Risk of Neurotoxicity in Children from General Anesthesia

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Disclosures

• Marisa Earley, MD has no relationships with commercial companies to disclose
• Some of the information in this presentation has been submitted for publication in Laryngoscope

Why is this important?

• It’s not just the surgeries
• More informed parents, families and patients

Learning Objectives

At the end of this presentation the participant will be able to:

• Discuss findings from otolaryngologic literature in regards to discussion of risk of neurotoxicity in children undergoing general anesthesia.

• Describe current recommendations and controversies regarding neurodevelopmental risks from pediatric anesthesia.

• List resources available to educate both providers and parents regarding the risks from general anesthesia in children
Who’s affected?

- 2010 Census: 20 million children in US < 5 years
  - 10% undergo general anesthesia/deep sedation each year
- Over 1.5 million *ambulatory* pediatric ENT procedures performed annually
- Does not include inpatient or urgent surgeries or imaging

Why I became interested

- Parent: So how safe is anesthesia? What do I need to know?
- Anesthesiologist: It’s safer than driving a car!
- Me: ???

Assessing Awareness
Why ENT is Unique

- Role of hearing loss in learning and language development
- Role of OSA in neurodevelopmental problems
- Syndromic children
- Emergent cases

Strategies for Mitigating Anesthesia Related NeuroToxicity in Tots
SMART Tots

Information, Communication Lacking for Neurotoxicity in Pediatric Anesthesia
CHANGE GEARS

• So what does the anesthesia research show?
  – General anesthetics given during peak synaptogenesis causes cell death, impaired neurogenesis and subsequent cognitive impairment

Animal Studies

• 2016: Early life single Sevoflurane exposure
  – Mice pups on post-natal day 7 were administered 2.3% Sevo for 2 hours compared to controls and were assessed for cognition and neuropsychiatric-like behavioral changes at 1-3 months of age
  – Exposed mice had a **deficit in learning and memory, as well as social interaction deficits, in peri-adolescence and adulthood**

First up...

ANIMAL STUDIES

Animal Studies

• 2016: Early life single Sevoflurane exposure
  – Mice pups on post-natal day 7 were administered 2.3% Sevo for 2 hours compared to controls and were assessed for cognition and neuropsychiatric-like behavioral changes at 1-3 months of age
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Animal Studies

• 2015: Neonatal mice exposed to titrated sevoflurane for 6 hours
  – Increased apoptosis
  – Impaired long-term memory
  – NO autism like behavior
  – NO change in general activity of anxiety
    • These results conflict with prior data during similar testing where sevoflurane exposure was constant and autism-like behavior was demonstrated

Animal Studies

• 2015: Potential adverse effects of prolonged Sevoflurane exposure on developing monkey brains
  – Neonatal monkeys were exposed to 2.5% Sevoflurane for 9 hours
    • Elevated cytokine levels in exposed brains;
    • Extensive neural damage found in frontal cortex
    • Most classes of lipids were reduced in Sevoflurane exposed brains
Animal Studies

• 2015: Potential adverse effects of multiple anesthetic exposures on neonatal monkeys’ emotional reactivity to acute stressors
  – Neonatal Rhesus monkeys were exposed to 2.5% Sevoflurane for 4 hours or brief maternal separations on PND 6-10 and again 2-4 weeks later
  – Monkeys were tested at 6 months of age
    • Increased anxiety-related behaviors in exposed v. controls

Is Precedex the Answer?

• Dexmedetomidine attenuates neurotoxicity induced by prenatal propofol exposure
  – Precedex is a selective alpha 2-adrenoreceptor agonist with antiapoptotic properties in several brain injury models
  – Precedex prevented neurocognitive deficit in fetal rats administered propofol AND preceded v. propofol alone in utero

Early Exposure and Learning Disabilities

• Population: Birth Cohort from Olmsted County Minnesota
  • 593 children with exposure <4 years born 1976-1982
• Outcome measures: Learning Disability and/or ADHD
• Findings: No differences with one exposure, but 2 or more were more likely to have abnormal outcome
• Limitations: Pulse ox and capnography not standard of care; Halothane and NO used; External validity and high migration rates

Cognitive and Behavioral Outcomes

• Population: Birth Cohort from Olmsted County Minnesota
  • 350 children with exposure <2 years born 1976-1982 matched to 2 unexposed control children
• Outcome measures: Learning Disability, Individualized Education program, and group administered tests of achievement and cognition
• Findings: No differences with one exposure, but 2 or more were more likely to have abnormal outcome
• Adjusted for health status
• Cases matched to controls including factors known to influence LD (gender, mom education, gestational age)

Behavioral and Developmental Disorders

• Population: NYS Medicaid Dataset
  • 383 children <3 years who underwent hernia repair with matched controls
• Outcome measures: Behavioral outcome code
• Findings: Adjusting for age, sex, race, confounding diagnoses at birth, hernia repair patients were more than twice as likely to have abnormal outcome
• Limitations: Unknown type, frequency and duration of anesthesia exposure

Next up...

RETROSPECTIVE COHORT STUDIES
Cognitive Performance
• Population: Netherlands Twin Registry
• Outcome measures: Educational achievements at age 12 years or problems reported by teachers
• Findings: Exposure <3 years had reduced outcomes; no differences between discordant twins
• Limitations: Small n for discordant twins (15% of sample) but no findings in this subset

Language and Cognitive Function
• Population: Raine cohort from Western Australia
• Outcome measures: complex neuropsychiatric tests, standardized test (school) performance, ICD-9 codes
• Findings: Exposed children <3 years had deficits in language and abstract reasoning
• Limitations: All surgeries (including neurosurgeries); unknown duration and frequency of exposure

Academic Performance
• Population: Danish birth cohorts from 1986-1990
• Outcome measures: Academic achievements in adolescence
• Findings: No difference after adjusting for known confounders (sex, birth weight, and maternal age and education)
• Limitations: Academic achievement does not test all neurodevelopmental domains

Meta-analyses
• 2012: Bayesian meta-analysis of 12 eligible studies suggest modestly elevated risk of adverse behavioral or developmental outcomes in children who were exposed to anesthesia/surgery during early childhood
• 2014: SR and meta-regression of 7 eligible studies suggest modestly elevated risk of adverse ND outcomes in children exposed <3 years, especially multiple
• 2015: Meta-analysis of 13 eligible studies assessing neurodevelopmental damage from single GA before 3 years suggest modestly elevated risk of ND disorders

ONGOING AND PROSPECTIVE STUDIES

Where are we now…
Pediatric Anesthesia and NeuroDevelopment Assessment

General Anesthesia compared to Spinal

Why it’s still a tough question to answer

Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood

Neurodevelopmental outcomes at 2 years of age after general anesthesia and awake-regional anesthesia in infancy (GABA): an international multicentre, randomised controlled trial

What about peds anesthesia?

• 87% provide information to faculty
• 97% provide information to residents and fellows
• 90% DO NOT have consensus on how to modify anesthesia to minimize risk
• 91% discuss risk with parents ONLY IF asked
– 6% discuss as a routine part of preoperative evaluation
– Very few programs had formal method of discussion or parent handout

Not All Tests Are Equal

- Many different tests used in outcome studies matters
- Neuropsychiatric tests > ICD-9 codes > academic performance
- The age at testing matters

Putting it all together...

- Animal studies fairly consistently show evidence of neurotoxicity
- Cohort studies inconsistently show abnormal neurodevelopmental outcomes
- Take home points
  - Consider necessity and frequency of interventions requiring GA
  - Combine multiple procedures
  - Consider conscious sedation or play therapy when possible

Future Directions—what can we do?

- Survey study to assess and increase awareness
- Engage parents and anesthesiologists in discussions
- Await ongoing study results; participate in studies when possible
- Assess risk of radiation from CT v. risk of anesthesia for an MRI

Thank you!

- Growing Pedi ENT team
  - Clinic availability 4 days per week
  - OR 4 days per week
- How to reach us
  - Page on call resident
  - Daytime attending call schedule
  - Clinic: (210) 358-0500

References


