Update on Anesthetic Neurotoxicity
Are We Injuring Children’s Brains?

Carolyn F. Bannister
Associate Professor of Anesthesiology
Chief of Service, Emory Pediatric Anesthesiology
Children’s Healthcare of Atlanta at Egleston
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Conflict of Interest

• None
6 Million children anesthetized in US annually
1.5 Million are 12 months of age or younger
Safety of anesthesia lead to children having more procedures at younger age
Animal Studies Showing Neural Damage

- Organelle Damage 1974,76 Chang/Katz
- Impaired synaptogenesis 1974,80,85 Quimby, Uemura, Levin
- Reduced dendritic branching 1974,85 Quimby, Uemura
- Decreased myelin synthesis 1974,79,80 Patsalos, Wiggins
- Altered neurotransmission 1977,82 Bowman, Gotsfeld
- Electrophysiology (EEG) Changes 1979,80 Clark, Fuller
- Apoptosis 1999
Neurobehavioral Toxicology of Halothane in Rats

PATTERNS OF NEURAL DAMAGE

- Organelle damage (cytoskeleton)
- Impaired synaptogenesis
- Reduced dendritic and axonal branching
- Decreased myelin synthesis
- Altered neurotransmitters (dopamine and serotonin)
- Electrophysiology changes
- Apoptosis

BEHAVIORAL EFFECTS

- Reduced exploratory behavior in environment
- Impaired spatial learning (maze tasks)
- Reduced locomotor activity (poor nociception response)
- Delayed social development
Inhaled agents – GABAa mimetics
N2O – NMDA antagonist
Ketamine – noncompetitive NMDA antagonist
Benzodiazepines/barbiturates - GABAa agonists
Propofol/etomidate – GABAa agonists
164 rat pups offspring of mothers given 4 different halothane exposures:

- control vs intermittent halothane (25ppm in air 8h/d, 5d/wk)
- intermittent halothane (100ppm in air 8h/d, 5d/wk)
- continuous halothane (25ppm in air 24hr/d, 7d/wk)
- continuous 100ppm DC due to weight loss

Synaptic density diminished in all halothane groups even up to 95 postnatal days
6month and 20 month old rats were acclimated to a maze for 3 days preanesthetic

Single dose of isoflurane 1.2% in 70% N2O for 2 hours – age matched controls received air/O2

48 hours postanesthetic completed maze testing
Fig. 1. Time to complete the maze. Aged rats performed worse than young rats and previously anesthetized rats performed worse than control rats. Data expressed as mean +/- SEM.

Conclusion: principal finding of this study is that a single isoflurane-nitrous oxide general anesthetic produces lasting impairment in the ability of both adult and aged rats to acquire and perform a spatial memory task.
Conclusion:

“...exposure of infant rats to an anesthetic cocktail (midazolam, isoflurane, N2O) that is commonly used in pediatric anesthesia triggers apoptosis in several major brain regions, resulting in deletion of many neurons from the developing brain and residual learning/memory deficits, coupled with dysfunction of hippocampal synaptic mechanisms putatively associated with memory.”
54 rat pups 5-7 days age
- 2 hr sevoflurane at 1.7% compared to control group and ETOH group
- Anes agent, O2, CO2, temp monitoring
- Brains examined for apoptosis and caspase3 activation

Outcomes
- Significant increase in caspase3 activation and apoptotic cells in sevoflurane treated rat pups
Silver staining of degenerating neurons in cortex and thalamus
6 day old mice treated with 3% sevoflurane for 6 hrs

- Increased caspase3 staining of apoptotic cells
- Decreased interaction with social targets compared to controls

Conclusion: “...shows that exposure of neonatal mice to inhaled sevoflurane could cause not only learning deficits but also abnormal social behaviors resembling autism spectrum disorder.
What do we do with this information?

- Large doses of drugs used in very young animal models
- Prolonged exposure to drugs in studies
- Anesthetic without surgery/painful stimulus
- Lack of precise physiologic monitoring in many cases
- Difficult to extrapolate useful conclusions across species (rapid brain growth spurt and vulnerability)
- Apoptosis is part of normal brain development
- What about neuroprotective effects of anesthetics?
Ketamine-Induced Neuronal Cell Death in the Perinatal Rhesus Monkey


- 18 monkeys
- 9 given 24 hours ketamine anesthesia
  9 controls
- 6 monkeys 5 days old
- 3 given 3 hours ketamine anesthesia
  3 controls
- Full monitoring
Ketamine-induced neuronal cell death in the perinatal rhesus monkey

- Ketamine 24 hour infusion produced significant increase in caspase3 cells in cortex of gestational and 5 day old but not in 35 day old monkeys.
- Ketamine 3 hr anesthetic showed no neuronal cell death in 5 day old monkeys.
PDA ligation in preterm infants

8 pts each:
O2/N2O/d-tubocurare
O2/N2O/d-tubocurare/Fentanyl 10mcg/kg
NonFentanyl Group

- Epinephrine/glucagon increased
- Glucose 3x higher
- Pyruvate/lactate increased
- Increased urinary nitrogen excretion

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Extremely preterm (<27wk gest) or extremely low birth wt (<1000 Gms) having surgery at initial hospitalization

Outcome measure of sensorineural disability at age 5 years

- 221 children
- 54 (24.4%) at least one surgical procedure
- 53 children at 5 years
  - 13.2% severely disabled
  - 15.1% mod disabled
  - 22.6% mild disabled
  - 49.1% no disability
Victorian Infant Collaborative Study

5 year tests: neurologic exam, visual test, hearing test, IQ test

- Severe: CP unlikely ever to walk, blindness or IQ <3 sd
- Moderate: CP in ambulatory pt, deafness or IQ 2-3 sd
- Mild: CP in ambulatory pt, or IQ 1-2 sd
Early Exposure to anesthesia and learning disabilities in a population-based birth cohort
Wilder et al. Anes 2009; 110; 796-804

- Olmstead County Birth Cohort
  - 5357 Children; 593 had anesthetic before age 4
  - One surgical procedure no increased risk
  - Learning disabilities (math, language or reading) higher in 2 or more before age 4 yrs

Strengths: Large sample, all MRs available, adjusted for age, sex, birth weight, maternal education

Limitations: Retrospective to 1976-82, lack of population diversity in demographic, cultural, racial/ethnic compared to overall US
Anesthesia for Cesarean Delivery and Learning Disabilities in a population-based birth Cohort
Sprung et al. Anes 2009; 111: 302-10

- Olmstead County Birth Cohort
  - 5320 children
  - 4823 vaginal delivery
  - 193 CS under GA
  - 304 CS under regional anesthesia

Incidence of learning disabilities similar between groups, slightly lower in CS with regional.
A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children

NY State Medicaid data
383 children with inguinal hernia repair prior to age 3 yrs
Comparison group 5050 age-matched children with no history of surgery

Exposed children 2.3 times more likely to be diagnosed with behavioral disorders

Limitations: Nonstandardized outcome, medicaid population higher risk due to low SES
Anesthesia and cognitive performance in children: no evidence for a causal relationship

Young Netherlands Twin Registry
1143 monozygotic twin pairs

No difference in academic achievement between twin pairs in which one had anesthetic before age 3 yrs. (Measured IQ at age 12 years)
What are Options?

- Delay surgery (not practical)
- Ignore findings as irrelevant in humans
- Search for less neurodamaging drugs
- Search for neuroprotective agents
- RCTs in humans (ongoing)
Are There any Neuroprotectants?

- Lithium?
- Dexmedetomidine?
- tPA, Plasmin, Xenon, melatonin, erythropoietin?
Lithium Protects Against Anesthesia-Induced Developmental Neuroapoptosis

- Ethanol-induced apoptosis is preceded by suppressed phosphorylation of protein kinase
- Lithium counteracts the suppressed phosphorylated protein kinase and counteracts ethanol-induced neuroapoptosis
- Do ketamine and propofol mimic ETOH in suppressing PK?
- If so, does lithium prevent anesthetic-induced neuroapoptosis?
5 day old mice treated with
propofol 50mg/kg ip
ketamine 40 mg/kg sc
lithium 6 mEq/kg ip
propofol/lithium
ketamine/lithium
propofol/saline
ketamine/saline
Findings:
- Ketamine and propofol suppressed phosphorylated protein kinase
- Lithium counteracted the suppressant action
- Lithium counteracted neuroapoptosis commonly seen with these anesthetic drugs

Conclusion: If further testing finds lithium to be safe for use in pediatric/obstetric medicine, administration of a single dose of lithium before anesthesia induction may be a suitable means of mitigating the anesthetic-induced developmental neuroapoptosis
What about Dex?

Ma et al.  European Journal of Pharmacology
502; 2004: 87-97

Dexmedetomidine produces its neuroprotective effect via the $\alpha_{2A}$-adrenoceptor subtype

- Dexmedetomidine exhibited dose-dependent protection against brain matter loss in vivo and improved the neurologic functional deficit induced by hypoxic-ischemic insult in wild-type mice.
2009 ASA Abstract  Marchand et al.

7 day old rat pups given 6 SC injections at 90 min intervals

Saline

Ketamine 20mg/kg

Dex 3mcg/kg

Dex 10 mcg/kg

Dex 30 mcg/kg
Brains examined for caspase3 activation after 24 hours

Ketamine induced extensive neurodegeneration in multiple areas of thalamus and cortex (areas central to memory, learning and emotional modulation)

All 3 doses of dex not significantly different than saline control
Dexmedetomidine is less pro-apoptotic than ketamine in the neonatal rat brain.

Soriano et al. ASA 2009

Cleaved caspase-3

fold change over control

con k5 k10 k20 dex50
FDA To Study Anesthesia Risks in Pediatrics
FDA’s Response

April 2007  Scientific Advisory Committee to determine whether any changes in anesthetics in infants were warranted.

No human data available

http://www.fda.gov/ohrms/dockets/ac/07/transcripts
SAFEKIDS Multicenter Study

- Safety of Key Inhaled and Intravenous Drugs in Pediatrics
- 2007 FDA’s Anesthesia and Life-Support Drugs advisory committee held public inquiry into relationship between anesthetics and CNS
- 2008 FDA launched SAFEKIDS under IARS
  - GAS study – worldwide prospective RCT (US, UK, Australia, Canada, Italy)
  - AND PANDA – Pediatric Anesthesia Neurodevelopment Assessment Study
GAS study – 600 patients

RCT comparing sevoflurane to regional anesthesia for infants undergoing hernia repair

Followup at 2 and 5 years to include standardized scales for developmental milestones and neuropsychological testing
PANDA study (Pediatric Anesthesia and NeuroDevelopment Assessment)

1000 children, 8 US sites

Sibling matched cohort study so 500 pairs

Single anesthetic exposure before 36 months of age in ASA I or II pts for inguinal hernia repair

Detailed neuropsychological battery between 8 and 11 years.
Pediatric Anesthesia Neurotoxicity panel at the International Anesthesia Research Society annual meeting in Vancouver, B.C.

Dr. Randall Flick  Mayo Clinic

Presented research which concluded multiple episodes of anesthesia exposure before age 2 is a “significant” risk factor for Attention Deficit Hyperactivity Disorder, even after adjusting for illness that might contribute to cognitive function difficulties in children.
Further RCTs needed
Non ASA I or II patient
Multiple or prolonged procedures

- Further funding needed

What is SmartTots?
SmartTots (Strategies for Mitigating Anesthesia-Related NeuroToxicity in Tots) is a Public-Private Partnership (PPP) between the US Food and Drug Administration (FDA) and the International Anesthesia Research Society (IARS) whose mission is to coordinate and fund a research program with the goal of insuring safe surgery for the millions of infants and young children who undergo anesthesia and/or sedation each year.