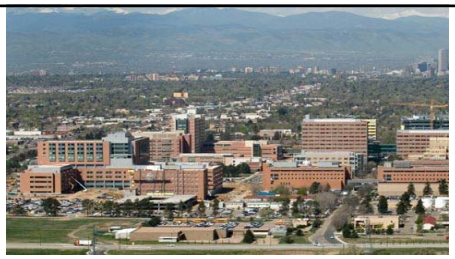
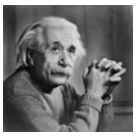
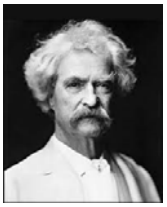


Update on Pediatric Anesthesia
CRASH 2016

Larry Schwartz, MD
Associate Professor, Director of Education
Department of Anesthesiology
Children's Hospital Colorado, University of Colorado
March 1, 2016

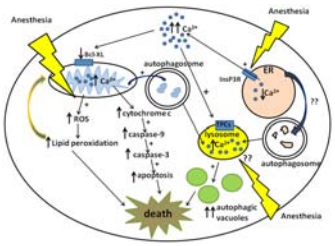




"If you always do what you always did, you will always get what you always got."

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



SmartTots
Funding anesthesia research to ensure pediatric safety

- 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

Smart Tots
Funding anesthesia research to ensure pediatric safety

- Consensus Statement, October 2015
- Animal Studies
  - Show brain injury, behavior/learning deficits
- Human Studies
  +/- on effects, confounding factors
- No definitive answers

Smart Tots
Funding anesthesia research to ensure pediatric safety

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

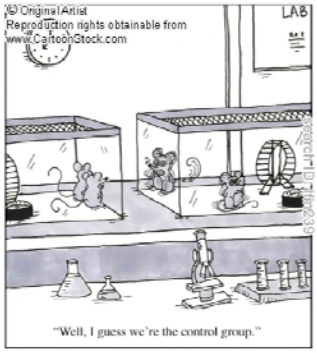
What we do not know

- 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

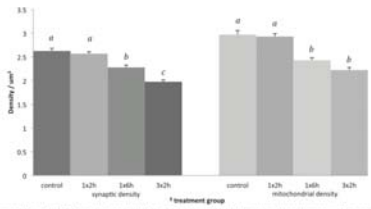
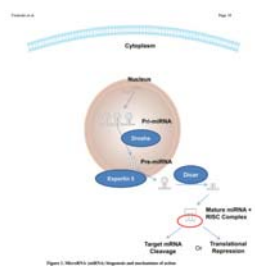


Fig. 3. Mean synaptic and mitochondrial density by treatment group: multiple and prolonged exposure to anesthesia was associated with greater reductions in both synaptic and mitochondrial density. Synaptic and mitochondrial density are expressed as mean ± SEM. §Treatment group (n = 5/group): 1×2h = single 2-h exposure postnatal day 7 (P7); 1×6h = single 6-h exposure (P7); 3×2h = three 2-h exposures (P7, P10, and P13). *a*, *b*, *c* indicates groups with differing superscripts (*a*, *b*, or *c*) are significantly different from one another (statistical significance defined as $P < 0.05$). For example, for synaptic density: the control and 1×2-h groups do not differ from each other, but both differ from the 1×6-h and 3×2-h groups, which also differ from one another.

Mechanisms - MicroRNA



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

miRNA-124

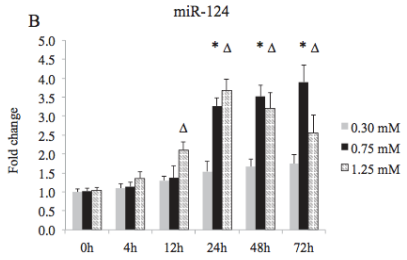
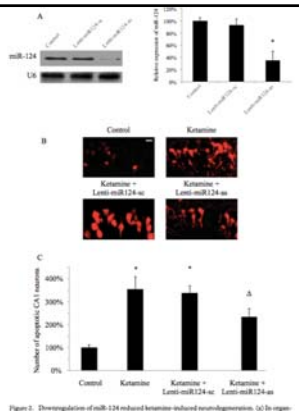


Figure 1. Ketamine upregulated hippocampal miR-124 *in vitro*.

Xu, *Int J Neurosci* 125(3): 2015



Xu, *Int J Neurosci* 125(3): 2015

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

PANDA STUDY
PEDIATRIC ANESTHESIA AND NEURODEVELOPMENT ASSESSMENT

- 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

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

Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern-Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium*

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 sevoflurane 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

The Cleft Palate-Craniofacial Journal 52(4) pp. 494–498 July 2015

BRIEF COMMUNICATION

Neonatal Anesthesia Neurotoxicity: A Review for Cleft and Craniofacial Surgeons

Donald R. Laub, Jr., M.S., M.D., F.A.C.S., Robert K. Williams, M.D.

There is growing evidence that the commonly used anesthetic agents cause some degree of damage to the early developing brain. The animal evidence for anesthetic neurotoxicity is compelling. Numerous confounders in human research prevent researchers from drawing definitive conclusions about the degree of risk. For every surgery, it should be assessed whether the benefits of an early surgical procedure justify a potential but unquantifiable risk of neurotoxicity of anesthetic agents. The timing and number of surgeries in our treatment protocols may need to be reevaluated to account for these potential risks.

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

The New York Times
HEALTH

Researchers Warn on Anesthesia, Unsure of Risk to Children

By DENISE GRADY FEB. 25, 2015

F.D.A. to Study Whether Anesthesia Poses Cognitive Risks in Young Children

U.S.News HEALTH

Should Surgery Wait? How Anesthesia Affects Kids

Learning about the potential risks on growing brains is important, experts say.

Pediatric Anesthesia
Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Neurotoxicity, general anesthesia in young children, and a survey of current pediatric anesthesia practice at US teaching institutions

Christopher G. Ward[1,*], Scott J. Hines[1,*], Lynne G. Maxwell[1], Francis X. McGowan[1] & Lena S. Sun[2,3]

1 Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA
2 Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, NY, USA
3 Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY, USA

- 22 question survey
- PALC & PAPDA – 104 respondents

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

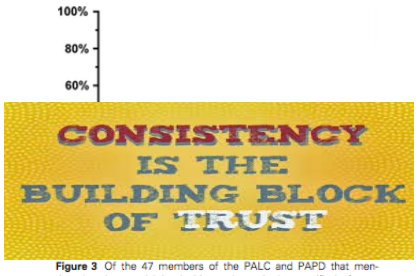


Figure 3 Of the 47 members of the PALC and PAPD that mentioned an 'age at risk,' only 38 members cited a specific 'safe age cutoff' for parents in which anesthetics given after that age were deemed safe. Nine individuals responded that although they made generalized statements about younger versus older children, they did not cite a specific age. The responses to the five options of 'No specific age' through 'Over 4 years' are displayed above for the question 'Do you cite a specific 'safe age cutoff' in your discussions of anesthesia-related neurotoxicity?'.

Ward, *Ped Anes, 2016*

SmartTots

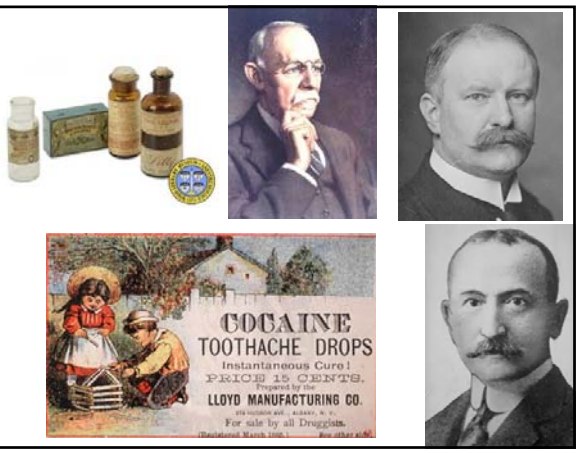
Funding anesthesia research to ensure pediatric safety

Healthcare Providers

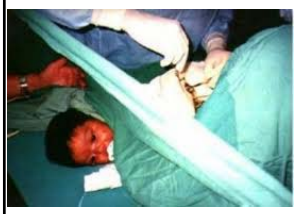
- Highlight difference between animal and human research findings
- Most meds have been implicated in animal studies
- Anesthesia is necessary for surgery, etc
- Decisions regarding timing should be discussed with all team members & family
- Elective procedures
  - Risk/Benefit of surgery vs delay

Parents

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



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%

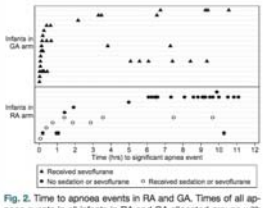


Fig. 2. Time to apnoea events in RA and GA. Times of all apnoea events in all infants in RA and GA allocated groups with RA group further divided into those with no sedation or sevoflurane (*closed circles*) and those exposed to sevoflurane or sedation (*closed squares*). Each *horizontal dashed line* represents one infant. GA = general anesthesia; RA = regional anesthesia.

Davidson, *ANES*, (123) 2015

GAS - Failure

Table 2. Awake Regional Techniques

Technique Attempted	Success, n (%)	Partial Failure, n (%)	Complete Failure, n (%)
Spinal (n = 222)	193 (86.9%)	16 (7.2%)	13 (5.9%)
CSCA (n = 117)	89 (76.1%)	7 (6%)	21 (17.9%)
Total	282 (83.2%)	23 (6.8 %)	34 (10%)

Anesthetic techniques included spinal or a CSCA. Success was defined as completion of surgery with awake regional anesthesia alone. Complete failure was defined as when any sevoflurane or sedative was given from before, or at the moment of knife to skin, and given continuously until last stitch. A partial failure was defined when patients received sevoflurane or any sedative agent (apart from glucose) for any part of the period between knife to skin and last stitch, and for part of the period between arriving in the operating room and knife to skin.
CSCA = combined spinal caudal anesthetic.

- 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

SPECIAL ARTICLE

The European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine Joint Committee Practice Advisory on Controversial Topics in Pediatric Regional Anesthesia

Giorgio Ivani, MD, Santhanam Suresh, MD,† Claude Ecoffey, MD,‡ Adrian Bosenberg, MB, ChB, FFA(SA),§ Per-Anne Lonnqvist, MD,|| Elliot Krane, MD, FAAP,** Francis Veyckemans, MD,†† David M. Polaner, MD, FAAP,‡‡ Marc Van de Velde, MD,§§ and Joseph M. Neal, MD||||*

1. PRA under GA & deep sedation
2. Test dose interpretation
3. Air loss vs. saline loss
4. Compartment syndrome

Reg Anesth Pain Med (40)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%)

4 large scale studies

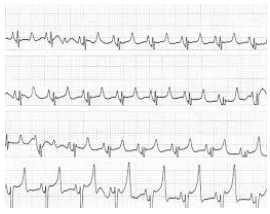
- French Language Society of Paediatric Anaesthesiologists (ADARPEF), 1996
  - 38 centers, 24409 RAs, 89% with GA
  - 0.9/1000 overall, 0 PNB, 1.5/1000 NAB
- UK Prospective National pediatric Epidural Audit, 2007
  - 10633 RAs
  - 96 complications; 5 serious, 9 major
- ADARPEF, 2010
  - 29870 blocks 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

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



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

Air LOR

- Nerve root compression, pneumocephalus, incomplete block, venous air embolism
- Associated with repeat, large bolus

Saline LOR

- Dural puncture detection, dilute dose, decrease CBF
- Volume dependent

- 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


Appendix 1

1	American Family Children's Hospital—U of Wisc.
2	University of Minnesota Children's Hospital
3	Boston Children's Hospital
4	Children's Hospital Colorado
5	Children's Medical Center Dallas
6	Children's Memorial Hermann Hospital/UT Houston
7	Children's Hospital at Dartmouth
8	Hospital Municipal Jesus—Rio de Janeiro
9	Lucile Packard Children's Hospital Stanford
10	Ann & Robert H. Lurie Children's Hospital of Chicago
11	Nationwide Children's Hospital
12	Oregon Health Sciences University
13	Seattle Children's
14	Texas Children's
15	The Cleveland Clinic
16	University of New Mexico
17	Columbia University*
18	University Hospital Rijeka*

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)

Table 2. Incidence of Specific Complications in Caudal Block

	Incidence (95% confidence interval)
Block failure	1% (0.8 to 1.1)
Blood aspiration	0.6% (0.5 to 0.8)
Positive test dose	0.1% (0.1 to 0.2)
Dural puncture	0.08% (0.005 to 0.01)
Cardiac arrest	0.005% (– to 0.002)
Seizure	0.005% (– to 0.002)
Sacral pain	0.005% (– to 0.002)
Muscle spasm	0.005% (– to 0.002)

Suresh, *A&A,* Jan 2015

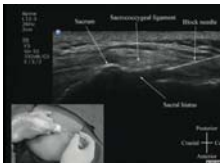
PRAN – Peripheral Nerve Catheters

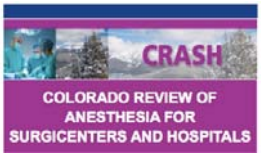
- 2074 PNCs
- 251 adverse events & complications, 12.1%
  - Catheter malfunction
  - Block failure
  - Infection
  - Vascular puncture
- No persistent neuro injury, serious infection, or LAST

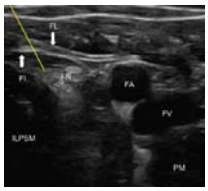
Table 4 Incidence of Specific Adverse Events and Complications

Complication	Incidence (95%CI)
Catheter malfunction (e.g. dislodgement, occlusion)	7.3% (6.2–8.5)
Abandoned or block failure	1.3% (0.8–1.7)
Catheter related infection	0.9% (0.5 to 1.4)
Vascular (e.g. blood aspiration, haematoma)	0.9% (0.5–1.3)
Excessive motor block	0.6% (0.3–1)
Difficult catheter removal	0.1% (0.04–0.3)
Other (e.g. foot swelling, muscle spasms, dizziness, burning sensation, adverse drug reaction, nausea and vomiting, contact dermatitis)	1% (0.6–1.5)

Walker, *BJA,* July 2015





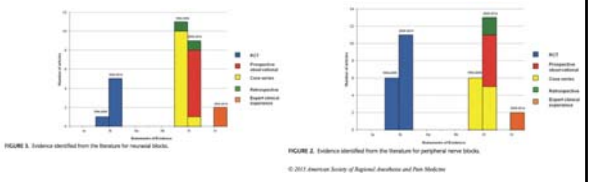


Today & Tomorrow

WORKSHOP
4:00-7:00pm Advance d Ultrasound-Guided Regional Anesthesia
$150.00 Kyle Marshall, MD; Alan Bielsky, MD; Christopher Ciarallo, MD; Matthew Fiegel, MD; Jeffrey Gonzales, MD; Adrian Hendrickse, MD; Glenn Merritt, MD; Olivia Romano, MD

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

PNB

- ↓ Performance time
- ↑ Block success
- ↑ Block quality
  - Excellent pain relief
  - Lower post-op opioid requirement
- ↓ Volume need

NAB

- Improve needling time
- Predict depth
- Improve catheter visualization
- ↑ Block quality

Lam, *Reg Anesth & Pain Med,* 2015

TABLE 10. Strength of Evidence—The Effect of USG on Patient Safety

PONS (III)
- Proving statistical differences in nerve injury as a function of nerve localization technique is likely futile
- Underpowered results from RCTs, registries, and large case series find no difference in surrogate markers of nerve injury, such as paresthesia during or immediately after block placement or transient PONS (level III evidence)
- UGRA appears to be associated with PONS at an incidence similar to historical reports of nerve injury associated with PNS (level III evidence)

LAST (Ia and III)
- Compared with PNS, USG lowers the risk of unintended vascular puncture, a surrogate outcome for LAST (level Ia evidence)
- Registry data provide strong support to the statement that USG reduces the incidence of LAST across its clinical continuum (level III evidence)
- US guidance does not completely eliminate the risk of LAST, therefore practitioners should remain vigilant and use other preventive and/or diagnostic modalities as appropriate (grade B recommendation)

HDP (Ib and IV)
- RCTs confirm the ability of low-volume USG to reduce (but not eliminate) the incidence and severity of HDP using the interscalene approach. The incidence of HDP ranges from nearly 0% to 34% with the USG supraclavicular approach (level Ib evidence)
- No RCTs or case reports address the role of USG brachial plexus blockade in patients at risk of pulmonary compromise from underlying severe pulmonary disease. Because HDP can still occur unpredictably, caution is warranted in any patient unable to withstand a 25% diminution of pulmonary function (grade C recommendation)

Pneumothorax (III)
- No adequately powered studies directly address the risk of pneumothorax with US-guided regional anesthesia
- Registry data and case reports describe the occurrence of pneumothorax despite the use of UGRA (level III evidence)

Neal, *Reg Anes & Pain Med, (41)* 2016

Adjuncts to local anesthetics

Journal of Clinical Anesthesia (2015) 27, 17–22

Journal of Clinical Anesthesia

Original Contribution

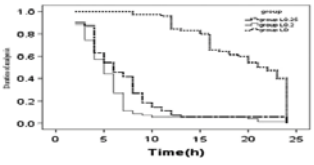
A prospective study comparing the onset and analgesic efficacy of different concentrations of levobupivacaine with/without dexmedetomidine in young children undergoing caudal blockade☆,☆☆

Ying-Jun She MD[a,b], Guan-Tu Xie MD[b], Yong-Hong Tan MD[b], Xiao-Hua Kuang MD[b], Gao-Feng Yu MD[b], Guo-Hua Lian MD[b], Xing-Rong Song MD[b,*]

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

Khaled R. Al-Zaben[1], Ibraheem Y. Qudaisat[1], Sami A. Abu-Halaweh[1], Subhi M. Al-Ghanem[1], Mahmoud M. Al-Mustafa[1], Aboud N. Alja'bari[1] & Hashem M. Al-Momani[2] *Ped Anesth,(25)* 2015

Table 2 Perioperative outcome data

Variable	Group B	Group BD1	Group BD2
Time to first analgesia (min)	360 (180–900)	600 (360–1330)*	720 (420–1400)*
Paracetamol doses per patient	3 (1–4)	1 (1–1)*	1 (1–3)*
Time to spontaneous eye opening (min)	15 (0–30)	60 (0–120)*	90 (0–120)* †
Endtidal sevoflurane (vol %)	2 (1–2)	1.5 (1–2)*	1 (0.5–2)*

Group B, bupivacaine group; Group BD1, bupivacaine + dexmedetomidine 1 μg·kg⁻¹; Group BD2, bupivacaine + dexmedetomidine 2 μg·kg⁻¹.
Values are reported as median (Range).
*P.value <0.001 when compared to group B.
†P.value <0.001 when compared to group BD1.

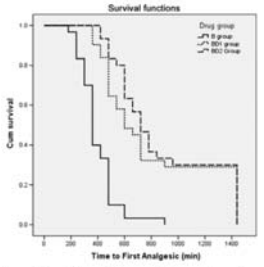


Figure 2 Kaplan–Meier analysis curve showing comparison of time to first analgesic administration between the three study groups.

Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Dexmedetomidine as adjunct to ilioinguinal/iliohypogastric nerve blocks for pediatric inguinal hernia repair: an exploratory randomized controlled trial

Märit Lundblad[1], Daniela Marhofer[2], Staffan Eksborg[3] & Per-Arne Lönnqvist[4]

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

Results

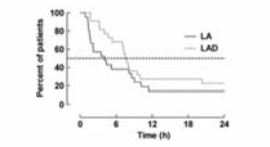


Figure 3 Kaplan–Meier Plot showing the number of patients not needing supplemental analgesia.

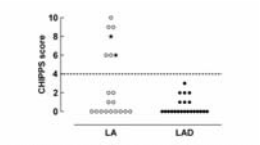
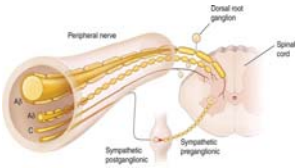


Figure 2 Pain scores at first assessment in PACU. ○: LA; •: Excluded patients; ●: LAD.

DEX and nociception

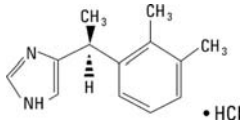


- Dexmedetomidine depresses the release of C-fiber transmitters
  - Effect hyperpolarization of postsynaptic dorsal neurons
- Combination of dexmedetomidine and local anesthetics produces a synergism
  - Block Aδ and C fibers
  - Decreasing local anesthetic absorption
  - Activating cholinergic neuron.

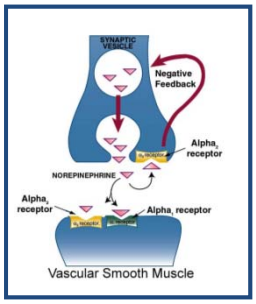
Woodcut by Veronese physician Joseph Gazola, 1716

Dexmedetomidine

- α_2-adrenergic receptor agonist
- α_2:α_1 selective binding 1600:1
- 7x more selective than clonidine



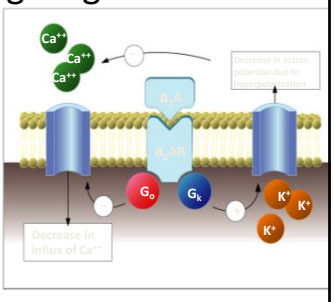
Cellular Mechanism of the α_2-Adrenergic Agonists



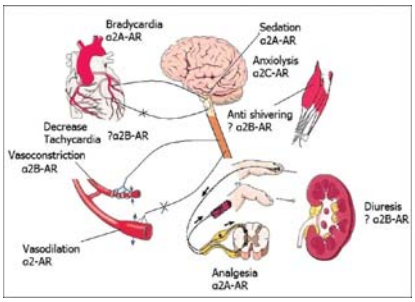
- Alpha-2 receptor provides negative feedback to inhibit NE release
- Decrease sympathetic response
- Clinical effectiveness tied to selectivity for alpha-2

Cellular Mechanism of the α_2-Adrenergic Agonists

- Alpha-2 agonist binds to receptor
- G-protein coupling
- Decrease cell membrane potential
  - Decrease Ca influx
  - Increase K efflux
- Hyperpolarized membrane less likely to fire
- Noradrenergic neuron does not release NE, inhibiting histamine release
- SLEEP



End organ effects of Dexmedetomidine



End Organ Effects - Neurologic

- Sedation via selective binding α_2 receptors in the locus ceruleus
  - Decreased noradrenergic output → increased GABA firing
  - Natural, non-REM sleep
    - Animal studies
    - Pediatric EEG

Nelson, *Anesth*, 2003
Mason, *Ped Anes, 2009*

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

2015 Papers

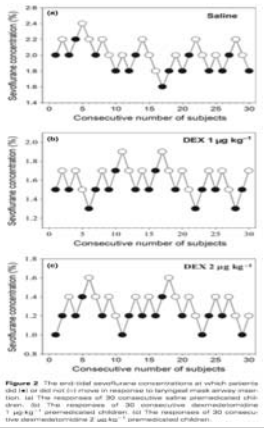
- Hauber, *Anesth & Analg*, Nov 2015
- Yao, *Ped Anes,* May 2015
- Liu, *Int J Clin Exp Med*, Sep 2015
- Hadi, *Int J Ped Otolaryng,* Feb 2015

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



Sevoflurane

1.92%

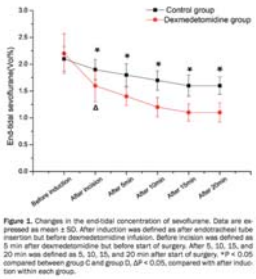
1.53%

1.23%

Yao, *Ped Anes,* 2015

Liu, *Int J Clin Exp Med,* 2015

- 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

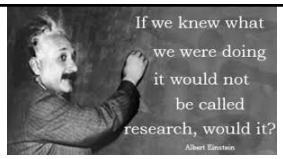
- Shorter mechanical ventilation, earlier extubation
- Less opioid requirements
- Decreased stress response: cortisol, glucose
- Improved hemodynamic stability
- No significant difference in hospital or ICU LOS

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