed, evidence to suggest anesthesia can modulate the stress response, improving outcome (6,28). All this suggests there should be no recommendation to limit the dose given.
5. *Are there any protective strategies?* While there is promising preclinical work, this would need to be tested in human trials before inclusion in any guidelines.

In conclusion, at this stage there is insufficient evidence to produce any firm clinical guidelines. Unfortunately, clinicians must continue to be guided by the rather vague statements already produced by the FDA or Davis & McGowan. We agree that the timing of anesthesia and surgery in the young needs appraisal. Clinicians should identify and delay surgical or investigational procedures that require anesthesia, provided that any delay does not incur additional risk. If delay does incur the reasonable possibility of added risk, then anesthesia and analgesia should be administered according to the current best practice at that institution.

There is a considerable amount of research underway addressing the issue of neurotoxicity. These are difficult questions to answer, and no single study is likely to provide the definitive answer; however, as more results appear, we shall inch closer to being able to generate more detailed evidence-based clinical guidelines. At this stage, no, it is not yet time for clinical guidelines.

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