Volatile Anesthesia for the pediatric brain: friend or foe?

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The story of volatile anesthetics being "friendly" for the brain originated many years ago with the observation that anesthetized patients seemed to experience minimal or no neurologic injury after cardiac arrest. In the ensuing years, animal cerebral ischemia models were studied to evaluate volatile anesthesia neuroprotection. (1) Although cardiac arrest rarely occurs in pediatric anesthesia, cerebral ischemia does occur during cardiac and cerebrovascular surgery, and the role of volatile anesthesia for these procedures should be clarified in light of recent data.

The story of volatile anesthetics being a "foe" for the brain began recently. A study in neonatal rats found these drugs to produce massive cell death in certain brain regions along with later learning impairment. (2) Despite years of seemingly safe use, the role of volatile anesthesia for neonatal surgery should now be clarified in light of this study.

My presentation will review the evidence for neurological protection and neurological toxicity and offer a rationale use for volatile anesthesia in pediatrics.

Is volatile anesthesia brain friendly?

Cerebral ischemia elicits many biochemical reactions during the ischemia and early reperfusion. These reactions damage the brain cell mitochondria, membranes, nucleus, and endoplasmic reticulum, which are usually triggered by excessive intracellular calcium from the energy failure that occurs during ischemia.

During energy failure, glutamate released from the neuronal vesicle binds to NMDA and AMPA receptors bringing calcium, sodium, and water into the cell. Moreover, energy failure also enables calcium to leak from intracellular stores (e.g. lysosomes, endoplasmic reticulum) through voltage gated calcium channels (e.g. L-type, Ca^{+2}-H^{+} exchange). Calcium in turn activates proteases, DNAases, and lipases to damage cell membranes, DNA, and proteins. As a result, the cell membranes leak, and the cell cannot generate sufficient ATP to restore homeostasis or synthesize protein to repair the damage.

The duration of the energy failure determines cell fate: fast death, delayed death, or repair (recovery). (3) In prolonged ischemia, sufficient water will enter the cell through the leaky membranes to cause swelling and rupture, spewing cellular contents into the extracellular space, which in turn induces secondary inflammation and further neuronal membrane damage, producing a vicious cycle. This "fast" cell death, known as necrosis, becomes

apparent within a few hours and may continue for a few days after reperfusion. Importantly, although oxygen may return to the tissue (reperfusion), the organelles have been damaged sufficiently that necrosis will occur anyway. In particular, damage to the endoplasmic reticulum and mitochondria inhibit the protein and energy synthesis needed to repair the cell.

In brief ischemia, the organelle damage is less extensive and the cell does not accumulate sufficient water to rupture. (3) With reperfusion, the cell is able to utilize oxygen and cellular energetics is restored, along with transcription and translation capability. However, the organized, higher end synaptic and plasticity functions remains impaired, leaving the cells in a "hibernating" condition. After a time, the cells will either be able to repair themselves and recover, or they will die by a process known as apoptosis. In apoptosis, the cells set in motion a complex "suicide" program requiring expression of genes, synthesis of proteins, and activation of pro-enzymes which break apart the DNA and cytoskeleton into membrane bound bits to be engulfed by resident macrophages. There is no secondary inflammation with apoptosis. The apoptosis-recovery phase following reperfusion lasts from days to months so that the full extent of the ischemic damage is not known for some time.

Developmental status, brain region, and cell type also influence cell fate following ischemia. (3) In the immature brain, the apoptosis program is particularly strong, such that following ischemia, neurons tend to die by apoptosis rather than necrosis. The brain contains many types of cells, including neurons, astrocyte, microglia (macrophages), oligodendricyte, endothelial cells, and smooth muscle cells. Neurons and oligodendricyte are especially vulnerable to ischemic cell death in the immature brain. Not all brain regions are equally susceptible to damage. In the immature brain, neurons and oligodendricyte in the neocortex, basal ganglia, and hippocampus are selectively vulnerable, whereas those in other areas are more resistant. (3,4)

Recent research has also shown the importance of the pre-conditioning environment to outcome following ischemia. (5,6) The pre-conditioning period is the time immediately before the onset of the ischemia. Studies have shown it is possible to make the brain more resistant to ischemic damage by conditioning it beforehand. Conditioning agents include spreading depression (seizure), hypoxia, brief ischemia, and certain drugs. In the brain, the conditioning agents appear to confer protection through the induction of certain genes and proteins.

Volatile anesthetics have been shown to block NMDA, AMPA and several voltages gated calcium receptors and to ameliorate intracellular calcium levels during ischemia and reperfusion. (7-10) Volatile anesthetics have also been shown to increase tissue oxygen during ischemia. (11) Given these mechanisms, in-vivo studies have administered volatile anesthetics in the ischemic and early reperfusion phases to look for neurologic protection.

To my knowledge, there have been 25 studies that have evaluated volatile anesthesia in survival animal models using neurologic function and histology as outcome endpoints. Most have been in the past 5 years. Of the models, 22 are in adult rat, 1 in adult dog, and 2

in newborn pig. All the volatile agents have been examined, varying in doses, ranging from 0.5 to 2 MAC (most were 1-1.5 MAC). In 21 studies, the agent was administered before, during, and immediately after the ischemia. In 3 studies, it was administered for a few hours at least one-day before the ischemia (pre-conditioning paradigm). In one study, it was administered during reperfusion only. The models included 7 focal ischemia and 16 global ischemia. In one adult rat study, hypothermic CPB was used. In the newborn pig studies, (11,12) one used CPB with deep hypothermic circulatory arrest and the other low-flow CPB. Volatile anesthesia groups were compared against no anesthesia (conscious) or opioid based anesthesia groups. Of the 21 studies administering the drug during the ischemia and early reperfusion, 18 found neuroprotection. In 2 of the studies not finding it, brain temperature was not controlled, confounding its validity. Both pre-conditioning paradigm studies found neuroprotection. The one study administering the agent during reperfusion only did not find protection.

Although the evidence for volatile anesthesia neuroprotection is very good, it is important to keep a few points in mind. First, the potency of the protection is not strong; it is equivalent to about 2^{o}C of hypothermia. (13) However, the protection is additive to that provided by hypothermia. (11,12) Second, the dose is uncertain, although it looks like 1 MAC or greater is needed during the ischemia and early reperfusion. Giving it after the fact does not work. Third, the role of pre-conditioning is unclear. The 2 pre-conditioning paradigm studies found neuroprotection, and all the other studies finding neuroprotection also administered it during the pre-conditioning period. Thus, it is possible the agent needs to be in the brain awhile before it will confer protection. Fourth, it doesn't protect against infarction (severe ischemia). It appears to protect best against less severe ischemic injury (selective neuronal necrosis and apoptosis). (14)

When should we use volatile anesthesia in pediatrics? I recommend that we should use it liberally (>1 MAC) during surgical procedures in which there is a risk of cerebral ischemia, such as congenital heart surgery and cerebrovascular surgery. In cardiac surgery, the volatile anesthesia should be administered before, during, and after CPB, corresponding to the pre-conditioning, ischemia, and early reperfusion phases. The opioid dose may need to be reduced for hemodynamic considerations. I prefer to use desflurane because of its rapid uptake and elimination and favorable hemodynamic profile. However, any of the agents could be used, as there is no data indicating one agent to protect more than the other.

Is volatile anesthesia neurotoxic?

Brain development involves a coordinated interaction of cell division, differentiation, cell migration, cell death (apoptosis), and synaptogenesis. This requires trophic factors and their intact signal transduction system, among which are glutamate and its receptors. Brain development begins shortly after conception and continues for a variable time, depending on the species. In humans, it is especially active during the first few years of life, whereas in rodents, the same level of activity is during the first few days after birth. Thus, brain development is much faster in the rodent than the human. For example, brain development

of a rat at postnatal day 10, 7, and 4 corresponds to the human at full term, 32 week premature, and 24 week premature, respectively.

Given the effects of volatile anesthesia on the glutamate system and the critical role of glutamate in brain development, a recent study examined the effect of inhalational anesthesia exposure on brain development in 7-day-old rat. (2) The baby rats received 6 hours of isoflurane, nitrous oxide, and midazolam for the anesthesia, and they were survived for days to months to perform brain histology and learning tests. The study found widespread neuronal death in certain brain regions in all animals within a day of exposure. This neurodegeneration was accompanied by learning deficits later in life.

The study certainly raises questions about the safety of inhalational anesthesia in neonates and infants. However, it is important to keep several things in mind. First, there is considerable experience with inhalational anesthesia in human neonates without neurotoxicity, although admittedly, it has not been closely looked for. Second, there are differences in toxicity from one species to another. Toxicity in the rat does not always transfer to the human. The FDA requires toxicity testing on 3 different species as part of its approval process. Third, it is important to consider comparable levels of exposure. Given the fast brain development of the rat, 6 hours of drug exposure is quite long and may not translate to the typical human neonatal anesthesia. Finally, the dose-response for neurodegeneration remains uncertain in the baby rat, much less the human. For now, I recommend that we hold are present course of treating neonates and wait for additional studies to be done before we consider changing it.

References

1. Warner DS et al Anesthesiology 2000; 92:1226-1228
2. Jevtovic-Todorovic et al, J Neurosci 2003 23:876-882
3. MacManus, JP J Cerebral Blood Flow Metab 1997:17(12): 815-832
4. Kurth CD et al. J Thorac Cardiovasc Surg, 118:1068-1077, 1999
5. Xiong L**,** Anesth Analg. 2003 96(1):233-7,
6. Kapinya KJ. Stroke. 2002 Jul;33(7):1889-98
7. Harada H et al Anesth Analg 1999; 89:1442-1447
8. Kimbro JR.et al Anesthesiology 2000; 92: 806-812
9. Patel PM. Anesthesiology 1995; 82:996-1
10. Hoffman WE, Anesthesiology. 2000 Feb;92(2):442-6
11. Kurth CD et al, Anesthesiology, 95:959-64, 2001
12. Loepke AL et al Anesthesiology 97:1521-1527, 2002
13. Popovic R**.** Anesthesiology. 2000 May;92(5):1343-9
14. Kawaguchi M., Anesthesiology 2000; 92:1335-1342