Anesthesia & Sedation & the Developing Brain: Update and Alternative?

Sally J. Bird MD FRCPC
Pediatric Anesthesia, IWK Health Centre
Assistant Professor
Dalhousie University Department of Anesthesiology, Pain Management and Perioperative Medicine
Objectives

- Recent evidence/discussion about the potential neurotoxicity of anesthetic agents on the developing brain
- Review the evidence of the human studies
- Discuss whether or not we should be concerned as health care providers for children
- Discuss possible alternatives/adjuvants to general anesthesia
  - Regional anesthesia – update on what we can do and what are doing at the IWK
Why Did I Choose this topic?

Elective procedures and anesthesia in children: pediatric surgeons enter the dialogue on neurotoxicity questions, surgical options, and parental concerns.

Byrne MW¹, Ascherman JA, Casale P, Cowles RA, Gallin PF, Maxwell LG.

Developmental synaptogenesis and general anesthesia: a kiss of death.

Jevtovic-Todorovic V.

[Neurotoxicity of general anesthetics in childhood: does anesthesia leave its mark on premature babies, newborns and infants?].


Functional implications of an early exposure to general anesthesia: are we changing the behavior of our children?

Jevtovic-Todorovic V.


Anesthesia for the young child undergoing ambulatory procedures: current concerns regarding harm to the developing brain.

Olsen EA¹, Brambrink AM.
Introduction

- General anesthesia is considered a safe intervention – allowing complex surgical procedures in seriously ill patients of all age groups.

- Anesthetics/sedatives exert their effects on the CNS – they influence major brain functions.

- So…do some of the effects of anesthetics persist after the patient regains consciousness?
History

- Late 90s
- “Blocking NMDA receptors and apoptotic neurodegeneration in the developing brain” Science 1999;283:370-4
- “Neurotransmitters and apoptosis in the developing brain” Biochem Pharmacol 2001;62:401-5
- And many more… but these were all in rodents and a few in rhesus monkeys…
History Cont’d – Human Studies

- Mid-2000s – Started to see some studies cropping up in the anesthesia literature, most discounting the findings due to confounders/lack of evidence
- 2011 – THIS appeared and then THIS
- More widespread interest and concern
- FDA started becoming concerned
- SmartTots was formed (circa 2010) – cooperation among the FDA, IARS, and multiple pediatric anesthesia societies
Cognitive and Behavioral Outcomes After Early Exposure to Anesthesia and Surgery
Randall P. Flick, Slavica K. Katusic, Robert C. Colligan, Robert T. Wilder, Robert G. Voigt, Michael D. Olson, Juraj Sprung, Amy L. Weaver, Darrell R. Schroeder and David O. Warner

Pediatrics 2011;128;e1053; originally published online October 3, 2011;
DOI: 10.1542/peds.2011-0351
Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia
Caleb Ing, Charles DiMaggio, Andrew Whitehouse, Mary K. Hegarty, Joanne Brady, Britta S. von Ungern-Sternberg, Andrew Davidson, Alastair J.J. Wood, Guohua Li and Lena S. Sun

*Pediatrics* 2012;130;e476; originally published online August 20, 2012;
DOI: 10.1542/peds.2011-3822
What do we know about the developing brain?

- Neurogenesis\textsuperscript{1}
- Elimination occurs through programmed cell death: Apoptosis\textsuperscript{2}
- Humans: synaptogenesis starts in 3\textsuperscript{rd} trimester\textsuperscript{1}
- Rapid brain growth occurs in different regions at different ages – nearly complete by age 2-3
- Neural circuit development slows after age 2-5 but continues through childhood and adolescence
Figure 1 Time scale of brain development.

From Sinner et al. General Anaesthetics and the developing brain: and overview. Anaesthesia 2014, 69, 1009-1022
How do Anesthetics Work?

- In general, effect neurotransmitters and synaptic transmission
- Block NMDA receptors
- Enhance GABA – A receptors
  - In adult brain GABA is an inhibitory neurotransmitter
  - In developing brain it is an excitatory neurotransmitter

(We don’t know exactly….)
Animal Studies

- Exposure to NMDA receptor antagonists (Ketamine) leads to widespread apoptotic neurodegeneration in the developing rat brain$^3$

- Exposure to GABA receptor agonists leads to neurodegeneration$^4$

- Exposure to multiple agents appears to be worse than exposure to single agent only***
Possible Mechanisms

- Induce inappropriate apoptosis – may accelerate apoptosis
- Influence neuronal development
- Influence neuronal differentiation and plasticity
- Effect synaptogenesis and network formations
- Reduce neurogenesis
- Mitochondrial dysfunction
Possible Mechanisms of Neurotoxicity\textsuperscript{5}
Which Drugs Have Been Implicated?

- Inhaled anesthetics (sevoflurane, isoflorane, desflurane)
- Benzodiazepines (e.g. Midazolam)
- Barbiturates
- Ketamine
- Propofol
- Etomidate
- Opioids?
BUT...Can we really compare?!

Peak synaptogenesis 1\textsuperscript{st} 2 weeks of life

Peak synaptogenesis up to 2-3 years!
Wilder et al. 2009: children exposed to GA two or more times or total duration of 120min, before age 4 were at increased risk of LD.

DiMaggio et al. 2009: Children who underwent hernia repair before age 3 had 2.3 fold increase in incidence of LD.

Boomsma et al. 2009: Twin research – no increase incidence of LD in twins who were exposed to GA vs. those who were not.
Confounders and Problems with Research

- Retrospective
- Children do not undergo anesthesia for no reason i.e. there is another issue at play
- Difficult to study: won’t get REB approval to randomize to GA vs. NONE
- Many uncontrollable variables
- Bottom line: if you required multiple anesthetics early life, there are other variables!
Factors Influencing Neurotoxicity

- Concerning themes have emerged:
  - Timing of exposure
  - Frequency and Duration of exposure
  - Dose Dependent
  - Multiple agents
Leads to the Dilemma

- Clear evidence in animal studies of neurotoxicity of common anesthetic agents
- Human research unclear
- Baby brains are vulnerable – especially neonatal and premature brains!
- Babies and children frequently require anesthesia/sedation

What now?!
Further Research - Prospectively

- **PANDA** – Pediatric Anesthesia and Neurodevelopmental Assessment: following children who had hernia repair prior to age 3, will assess at age 8 and 15

- **GAS** – General Anesthesia and Spinal: randomized infants having hernia repair to either GA or spinal anesthesia. Results expected in 2015

- **MASK** (MAyo Safety in Kids): cohort study of children who receive one or more Gas prior to age 3
But until we KNOW

- Advocate for your patients – is this surgery/test/procedure necessary right NOW?
- Consider delay until after age 4 if possible
- Shortest possible procedure - ??? Teaching?
- Risks vs. benefits: avoiding GA vs. not having procedure
- Explore alternatives: Regional anesthesia, single agent sedation, procedure done under local
What is Regional Anesthesia?

Regional anesthesia is the technique of rendering a portion of the patient’s body insensate for purpose of surgical stimulation or pain management.

Techniques may be:
- Central
- Peripheral
RA: Knowledge of Anatomy

- Dermatomes - remember those?
- We can block any region of the body with knowledge of what nerves supply that area
Regional Techniques Performed in Children

- Caudal *
- Epidural *
- Supraclavicular
- Trunk blocks: TAP, ilioinguinal, rectus sheath
- Femoral
- Sciatic
- Popliteal
Central vs. Peripheral Blocks

- Place LA at the level of the spinal cord to “block” nerves
- Central, hemodynamic effects
- Block below the umbilicus
- Caudal, epidural, spinal
- Rare, catastrophic complications

- LA placed at site of specific nerve to “block” single body part
- Targeted approach
- No central effects
- Complications local
- Requires larger volumes of LA
- Few contraindications
Benefits of RA

- Improved post-operative pain management
- Decrease opioid requirement – less S/E, early eating
- **Decreased general anesthetic requirements**
- Generally smoother emergence from anesthesia
- Can have lasting analgesic effects from even single shot of LA
- Micro vascular dilation and improved perfusion of tissues (important for wound/graft healing)
Disadvantages of PNBs

- Technical expertise and learning curve
- Surgical site can span more than one nerve, requiring multiple injections
- Time
- Unable to (routinely) use continuous techniques at IWK (yet!)
- Potential for large volumes of LA
What are the risks of RA?

- Infection
- Hematoma (epidural hematoma can be devastating)
- Local anesthetic toxicity
- Inadequate block/pain control
- Minor, resolving nerve damage
- Major permanent nerve damage
How long do blocks last?
Using standard Ropivicaine 0.5% with Epi

<table>
<thead>
<tr>
<th>Block</th>
<th>Onset (min)</th>
<th>Duration (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudal (Ropi 0.2% or Bupi 0.25%)</td>
<td>10 - 20</td>
<td>6 - 18</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>15 - 20</td>
<td>8 - 12</td>
</tr>
<tr>
<td>Trunk Blocks</td>
<td>15 - 30</td>
<td>8 - 24</td>
</tr>
<tr>
<td>Femoral</td>
<td>15 - 30</td>
<td>5 - 12</td>
</tr>
<tr>
<td>Sciatic</td>
<td>15 - 20</td>
<td>6 - 24</td>
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What Should we Tell this Mum?

- Safety?
- Risks are low
- Short duration unlikely to cause harm
- Risk of delaying
- Consider RA if appropriate
Additional References


