Anesthesia and Neurotoxicity in Children: Update and Review

Kevin Hughes M.D.
Anesthesia Consultants Inc.
“As the mortality rate for all congenital heart surgery trends downward toward 1-2% in most large centers, attention has increasingly turned to other morbidities affecting quality of life, none of which is more important than neurological outcome.”

Dean B. Andropoulos, M.D

Texas Children’s Hospital
Some Methods Used to Improve Neurological Outcome

- Regional Low-Flow Cerebral Perfusion
- Rate of Cooling and Rewarming on Bypass
- Neuroprotectant Agents
- Near-Infrared Spectroscopy (NIRS) measuring cerebral tissue oxygenation
- Anesthetic Choice ????????
Will anesthesia make my kid dumb?

- Many times, especially when a baby is receiving a second anesthetic on the same day, the parents ask if it is safe.

- We always reassure them it's not a problem. We tell them that we give anesthesia to kids all the time and they will be fine.

- That answer may be too simple and not entirely true.
“Faced with mounting evidence that general anesthesia may impair brain development in babies and young children, more research is greatly needed and that when planning surgery for a child, parents and doctors should consider how urgently it is required, particularly in children younger than 3 years.”
Recent study suggests that children who had general anesthesia for surgery before 4 years old have diminished language comprehension, lower IQ and decreased gray matter density in the posterior brain.
-A quick Google search about anesthesia risk may make a parent anxious.
-As providers we should be able to give honest answers to our patient’s family.
Objectives of this lecture

- Review the basic neurophysiology
- Review the history of anesthesia related neurotoxicity from rat, primate and retrospective human studies
- Discuss possible alternatives
- Future research and findings
Can’t blame anesthesia for this one!
• Adult Brain- Glutamate is the major excitatory neurotransmitter. Gamma-aminobutyric acid (GABA) is major inhibitory neurotransmitter.

• GABA acts a excitatory transmitter in the developing central Nervous system

• In the developing brain Glutamate and GABA have central role in brain morphogenesis(synapse formation, proliferation, migration, differentiation and neuronal survival) (1)
Different types of Glutamate and GABA receptors need to be expressed at right time and place for normal brain structure and function.

N-Methyl-D-aspartate (NMDA) type glutamate receptors also play a key role in brain development.

All anesthetics and Sedatives including inhaled agents, benzodiazepines, barbiturates, ketamine, propofol, and etomidate are believed to block NMDA receptors and/or enhance GABA-A receptors to varying degree. (1)
Normal Brain Development

- Neurogenesis- In early stages of brain development neurons are produced in excess and the elimination (apoptosis) of this excess (as much as 50-70% of neurons and progenitors cells) is required for normal brain structure and function.

- Synaptogenesis- later stage of brain development which is tightly controlled and very few neurons undergo apoptosis. (1)
In mice and rats the peak period of synaptogenesis is first 2 weeks of life.

In humans synaptogenesis begins during the 3rd trimester and rapid brain growth occurs at different ages in varying brain regions. By 2-3 years old rapid brain growth in nearly all brain regions is mostly complete.

Normal human brain development also involves formation of neuronal circuits across different brain regions, this slows by 2-5 years old but continues into adolescence. (1)
Some people’s brain gets stuck in adolescence
• When anesthetics and sedative agents are given to rodents during synaptogenesis or rapid brain growth they cause widespread neuronal apoptosis, neurodegeneration, and changes in neuron growth and cell structure.

• Let’s look at some of these studies that started us on this path
Rat Brain Studies

- In 1999 Ikonomidou et al. showed blockade of NMDA receptors induced widespread neuronal apoptosis in immature rat brain when administered during synaptogenesis.

- In 2003 Jevetovic-Todorovic, V et al. showed exposure of infant rats to an anesthetic cocktail (midazolam, isoflurane, N₂O) commonly used in pediatric anesthesia triggers apoptosis in several major brain regions. Deletion of many neurons from the developing was shown.
Triple anesthetic cocktail induces apoptotic neurodegeneration. a–l are light micrographic scenes from various brain regions of either a control rat (a, f, h, j) or a rat exposed to the triple anesthetic cocktail (b–e, g, i, k, l).

Early exposure to common anesthetic agents cause widespread neurodegeneration in the developing rat brain and persistent learning deficits.

- In addition to showing increased neurodegeneration brain. Jevetovic-Todorovic, V et al. showed residual learning/memory deficits lasting into adolescence and adulthood.

- Animals exposed to this anesthesia protocol displayed deficits in spatial reference memory capabilities as manifested by slower place learning acquisition as juveniles and by significant impairments in both spatial reference and working memory as adults.
Isoflurane-induced apoptosis of oligodendrocytes (OL) in neonatal *rhesus* macaque

- After 5 hours of isoflurane exposure widespread apoptosis and OL’s were seen throughout the brain

Ketamine-induced neuroapoptosis and long-lasting cognitive deficits

- At fetal and neonatal age 5 hours of Ketamine was sufficient to induce significant neuroapoptosis

- A single 24 hour episode of Ketamine exposure at 5-6 postnatal days cognitive impairment was seen at 10 months of age and continued past 3.5 years of age.
Good thing we are not monkeys?
Human Retrospective Studies

- Of 5,357 children in cohort 593 received General anesthesia before age 4.
- Compared to those not receiving anesthesia (N=4,764), single dose (N=449) was not associated with increased risk of learning disorder (hazard ratio=1).
Early Exposure to Anesthesia and Learning Disabilities in a Population-Based Birth Cohort cont.

- Children receiving 2 anesthetics (N=100) were at increased risk of learning disorders (hazard ratio= 1.59)

- Children with 3 or more anesthetics were at the highest risk for learning disorders (hazard ratio =2.6)

- Risk of learning disorders increased with longer cumulative duration of anesthesia exposure
Long-term differences in language and cognitive function after childhood exposure to anesthesia

- In 2012, Ing, C et al. conducted a retrospective study of 2608 children. Of these, 321 children were exposed to anesthesia before age 3.

- After adjustment of demographic characteristics, exposure to anesthesia was associated with an increase risk of language disability (adjusted risk ratio 1.87) and cognition (adjusted risk ratio 1.69).

- Even after a single exposure, an increased risk ratio for language and cognitive disabilities was found.
More Evidence That General Anesthesia May Affect Young Brains

- MONDAY, June 8, 2015 (HealthDay News) -- Having general anesthesia during surgery at a very young age may be linked to poorer brain development, new research suggests.
Cognition and Brain Structure Following Early Childhood Surgery With Anesthesia

- *Pediatrics* June 2015- Retrospective study performed by Loepke, Backeljauw et al.. from Cincinnati Children’s compared scores from language development study of 53 children that underwent surgery before 4 yrs and unexposed peers that were matched for age, gender, handness, and socioeconomic status.

- Neurocognitive assesments included Oral and written Language Scales and Weschsler Intelligence Scales. Brain structural comparisons were done using T1-weighted MRI scans.
Cognition and Brain Structure continued

- Average test scores were within population norms, regardless of surgical history.

- Previous exposed children scored significantly lower in listening comprehension and performance IQ. Potential loss of 5 or 6 IQ points.

- No evidence of gross elimination of gray matter as seen in animal studies but those with decreased performance IQ and language comprehension had lower gray matter density in the occipital cortex and cerebellum.
Cognition and Brain Structure Study
Conclusions

- Although all test scores are within normal range, a loss of 1 point on IQ scale was shown in 2008 study to decrease potential lifetime earning by $18,000. Factoring in potential loss of 5 or 6 IQ points and an estimated 6 million children a year who undergo surgery in the US, the lifetime potential earning loss could be $540 billion.

- Loepke “It is important to note that no surgeries are truly elective in young children. Many surgical procedures early in life treat life-threatening conditions, avert serious health complications, or improve quality of life. These cannot be easily avoided or postponed.”
For some people a drop of 1 IQ point can cost a lot more than $18,000
So if anesthesia does cause decreased learning capabilities what are the options?

- Postpone surgery - rarely an option as described earlier

- No anesthesia or analgesia: Bad idea! In 1988 a study in UK showed only 11% of Anesthesiologist administered opioids to neonates for major surgery. In 1995, after multiple studies showed increased morbidity and mortality of neonates with poor pain control the percentage increased to 91%.

- Different anesthetics - Only class of anesthetics that have not been shown to cause neurodegeneration is opioids, which must be given at a large dose to achieve anesthesia.
More Answers Needed

- PANDA Study- Pediatric Anesthesia & Neurodevelopment Assessment (PANDA) project is a large scale, multi-center sibling matched cohort study.

- Study based at the Morgan Stanley Children’s Hospital of New York. Participating sites: Boston Children’s, Children’s Hospital of Philadelphia, Chicago Children’s Memorial, Cincinnati Children’s Hospital, Pittsburgh Children's Hospital, Mott Children’s Hospital and Vanderbilt Children’s Hospital

- Examine two groups of children - those who have been exposed to a single episode of general anesthesia during inguinal hernia surgery before age three years and those who are siblings of the first group who have not. Then assess their neurodevelopment and cognitive functions between ages 8 to 15 years.
• GAS- Large scale, international, multisite, randomized controlled prospective study of General Anesthesia with Sevoflurane versus spinal anesthesia in infants undergoing inguinal hernia repair.

• Study based at Children’ Hospital of Boston with 9 other US contributing sites and other international site in Canada, Australia, UK, and other European countries. Goal enrollment of 720 kids.

• Newborns undergoing hernia surgery are randomly assigned to receive general or spinal anesthesia.

• Then undergo developmental testing at age 2 and neurodevelopmental and intelligence testing at age 5 to determine whether there are neurocognitive differences between the groups.

• Study Limitations; Does not address children having longer procedures which from animal studies are the ones at greatest risk.
Time for Dessert. Thank You!
References


4. Brambrink, AM et al.. Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. *Anesthesiology* 2012 Jan 4


