The Developing Brain & Anesthesia

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Disclosures

No financial relationships to disclose
No discussion of off label use and/or investigational drugs
Objectives

- Media spotlight on anesthesia in infants
- What we’ve learned from animals
- What we know from observational trials
- Latest Research Efforts
- Resources for parents and pediatricians
Researchers Warn on Anesthesia, Unsure of Risk to Children

Could Anesthesia Cause Developmental Disorders?

Study: Anesthesia in Infancy Linked to Later Disabilities
A Less Risky Anesthesia for Babies

More hospitals evaluate spinal anesthesia for surgeries that last 1½ hours or less

Lisa and Mike Barr chose to have their infant, Mira, undergo spinal anesthesia during surgery, a new approach to anesthesia that leaves infants awake and pain free with fewer complications. WSJ’s Laura Landro and pediatric anesthesiologist Dr. Robert Williams discuss the procedure. Photo: The Barr Family
The Initial Link

Ethanol-Induced Apoptotic Neurodegeneration and Fetal Alcohol Syndrome

- 7 day old rats
- SQ EtOH
- Apoptosis by:
  - NMDA blockade
  - $\text{GABA}_A$ agonism

Ikonomidou et al, Science 2000, 287:1056-60
Anesthetic Agents

Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

- 7 day old rats
- Isoflurane +/- Midazolam +/- Nitrous Oxide
- 6 hr exposure

Jevtovic-Todorovic et al, J Neurosci 2003, 23(3):876-882
Effect of Anesthetic Agents

Does Apoptosis = Disability?

Jevtovic-Todorovic et al, J Neurosci 2003, 23(3):876-882
Anesthetic Culprits
Animal Models: Issues

- Window of “Vulnerability”
- Duration/Dose of Anesthetic Exposure
- Lack of Physiologic Monitoring
- Lack of Resuscitation
- Lack of Surgical Stimulus
- Interspecies Variability
What about the children?!

How does this translate to humans?
Retrospective Data

Long-term Differences in Language and Cognitive Function After Childbirth Exposures to Anesthesia

- GA (n=350) vs Controls (n=700) prior to age <2
  - Single GA ↑ risk learning disability

- GA (n=321) vs Controls (n=2287) prior to age <3
  - Single GA ↑ risk of Language and Cognition Disability

- GA (n=593) vs Controls (n=2,764) prior to age <4
  - Multiple – not single – GA ↑ risk learning disability

Flick et al, Pediatrics 128(5) 2011.
Ing et al, Pediatrics 130(3) 2012.
Wilder et al, Anesthesiology 110(4) 2009
Retrospective Data

Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

- 1,143 Monozygotic Twin pairs with GA <3y and GA <12 yrs
- Discordant pairs had similar test scores

Academic Performance post initial Hernia Repair in Infants

- GA (n=2,689) vs Controls (n=14,575) prior to age < 1yr
- No evidence of disability in GA group

Educational outcomes after pyloric stenosis repair before 3 months of age: nationwide cohort study

- GA (n=779) vs Controls (n=14,665) prior to age < 3 month
- No evidence of disability in GA group

Recent Research Efforts
Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

- International, Multicenter, Observer-Blind, RCT
- < 60 weeks post-conceptual age, >26 Gestational age
- Unilateral or bilateral inguinal hernia repair
- GA vs Spinal Anesthesia
- Primary Endpoint -> 5 year IQ testing
- Secondary Endpoint -> 2 year developmental testing
G.A.S. Study Design

n = 722

Spinal Anesthesia (n=363)
- Spinal: 0.1mg/kg 0.5% bupivacaine
- Caudal: 2.5mg/kg 0.25% bupivacaine
- Combined spinal-caudal +/- ilioinguinal and field blocks

287 in per-protocol analysis
238 completed analysis

General Anesthesia (n=359)
- Sevoflurane
- No opioid, no N2O
- Caudal, ilioinguinal block OK
- Tylenol allowed

356 in per-protocol analysis
294 completed analysis

* Median duration of GA was 54 min
<table>
<thead>
<tr>
<th>Composite Score</th>
<th>RA as per protocol</th>
<th>GA as per protocol</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>98.6 (14.2)</td>
<td>98.2 (14.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Language</td>
<td>94.6 (15.4)</td>
<td>94.0 (15.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>Motor</td>
<td>98.3 (13.2)</td>
<td>97.9 (13.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Social-Emotional</td>
<td>97.4 (19.0)</td>
<td>95.4 (18.3)</td>
<td>2.0</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>93.1 (15.6)</td>
<td>94.3 (14.7)</td>
<td>1.2</td>
</tr>
<tr>
<td>MacArthur-Bates % score</td>
<td>32.4 (27.9)</td>
<td>34.7 (28.7)</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Data are mean (SD)
G.A.S. Conclusion

“Strong evidence that exposure of <1h to a sevoflurane based general anesthetic in infancy does not increase the risk of adverse neurodevelopmental outcome at 2 years of age”
Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood

- 105 sibling-pairs, Retrospective Cohort Study
- Currently 8-15 years old, age gap ≤ 3 years
- Single exposure to general anesthesia for inguinal hernia surgery before 3 years old
- **Primary outcome**: Global cognitive function (IQ)
- **Secondary outcomes**: Domain-specific neurocognitive functions and behaviors
## Results

<table>
<thead>
<tr>
<th>Age at anesthesia exposure, mo</th>
<th>No. of Sibling Pairs</th>
<th>Mean (95% CI)</th>
<th>Difference, Exposed – Unexposed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11</td>
<td>33</td>
<td>112 (108-116)</td>
<td>1 (-4.1 to 6.1)</td>
</tr>
<tr>
<td>12-23</td>
<td>39</td>
<td>111 (107-115)</td>
<td>1 (-3.5 to 5.4)</td>
</tr>
<tr>
<td>24-36</td>
<td>33</td>
<td>110 (105-115)</td>
<td>-1 (-5.8 to 3.8)</td>
</tr>
</tbody>
</table>
“Among healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure, there were no statistically significant differences in IQ scores later in childhood”
A Population-based Study Evaluating the Association between Surgery in Early Life and Child Development at Primary School Entry

- 28,000 children exposed to GA vs > 55,000 matched controls

Primary Outcome: Developmental outcomes at age 5-6

*Early Development Instrument (EDI)* – validated teacher questionnaire to assess child in five major domains:

- Physical health and well-being
- Social Knowledge and competence
- Emotional Health and Maturity
- Language and Cognitive Development
- Communication skills and general knowledge
## Results

### Vulnerability increased in exposed group

- **Any surgery**
  - <2 years
  - ≥2 years

- **A single surgery with length of stay <2 days**
  - <2 years
  - ≥2 years

- **Frequency of surgery**
  - 1
  - 2
  - 3
  - ≥4

Vulnerability **NOT increased in exposed group <2 yrs old** (OR 1.04; CI 0.98 to 1.10)

Vulnerability increased in exposed group (OR 1.05; CI 1.01-1.08)
“Big Data” Study Conclusion

- Increased risk of early developmental vulnerability in children exposed to anesthesia, but the magnitude is very small.

- Surgery before age 2 does not increase the risk of adverse development.
Summary

• Anesthetics cause apoptosis in animals

• Unclear if animal data translates to humans

• Small Retrospective studies are inconclusive

• Recent large studies are reassuring

• No single preferred method of anesthesia

• **NO convincing evidence** that exposure to a short GA in infancy will cause disability

• Data is still not conclusive
When it comes to pediatric anesthesia research... we’ve got your baby’s back!