

Anesthetic Agents and the Immature Brain: Are These Toxic or Therapeutic?

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ABOUT 1.5 million fetuses or newborns are exposed to anesthetic agents each year.¹ After their initial report in *Science*² suggesting that anesthetic drugs such as nitrous oxide, ketamine or other *N*-methyl-D-aspartate receptor antagonists lead to enhanced apoptosis in immature neurons, Olney *et al.* have reported that newborn rats exposed to commonly used anesthetic agents (isoflurane, midazolam, and nitrous oxide) also develop neurodegenerative changes in multiple areas of the brain, associated with long-term deficits in learning and memory.³ The same investigators have reported similar neurodegenerative changes in rat pups exposed to other anesthetic agents, anticonvulsant drugs, or ethanol^{2,4-7} and voiced their "concern that agents used in pediatric and obstetrical medicine for purposes of sedation, anesthesia, and seizure management may cause apoptotic neuronal death in the developing human brain."⁵ This has led to public outcry over the long-term effects of anesthesia or sedation given to pregnant women or to newborn infants requiring surgical operations after birth.⁸⁻¹³ Calls for avoiding these agents in newborns raises the specter of surgical procedures being performed with minimal or no anesthesia, as was routine practice 20 years ago.¹⁴

Accumulating data on the development of the pain-responsive¹⁵⁻¹⁹ and stress-responsive²⁰⁻²² systems in the developing brain, together with increases in stress responses, morbidity, and mortality in lightly anesthetized neonates,²³⁻²⁵ have led to the routine use of anesthesia and postoperative analgesia even for critically ill new-

borns.^{26,27} Are the findings of Olney *et al.* significant enough to withhold anesthesia from neonates undergoing surgical operations or other invasive procedures? This issue needs to be addressed urgently, especially as no clinician would like to withhold anesthetics during a surgical procedure nor would any wish to expose their neonatal patients to potentially neurotoxic drugs.

Anesthetic Agents and Neurodegenerative Mechanisms

Brain development in preterm and term neonates is characterized by naturally occurring neuronal death by apoptotic mechanisms.²⁸⁻³⁰ The cellular expression of regulator protein Bcl-2 and effector enzyme caspase-3 appear to mediate the increased vulnerability to neuronal apoptosis in the immature brain,^{31,32} which affects more than 50 percent of cortical neurons after 28 weeks of human gestation.²⁸ An increased vulnerability to apoptosis is not limited to neurons but extends to immature oligodendroglia and astrocytes as well, particularly following free radical injury.^{33,34} Immature neurons are also susceptible to excitotoxic damage because of an increased magnitude of ligand-gated calcium currents mediated *via* excitatory *N*-methyl-D-aspartate receptors,³⁵⁻³⁷ ultimately leading to neuronal excitotoxic damage.^{38,39}

Accentuated neurodegenerative mechanisms in the immature brain thus increase neuronal susceptibility to various metabolic events (hypoglycemia, hypoxia, infection, ischemia, seizures) or exposure to anesthetic agents.⁴⁰ Anesthetic and anticonvulsant drugs that block *N*-methyl-D-aspartate receptors (*e.g.*, ketamine) or activate γ -amino butyric acid-type A receptors (*e.g.*, midazolam) consistently increase neuronal apoptosis in the neonatal brain,²⁻⁷ suggesting that the physiologic stimulation of *N*-methyl-D-aspartate receptors is necessary for neuronal synaptogenesis, differentiation, and survival during development. Lack of *N*-methyl-D-aspartate receptor activation by glutamate decreases synaptogenesis and cell-to-cell interactions.^{41,42} Anesthetic agents directly suppress neuronal activation and also reduce extracellular concentrations of excitatory neurotransmitters,⁴³ thereby reducing the developmental inputs to immature neurons.

In evaluating the clinical relevance of these findings, we must consider the major differences in complexity and adaptability between human and rodent brains and also the developmental differences between neonatal

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rats and humans.^{44,45} Additional methodological issues to be considered before extrapolating these results to neonatal anesthesia in humans include (a) a prolonged duration of exposure to anesthetic agents; (b) the nutritional and metabolic needs of neonates receiving general anesthesia; (c) the routine use of continuous respiratory, hemodynamic, and other forms of monitoring and support during anesthesia; (d) dose-related effects of certain anesthetic agents; and (e) divergent effects of anesthetic drugs given in the presence or absence of surgical pain or stress. Each of these issues is discussed below.

Duration of Exposure to Anesthetic Drugs

Neurodegenerative changes in the developing brain occurred following prolonged exposure to anesthesia in neonatal rats,^{2,6} confirming earlier findings from exposure to halothane or *N*-methyl-D-aspartate receptor blockade.^{46,47} From a developmental perspective, this duration of exposure would be equivalent to producing general anesthesia for several weeks in the human neonate,⁴⁴ which occurs rarely, if ever, in the clinical setting. Repeated ketamine injections increase neuronal cell death in multiple areas of the neonatal rat brain and lead to a significant decrease in weight gain.⁴⁸ Rat pups receiving ketamine for 6–9 h exhibited poor feeding behavior and increased neurodegeneration, whereas single doses of ketamine did not affect weight gain or neuronal cell death. These studies suggest that prolonged exposure to anesthetic drugs may be an essential factor in this phenomenon.⁴⁸ Although recent data presented at the annual meeting of the American Association for the Advancement of Science on February 14, 2004⁴⁹ suggest that brief exposure to alcohol or anesthetic drugs may also trigger two- to fourfold increases in neuronal apoptosis,⁵⁰ it remains unclear whether these neurons would have died at later developmental stages and whether these transient increases in neuronal apoptosis have any long-term consequences.

Effects of Malnutrition on the Immature Brain

Rodent pups do not suckle during or after general anesthesia. Decreased weight gain following prolonged ketamine anesthesia points to the role of nutrition in early brain development.⁴⁸ Clinical and experimental research have linked malnutrition to decreased brain growth and learning disabilities,^{51–53} although Olney *et al.* do not report the nutritional support given or weight gain data from their experiments.^{2–7} The identification of milk in the gastric contents of neonatal rat pups does not imply adequate nutrition because both general anesthesia and breast milk significantly delay gastric emptying in neonates.⁵⁴ Human neonates routinely receive nutritional support and metabolic monitoring in the perioperative period, thus minimizing the risks for hypoglycemia and impaired nutrition.

Anesthesia and Cerebral Oxygen Delivery

Anesthetic drugs suppress brain activity but also depress circulation and respiration in a dose-dependent manner, leading to decreased cerebral perfusion and hypoxia. Administration of anesthetic drugs to human neonates is accompanied by continuous monitoring of blood pressure, heart rate, and oxygen saturations, with multiple therapies aimed to optimize these parameters. Hypoxia and ischemia during prolonged anesthesia could easily trigger widespread neurodegeneration in the immature brain,^{55–57} given the lack of similar monitoring or support in newborn rat pups.^{2–7}

Dose-Related Effects of Anesthetic Agents

Anesthetic drugs also have dose-dependent cellular effects. For example, ketamine acts as an antiinflammatory agent at subanesthetic concentrations (0.1–0.5 $\mu\text{g}/\text{ml}$),^{58,59} whereas higher concentrations (50–200 $\mu\text{g}/\text{ml}$) produce a nonspecific cytostatic effect.⁶⁰ High doses of ketamine may also promote seizures,⁶¹ a property shared by other anesthetic agents.⁶² The ketamine doses used by Ikonomidou *et al.*² (140 mg/kg) would be expected to produce cytostatic or epileptogenic effects in neonatal rats, which may significantly contribute to the neuronal apoptosis^{63,64} reported in these studies.

Anesthesia With and Without Painful Stimulation

Prolonged anesthesia produces a loss of developmentally important sensory inputs during this critical window, a condition that is perhaps not dissimilar from maternal separation.⁶⁵ Repetitive pain and maternal separation in newborn rat pups lead to long-term changes in behavior,^{20,66,67} some of which are prevented by analgesic therapy.^{68,69} These data suggest that the long-term effects of analgesic/anesthetic drugs would depend on whether they are given in the presence or absence of painful stimulation. The clinical use of anesthetic agents occurs during painful stimulation, but Olney *et al.* administered anesthesia without any painful stimulation. Based on the neuronal stimulation hypothesis,⁴² we speculate that painful stimuli during surgery activate *N*-methyl-D-aspartate and other excitatory receptors in the immature brain and that therapeutic doses of anesthetic drugs will reduce extreme degrees of neuronal excitation.^{40,70} Thus, the effects of surgery without anesthesia as well as the effects of anesthesia without surgery may be detrimental to the developing brain. Clinical extrapolation from these rodent models^{2,5,6} requires that the experimental conditions should be similar to those associated with surgical anesthesia in human neonates.

Consequences of Withholding Anesthesia/Analgesia

In addition to humanitarian concerns, multiple lines of evidence support the necessity of adequate anesthesia in term or preterm neonates undergoing surgery. Short-

term consequences of withholding anesthetic agents during neonatal surgery include an increased incidence of intraoperative and postoperative complications,^{23-25,71} leading to poor surgical outcomes.⁷¹⁻⁷⁵ Long-term consequences of repetitive and prolonged pain in the neonatal period include prolonged changes in pain sensitivity and pain processing,⁷⁶⁻⁷⁹ as well as a variety of neurodevelopmental, behavioral, and cognitive deficits manifesting in later childhood.^{40,74,80-82} The evidence for improved clinical and developmental outcomes highlighting the importance of adequate anesthesia and pain control in the surgical neonate continues to mount, which must be weighed carefully against the recent experimental data showing the neurotoxic effects of anesthetic agents.

Conclusions

There is no doubt that prolonged exposure of newborn rat pups to anesthetic and anticonvulsant drugs leads to accelerated neurodegeneration and long-term behavioral deficits. Similarly, preterm and term neonates subjected to prolonged pain and surgical stress are also at risk for long-term adverse outcomes. Further investigations in this area may consider an experimental design in which the neurobiological and clinical effects of anesthesia with and without surgery are compared to increase its relevance to the clinical situation. Clearer understanding of the mechanisms by which exposures to pain/stress or prolonged anesthesia in the perinatal period can alter the survival or development of immature neurons and glia may prevent some long-term neurobehavioral abnormalities in humans. In the meantime, clinicians should administer anesthetic agents to newborn infants or pregnant mothers but avoid prolonged periods of anesthetic exposure. The experimental findings of Olney *et al.* are certainly sound but it may be premature to apply them to clinical settings at this time. Alleviation of pain and stress during the perinatal period should remain an essential clinical goal until further research defines the clinical importance of these results.

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