Update on Pediatric Anesthesia
CRASH 2016
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"If you always do what you always did, you will always get what you always got."

Participants will be able to...

• Describe possible implications of the neurodevelopmental effects of anesthesia on young infants and children.

• Understand advances in pediatric pain management and regional anesthesia.

• Discuss growing use of dexmedetomidine in pediatric patients

Disclosures

• Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots
• 2012 response to a 2009 FDA request
• Public-private partnership
  – International Anesthesia Research Society
  – FDA
  – Other stakeholders
• Coordinate and fund research
• SmarTTots.org
• Consensus Statement, October 2015
• Animal Studies
  – Show brain injury, behavior/learning deficits
• Human Studies
  +/- on effects, confounding factors
• No definitive answers

Healthcare Providers
• Highlight difference between animal and human research findings
• Most meds have been implicated in animal studies
• Anesthesia is necessary for surgery, etc
• Decisions regarding timing should be discussed with all team members & family
• Elective procedures
  – Risk/Benefit of surgery vs delay

Parents
• Discuss timing of procedure with PMD, surgeon, anesthesiologist.
• Weigh unknown risk of anesthesia vs potential harm of postponing surgery
• Individualized decisions
• Smarttots.org

Anesthesia and the developing brain: a way forward for clinical research
Davidson, Peds Anesth (25)2015
• 2 day meeting in Genoa, Italy
• Pediatric Anesthesia and Neurotoxicity: From the GAS study to future collaborative trials.
• May 23 – 24, 2014
• Pediatric anesthesiologists, basic science & clinical researchers, project coord., neonatologists, neuropsychologists, surgeons, peds anesth society leadership
• Summarize current/ongoing research
• Develop key questions to drive future research

What we know
• Animals studies
  – Many GAs have effects of developing brain: apoptotic cell death, impaired synaptogenesis, potential long term neurologic dysfunction.
• Effects greatest in very young animals
• Mixed evidence for association b/w anesthesia and poor neurodevelopment in animal models
• Some interventions mitigate changes observed
• Several plausible mechanisms implicated
• Mixed evidence for association between anesthesia and risk of poor ND outcome in children

What we do not know
• Which children (age of exposure, dose) are at greatest risk for poor developmental outcome
• Which neurological domains are affected
• The mechanism involved
  – Hypotension, hypoxia inflammation, illness, surgery, direct toxicity, socio-economics?
• Possible neuroprotective effects
• Which interventions would reduce the risks

3 Approaches to Research
• Determine if clinically relevant toxicity exists
• Accept toxicity exists.
  – Find thresholds and mitigating mechanisms
• Make no assumption on association
  – Identify greatest risk population
  – Can we alter risk and change anesthetic techniques
2015 Basic Science

Dosing and Timing

Mechanisms - MicroRNA

- Small, endogenous, non-coding segments
- Negatively regulate target gene expression
- Implicated in disease processes, including (most recently) neurotoxicity

miRNA-124

What to do with the animal data?

- Does the animal data translate?
- NT is multifactorial
- Very young animal with high dosing

But there is a lot of alarming data
What about non-rodents

- Conflicting data
- Retrospective studies
- Power
- Learning & behavior is multifactorial

- Need better studies
  - Prospective
  - Large
  - Multi-institutional

Mayo Anesthesia Safety in Kids (MASK) Study

Gleich, Contemporary Clin Trials, 41: 2015

- Morgan Stanley Children’s Hospital, Columbia University
- Pilot study published 2012
- Prospective study underway
  - Children exposed at 0-3 years of age
  - Compare exposed and unexposed siblings ages
  - Neuropsychological and behavioral testing at ages 6-18

Lancet, January 16, 2016

First randomized controlled trial assessing the effect of general anesthesia in infancy on neurodevelopmental outcome

GAS

- Subjects
  - < 60 weeks gestation, born >26 weeks
  - Inguinal herniorrhaphy
  - 28 hospitals: Australia, Italy, USA, UK, Canada, Netherlands, New Zealand

- Study
  - Feb 9, 2007 – Jan 31, 2013
  - Randomized to receive GA (359) or awake/spinal (363)
  - Primary outcome: Wechsler Preschool and Primary Scale of Intelligence III Full Scale Intelligence Quotient, at age 5 yrs
  - Secondary outcome: Bayley Scales of Infant and Toddler Development III, at age 2 years

GAS

- Outcome data available for 238 A/R and 298 GA
  - Median duration of GA 54 minutes
  - Cognitive composite score (mean [SD])
    - 98.6 [14.2] in the awake/regional group
    - 98.2 [14.7] in the general anesthesia group

- Found no evidence that less that 1 hour of sevofurane anesthesia in infancy increases the risk of adverse ND outcomes at 2 years of age compared with awake-regional anesthesia

- Strongest clinical evidence to date, but still not definitive.
The surgeons are taking notice

Surgical adaptation

- TOPS Trial – Timing of Primary Surgery for Cleft Palate
  - 6 months vs. 12 months
- Orthopedics
  - Club foot, digits, hips – wait?
  - Urgent trauma, infections - can’t wait, but can decrease # I&D procedures
- General Surgery
  - Hirschsprung Disease – early intervention improves outcomes
  - Non-surgical approach to abdominal wall defects

PALC survey results

- Most are getting some education
  - Journal Clubs, Grand Rounds, Conferences
- Providing parents with information
  - 91% discuss only if asked
  - 6% discuss NT routinely
  - 1 program is adding to their consent
  - 25% have a formalized mechanism to provide information
Healthcare Providers
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Regional Anesthesia in Children
- Benefits
  - Perioperative pain relief
  - Decrease opioids
  - Decreased general anesthesia*
  - Growing experience
  - PNB, NA
- Questions
  - Safety
  - Ultrasound
  - Awake vs. asleep

Asleep vs Awake
Peripheral nerve blocks
Ultrasound
Neuroaxial
Neurotoxicity
Avoid general anesthetics

General Anesthesia compared to Spinal anesthesia study (GAS)
- Apnea post-anesthesia in infants
  - < 60 weeks gestation, born >26 weeks
  - Inguinal herniorrhaphy
  - Randomized to receive GA (359) or awake/spinal (363)

GAS – Apnea results
- Overall incidence of apnea, 0-12hrs
  - RA 3% vs GA 4%
- Early apnea, 0-30mins
  - RA 1% vs GA 3%, OR 0.2
- Late apnea, 30min-12hours
  - RA & GA 2%

Note: GAS = General Anesthesia, RA = Regional Anesthesia.
GAS - Failure

- Failure of regional neuroaxial technique was 10%
- Bloody tap predicts failure, OR 2.46
- Heterogeneity of technique and experience limits ability to comment on preferred method

Frawley, ANES, (123) July 2015

Awake vs. GA/Sedation

- Turns out it’s not....
- 4 major large scale studies.
- No incidence of paralysis with neuroaxial anesth/anal
  – 95%CI 0(0% - 0.004%)

ESRA/ASRA Conclusion

- Performance of PRA under GA/DS is safe and should be viewed as standard of care
- Overall complication risk is 0.66% (95% CI, 0.6% - 0.7%)
  – Risk of paralysis is 0 (95% CI, 0% - 0.004%)
- Should maintain a high index of suspicion for serious complications/neurologic injury

Test dosing in kids

- PRAN
- 26,949 blocks with a test dose
  – 0.21% incidence of +TD
  – All but 1 with caudal or epidural
- Careful dose calculation > test dose

4 large scale studies

- French Language Society of Paediatric Anaesthesiologists (ADARPEF), 1996
  – 38 centers, 24409 RAs, 89% with GA
  – 0.9/1000 overall, 0 PNB, 1.5/1000 NAB
- UK Prospective National pediatric Epidural Audit, 2007
  – 10533 RAs
  – 96 complications; 5 serious, 9 major
- ADARPEF, 2010
  – 29870 blocks with GA
  – 41 complication, 0 long-term
- Pediatric Regional Anesthesia Network report, 2014
  – Internet database, 2007-2012
  – 53,564 PRAs
  – PRA under GA +/- NMB demonstrated no increase in complications
  – PRA with GA had less complication rate than awake or sedated

Reg Anesth Pain Med [40] 2015
Problems with interpretation

- GA and dose at the time
- Higher resting heart rate
- Age-dependent CV reactivity to epinephrine
- Premedication received
- Type of local anesthetic received
- Type of general anesthetic received

Committee Recommendations

- Difficulty interpreting negative TD
  - False negative TD occur
  - LA solutions given slowly and small aliquots (0.1-0.2 ml/kg)
- Any T wave or heart rate changes within 30-90 second should be considered positive IV injection. No False Positives
- Imaging modalities may help.

Either is okay

<table>
<thead>
<tr>
<th>Air LOR</th>
<th>Saline LOR</th>
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<tbody>
<tr>
<td>Nerve root compression, pneumocephalus,</td>
<td>Dural puncture detection, dilute dose,</td>
</tr>
<tr>
<td>incomplete block, venous air embolism</td>
<td>decrease CBF</td>
</tr>
<tr>
<td>Associated with repeat, large bolus</td>
<td>Volume dependent</td>
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- No evidence one is better than the other
- Consider combination
- limit volume to 0.5 – 1 ml in neonate/infants

Compartment Syndrome

- Case reports
  - Root cause analyses reveal poor monitoring and poor positioning
- Diagnosis
  - 30mmHg
  - 4 hours to tissue loss
- Concern for masking
  - Breakthrough pain may be an early sign

Committee Advice

- No current evidence that RAs increase risk for Acute Compartment Syndrome or delay diagnosis in children
- Preop conversation with parents about risk

- “Best Practice”
  - Single shot 0.1 – 0.25% bupi, ropi
  - Continuous infusion up to 0.1%
  - Restrict volume and concentration in catheters for tibial compartment
  - Cautions with additives
  - Follow up/monitoring by APS
  - Measure compartment pressures if suspected

PRAN

- Internet Database for PRA
- Prospective data
- Established 2006
- Data 2007-2012
- 2015 Publications
  - Caudal Safety
  - Peripheral Nerve Block Safety
PRAN - Caudal

- 18,650 children received a caudal block
- Complications
  - Overall rate 1.9% (1.7-2.1%)
  - Higher association with younger patients
    - Median 11 months vs. 14 months
- Most common complications
  - Block failure (1%); Blood aspiration (0.6%); iv injection (0.1%)
  - No temporary or permanent sequelae
  - 24.6% received potentially unsafe dose (>2mg/kg)


PRAN – Peripheral Nerve Catheters

- 2074 PNCs
- 251 adverse events & complications, 12.1%
  - Catheter malfunction
  - Block failure
  - Infection
  - Vascular puncture
- No persistent neuro injury, serious infection, or LAST

Walker, BJA, July 2015

Evidence for the use of US in PRA

- Initial review 1994-2009
- Current review 2009-2014, 37 RCT and prospective observational studies.

Lam, Reg Anesth & Pain Med, 2015

Summary of findings

<table>
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<tr>
<th>PNB</th>
<th>NAB</th>
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<tbody>
<tr>
<td>• ↓ Performance time</td>
<td>• Improve needling time</td>
</tr>
<tr>
<td>• ↑ Block success</td>
<td>• Predict depth</td>
</tr>
<tr>
<td>• ↑ Block quality</td>
<td>• Improve catheter visualization</td>
</tr>
<tr>
<td>• Excellent pain relief</td>
<td>• ↑ Block quality</td>
</tr>
<tr>
<td>• Lower post-op opioid requirement</td>
<td></td>
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Lam, Reg Anesth & Pain Med, 2015


Schwartz, Lawrence, MD
Update on Pediatric Anesthesia
Adjuncts to local anesthetics

- 212 children, ASA 1-2, 1-3 years, 8-18 kg
- Elective inguinal hernia/hydrocele repair
- Treat with caudal injection
  - 0.25% levobupivacaine
  - 0.2% levobupivacaine
  - 0.2% levobupivacaine + Dexmedetomidine 2mg/kg

Results

- No change in block onset time
- Increase mean block duration
  - 0.25% LB → 7.23 hours
  - 0.2% LB → 5.84 hours
  - 0.2% LB + DEX → 19.6 hours

Comparison of caudal bupivacaine alone with bupivacaine plus two doses of dexmedetomidine for postoperative analgesia in pediatric patients undergoing infra-umbilical surgery: a randomized controlled double-blinded study

<table>
<thead>
<tr>
<th>Group</th>
<th>Time to block onset (min)</th>
<th>Time to complete surgery (min)</th>
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<tbody>
<tr>
<td>Dose 1</td>
<td>3.0 ± 1.6</td>
<td>18.5 ± 2.8</td>
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<tr>
<td>Dose 2</td>
<td>5.0 ± 2.8</td>
<td>24.0 ± 3.2</td>
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Dexmedetomidine as adjunct to ilioinguinal/iliohypogastric nerve blocks for pediatric inguinal hernia repair: an exploratory randomized controlled trial

1.5 – 8 year old children, ASA 1-2, double blind
21 received local anesthetic; 22 local anesthetic + DEX
Results

- Dexmedetomidine depresses the release of C-fiber transmitters
  - Effect hyperpolarization of postsynaptic dorsal neurons
- Combination of dexmedetomidine and local anesthetics produces a synergism
  - Block Aδ and C fibers
  - Decreasing local anesthetic absorption
  - Activating cholinergic neuron.

Dexmedetomidine

- $\alpha_2$-adrenergic receptor agonist
- $\alpha_2: \alpha_1$ selective binding 1600:1
- 7x more selective than clonidine

Cellular Mechanism of the $\alpha_2$-Adrenergic Agonists

- Alpha-2 receptor provides negative feedback to inhibit NE release
- Decrease sympathetic response
- Clinical effectiveness tied to selectivity for alpha-2
End organ effects of Dexmedetomidine

End Organ Effects - Neurologic

- Sedation via selective binding $\alpha_2$ receptors in the locus ceruleus
  - Decreased noradrenergic output $\rightarrow$ increased GABA firing
  - Natural, non-REM sleep
    - Animal studies
    - Pediatric EEG

Why the excitement

- Airway maintained
- Respiratory drive
- Cardiovascular stability
  - Heart rate, blood pressure
- "natural" sleep
- Possible organ protection
  - Ischemic/reperfusion, inflammation, CPB, sepsis
- Not implicated in neurotoxicity.
- May be neurologically protective

Areas of use

- Preoperative sedation
- Treatment of post-anesthesia shivering
- Procedural sedation
- MRI, radiology
- Anterior mediastinal mass
- Difficult airway
- Bronchoscopy
- Sedated echocardiography
- Sleep studies
- EEG
- Narcotic withdrawal
- Emergence delirium
- ICU sedation
- Cardiac anesthesia
- Regional anesthesia
- Spine surgery (evoked potentials)

Typical patient

- 6 month old infant with HLHS
  - s/p Atrial balloon septostomy DOL 0
  - s/p Norwood, Stage I repair, DOL 3
  - Sedated ECHO @ 1 month, 3 months, 4 months, CT angio @ 4 months
- Requires sedated preoperative ECHO today, in anticipation of modified bi-directional Glenn, tomorrow.

Intranasal use for transthoracic ECHO

- 115 kids, < 3 years old, acyanotic CHD
- 100 (87%) had satisfactory sedation
- Mean onset 16.7 +/- 7 minutes
- Wake up time 44.3 +/- 15 minutes
- Overall, no change in HR, BP, SpO$_2$
- 1 patient required NCO$_2$
- 4 patients with bradycardia < 90, no hypotension, no intervention

Li, Ped Anes (25), 2015
Emergence Delirium

Sleep: It is Worth the Fight

2015 Papers

- Hauber, Anesth & Analg, Nov 2015
- Yao, Ped Anes, May 2015
- Hadi, Int J Ped Otolaryng, Feb 2015

Summary

- Typical doses of dexmedetomidine (0.3–1 mcg/kg)
- Used as premed, part of the anesthetic, at the EOS
- Reduce the risk of PAED
  - Half to one third
- Reduce the severity of PAED
- Wake up time can be extended
- PACU time not significantly increased

Added benefits

- Decrease amount of opioids
- Decrease sevoflurane concentration


- 40 control, 40 DEX pts
- Mean age 6 years
- Treated at induction with Saline vs. DEX 0.5mcg/kg
- Sevoflurane to maintain BIS 45-55
DEX and Congenital Heart Disease

- Most complex patients are often the most young and require high dose, long, repetitive anesthetics
- Cardiopulmonary bypass + myocardial ischemia + hemodynamic instability + hypoxemia + anesthesia neurotoxicity risk factors = neurodevelopmental injury?

Benefits of Dexmedetomidine in CHD

- Shorter mechanical ventilation, earlier extubation
- Less opioid requirements
- Decreased stress response: cortisol, glucose
- Improved hemodynamic stability
- No significant difference in hospital or ICU LOS

Pan, Ped Anes, 2016

Potential Benefits

- Animal Studies
  - Attenuate ischemic-reperfusion injury
  - Decrease inflammatory molecules
  - Decrease neuroapoptosis, memory function

How this relates to clinical outcomes is unknown

- There is a growing body of scientific literature implicating most anesthetics in neurotoxic pathways
- The clinical impact of anesthetic toxicity is unknown
- Recommendations revolve around open and clear communication
- Pediatric Regional Anesthesia is growing strongly
- It’s safety and efficacy is now well established
- PRA may provide a avenue to avoid toxic anesthetics
- Dexmedetomidine use is growing in many arenas of pediatric anesthesia
- It’s appears to offer a growing number of clinical benefits to pediatric patients
- Preclinical research suggests it may attenuate cellular injury associated with inflammation, ischemia, and anesthesia-related neurotoxicity. However, the clinical data here is lacking.

Thank you