Let's Not Throw the Baby Out With the Bath Water: *Potential* Neurotoxicity of Anesthetic Drugs in Infants and Children

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Recently, Jevtovic-Todorovic and colleagues reported that the rat pups exposed to combination of isoflurane, midazolam and nitrous oxide developed significant neurodegeneration and delayed deficits in learning and memory testing[1]. Previous investigations from the same group reported similar patterns of accelerated neurodegeneration in rat pups exposed to NMDA and GABA antagonists and anticonvulsant drugs[2-4]. Thereby prompting these authors to claim, "there is basis for 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 issue is of paramount interest to pediatric anesthesiologist and intensivists because it questions the safety of anesthetics used for fetal and neonatal anesthesia. The landmark studies by Anand and Aynsley-Green revealed that neonates undergoing surgical procedures mount a stress response to surgical procedures and provoked a fundamental change in the perioperative care of neonates[6,7]. Experimental paradigms of painful stimuli and maternal withdrawal in newborn rat pups have convincingly demonstrated abnormalities in long-term behavior and pain perception[8-10]. Prior to Anand and Aynsley-Green's work, the practice of the "Liverpool Technique" which consisted of nitrous oxide and curare was prevalent in the neonatal "anesthesia" circles. Fortunately, anesthetic agents that provide more hemodynamic stability and more precise monitoring techniques have been applied to the surgical neonate. These developments resulted in the current humane practice of administering anesthetics and analgesics even to the most critically ill neonates during and after surgery.

Are the findings of Jevtovic-Todorovic and Olney relevant enough to withhold anesthetics from neonates undergoing surgery and painful procedures? Certainly, no parent or anesthesiologist/intensivist would allow neonates or pregnant mother to be exposed to a neurotoxin. However, methodological issues make the interpretation of results in rats questionable in the setting of the administration of anesthetic drugs to humans. Furthermore, cross species differences make the relevance to human neonates even more remote[11].

There is no doubt that the developing central nervous system is exquisitely sensitive to the deleterious effects of derangements in the internal milieu[12]. In 1972, Dobbing and Sands demonstrated that peak synaptogenesis occurs between the 3rd and 7th post-natal week in rats[13]. This is equivalent to the period between 25 gestational week and 1 year of age in humans[14] Therefore, non-physiologic exposure to various drugs and stressors (painful stimuli, hypoglycemia, hypoxia and ischemia) during this critical window, leads to neurodegeneration. The immature brain undergoes some degree of baseline neurodegeneration by apoptotic processes as part of normal development[15]. However, several reports from the Olney group have

consistently shown in rodent models that perinatal exposure to commonly used anesthetic and anticonvulsant drugs and ethanol accelerate this apoptotic process. Thereby resulting in increased neuronal dropout in the drug treated rat pups. These findings beg the question of whether other confounding variables are involved in this process.

Does prolonged exposure to anesthetic drugs directly accelerate apoptosis in the developing brain? Anesthetic drugs suppress neuronal activity by yet unknown mechanisms. However, ketamine and midazolam alter glutamate signaling by NMDA receptor blockade and $GABA_A$ receptor activation, respectively. The brain develops under the influence of neural input as the animal interacts with its environment. Certainly, physiologic simulation of the NMDA receptor promotes neuronal survival during development. Anesthesia removes the input and suppresses normal neural traffic. Prolonged exposure to ketamine and other NMDA receptor blockers results in a significant reduction of extracellular concentrations of glutamate, aspartate and glycine[16]. Lack of physiologic activation of neuronal populations by glutamate decreases synaptogenesis and cell to cell interaction[17,18]. Taken together, prolonged rather than acute exposure to various anesthetic agents appears to mediate neurodegeneration in rat pups. Perhaps it is the anesthetic-induce blockade of synaptic activity/transmission induced that mediates neurodegeneration. Woodall and colleagues recently demonstrated that long-term propofol treatment (18-24 hours) of *lymnaea* neuronal cell cultures reversibly blocked synaptogenesis[19]. Wash out of the drug resulted in delayed synaptogenesis. Their data demonstrates that prolonged exposure to an anesthetic drug, propofol, may inhibit synaptogenesis and lead to accelerated neurodegeneration.

Anesthetic drugs not only suppress the central nervous system but also depress circulation and respiration, leading to low tissue perfusion and hypoxia. These mild insults can easily induce neurodegeneration in immature brains. Administration of an anesthetic in clinical practice is always accompanied by frequent measures of blood pressure and oxygenation, thereby minimizing the side effects of the anesthetic drug. The same level of hemodynamic monitoring is not feasible in the rodent experimental paradigms. Furthermore, the anesthetized rat pups do not suckle during the administration of the anesthetic. Hayashi and colleagues have demonstrated attenuated weight gain in the anesthetized group, suggesting that malnutrition may be a contributing factor[20].

Certainly there are a wealth of data in the literature linking malnutrition to decreased brain growth and learning disabilities[21]. Prolonged exposure to isoflurane and nitrous oxide could potentially alter feeding behavior and would likely lead to decreased weight gain. However, the Olney group did not report these data in the studies. The experimental paradigms utilized in these rodent models do not provide nutrition to the rat pups during the prolonged period of anaesthesia. Neonates undergoing general anaesthesia, routinely receive nutritional support during the perioperative period. Thus, minimizing the risk for hypoglycemia and malnutrition. In this case, the rodent experimental model does not reflect the clinical phenomenon in human neonates.

Furthermore, the revelation of behavioral deficits after prolonged exposure to anesthetics is not a new issue. In 1985, Uemura and colleagues reported that prolonged exposure to halothane resulted in decreased synaptic density and stunted behavioral development.[22] Similar findings have been observed in rat pups revealing a NMDA receptor blocker, MK-801[23]. Hayashi and colleagues reported that prolonged rather than limited exposure to ketamine increased neurodegeneration and that the former lead to a significant decrease in weight gain[20]. Rat pups receiving ketamine continuously for nine hour exhibited poor feeding behavior and increased neurodegeneration. Whereas single doses of ketamine did not affect weight gain and

neurodegeneration. These studies suggest that prolonged exposure to these drugs may be an essential factor in this phenomenon. A rat brain develops over a matter of weeks while a human brain develops over years. Six hours of anesthesia in a neonatal rat pup equates to weeks in a human neonate. Would an infant develop normally if it were fully anesthetized for a month?

There is no doubt that prolonged exposure to anesthetics (and other drugs and mild insults) leads to accelerated neurodegeneration and behavioral deficits in the already vulnerable neonatal rat brain. Similarly, fetuses and neonates subjected to pain and stresses associated with painful procedures are also at risk for long-term adverse outcomes. Future investigations into these problems are needed to delineate the mechanisms associated with the neurodegenerative changes observed and determine if perinatal exposure to anesthetic drugs truly leads to neurobehavioral abnormalities in humans. An overriding theme in this phenomenon is that prolonged exposure of both paradigms is the prolonged and persistent nature of the exposure to either anesthetics or pain/stress. Fetuses and neonates are vulnerable to the long-term consequences stress and pain. Clinicians should continue administering but minimize the duration of anesthetics during surgery and painful procedures. The experimental findings of Jevtovic-Todorovic and Olney are scientifically sound and merit further investigation as to its pertinence to humans. Given the potential harm that withholding anesthetics have, alleviation of pain and stress during the perinatal period is essential and humane. As clinicians we *should not throw the baby out with the bath water.*

References

1. Jevtovic-Todorovic,V., Hartman,R.E., Izumi,Y., Benshoff,N.D., Dikranian,K., Zorumski,C.F., Olney,J.W., & Wozniak,D.F. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J. Neurosci.* **23**, 876-882 (2003).
2. Ikonomidou,C., Bosch,F., Miksa,M., Bittigau,P., Vockler,J., Dikranian,K., Tenkova,T.I., Stefovska,V., Turski,L., & Olney,J.W. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* **283**, 70-74 (1999).
3. Ikonomidou,C., Bittigau,P., Ishimaru,M.J., Wozniak,D.F., Koch,C., Genz,K., Price,M.T., Stefovska,V., Horster,F., Tenkova,T., Dikranian,K., & Olney,J.W. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science* **287**, 1056-1060 (2000).
4. Bittigau,P., Sifringer,M., Genz,K., Reith,E., Pospischil,D., Govindarajalu,S., Dzietko,M., Pesditschek,S., Mai,I., Dikranian,K., Olney,J.W., & Ikonomidou,C. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc. Natl. Acad. Sci. U. S. A* **99**, 15089-15094 (2002).
5. Ikonomidou,C., Bittigau,P., Koch,C., Genz,K., Hoerster,F., Felderhoff-Mueser,U., Tenkova,T., Dikranian,K., & Olney,J.W. Neurotransmitters and apoptosis in the developing brain. *Biochem. Pharmacol.* **62**, 401-405 (2001).
6. Anand,K.J. & Aynsley-Green,A. Measuring the severity of surgical stress in newborn infants. *J. Pediatr. Surg.* **23**, 297-305 (1988).
7. Anand,K.J., Sippell,W.G., & Aynsley-Green,A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* **1**, 62-66 (1987).

8. Liu,D., Diorio,J., Tannenbaum,B., Caldji,C., Francis,D., Freedman,A., Sharma,S., Pearson,D., Plotsky,P.M., & Meaney,M.J. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* **277**, 1659-1662 (1997).
9. Anand,K.J., Coskun,V., Thrivikraman,K.V., Nemeroff,C.B., & Plotsky,P.M. Long-term behavioral effects of repetitive pain in neonatal rat pups. *Physiol Behav.* **66**, 627-637 (1999).
10. Ruda,M.A., Ling,Q.D., Hohmann,A.G., Peng,Y.B., & Tachibana,T. Altered nociceptive neuronal circuits after neonatal peripheral inflammation. *Science* **289**, 628-631 (2000).
11. Berde,C. & Cairns,B. Developmental pharmacology across species: promise and problems. *Anesth. Analg.* **91**, 1-5 (2000).
12. Bhutta,A.T. & Anand,K.J. Vulnerability of the developing brain. Neuronal mechanisms. *Clin. Perinatol.* **29**, 357-372 (2002).
13. Dobbing,J. & Smart,J.L. Vulnerability of developing brain and behaviour. *Br. Med. Bull.* **30**, 164-168 (1974).
14. Dobbing,J. & Sands,J. Quantitative growth and development of human brain. *Arch. Dis. Child* **48**, 757-767 (1973).
15. Kuan,C.Y., Roth,K.A., Flavell,R.A., & Rakic,P. IMechanisms of programmed cell death in the developing brain. *Trends Neurosci.* **23**, 291-297 (2000).
16. Rozza,A., Masoero,E., Favalli,L., Lanza,E., Govoni,S., Rizzo,V., & Montalbetti,L. Influence of different anaesthetics on extracellular aminoacids in rat brain. *J. Neurosci. Methods* **101**, 165-169 (2000).
17. Rakic, P. and Komuro, H. The role of receptor/channel activity in neuronal cell migration. J.Neurobiol. 26, 299-315. 1995.
18. Lipton,S.A. & Nakanishi,N. Shakespeare in lovewith NMDA receptors? *Nat Med* **5**, 270-271 (1999).
19. Woodall,A.J., Naruo,H., Prince,D.J., Feng,Z.P., Winlow,W., Takasaki,M., & Syed,N.I. Anesthetic Treatment Blocks Synaptogenesis But Not Neuronal Regeneration of Cultured Lymnaea Neurons. *J Neurophysiol* **90**, 2232-2239 (2003).
20. Hayashi,H., Dikkes,P., & Soriano,S.G. Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. *Paediatr. Anaesth.* **12**, 770-774 (2002).
21. Dobbing,J. Undernutrition and the developing brain. The relevance of animal models to the human problem. *Am. J. Dis. Child* **120**, 411-415 (1970).
22. Uemura,E., Levin,E.D., & Bowman,R.E. Effects of halothane on synaptogenesis and learning behavior in rats. *Exp. Neurol* **89**, 520-529 (1985).
23. Griesbach,G.S. & Amsel,A. Immediate and long-term effects of neonatal MK-801 treatment on nonspatial learning. *Proc. Natl. Acad. Sci. U. S. A* **95**, 11435-11439 (1998).