Preoperative Clearance in Children: 
*Update for the Primary Physician*

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Objectives

• Describes ideal perioperative “clearance”
• Review the typical approach to anesthesia for the most common pediatric surgical procedures
• Review the current concerns regarding neurotoxicity in general anesthetics
No Conflicts of Interest to Disclose

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Pretest (T/F)

• A perfect prep evaluation will decrease risk of perioperative complications?
• Anesthetics cause neuronal apoptosis in young mammalian brains?
• Severe egg allergy is a contraindication to propofol administration?
• Tonsillectomy is the best treatment for pediatric OSA?
Why do we need Preoperative Clearance in Children?
Five Year Old Dies After Tonsillectomy

By Kristin Hayes, R.N.  June 1, 2009
My Bio  Headlines  RSS

(1) Krista bright says:

April 14, 2010 at 4:09 pm

WOW, I read this while looking on the internet. My 2 year old died the same way. on March 21, 2010. Hers was the lingual artery, a branch of the carotid. There was nothing I could do to stop the blood...I was helpless. People do need to understand that while this is a rare complication, it can happen.

Does Preoperative “Clearance” change risks?
Adults vs Children
- Helps streamline the day of surgery
- Helps eliminate the preventable causes for cancellation of surgery
- Helps to optimize medical management
- Helps familiarize child and parent to the hospital
- Reduce the percentage of cancellations and OR delays
- Enhance the utilization of OR time

Preop Assessment- What we are really looking for...

(things we really cannot figure out on our own or are really good to know about ...)
Airway

• History
• Previous Intubations
• Syndromes
Cardiac Disease

• Congenital Lesions
• Murmurs
• Syncope, Apnea, Cyanosis
• ALTE
• Long QTc/ Family Hx
Pulmonary Disease

- Recent URI
- Pneumonia
- Chronic Dx
  - CF
  - Asthma
  - Bronchopulmonary Dysplasia
High Risk Conditions

- Mucopolysaccharidoses
- Sickle Cell Dx
- Diabetes Melitus
- OSA
- Obesity
- Seizures
- Neuromuscular Diseases
- Coagulopathy
Anesthesia Specific Conditions

• Malignant Hyperthermia
• Pseudocholinesterase Deficiency
• Hyperkalemia
• Physical Issues: Positioning, Skin risks, Access
Previous Surgical History

• Any complications

• Any Parental concerns
  – Behavioral Issues
  – Negative interactions with Anesthesia Team

• Reason for Surgery
When to refer for Pediatric Anesthesiology for Consultation

- Parent request
- MH
- Known/ Likely Difficult Airway
- Sickle Cell
- IDDM
- Myopathy/ NM Dx
- Structural Heart Disease
- Very Young Age
- Behavioral Concerns, ASD
- Complex Medical Condition, Syndrome
When is testing necessary

- No ROUTINE tests are ever needed
- Anemia in Ex-Premature = Apnea Risk
- Structural Heart disease
- HbS fraction
- Blood Sugar in IDDM
- K+ in renal or NeuroMusc Dx
- PSG: recommended for age <3y, syndromes to assess post-op apnea risk
NPO Guidelines

- Clear Liquids
- Breast Milk
- Formula
- Non-human Milk
- Light meal
- Solids
- 2 hr
- 4 hr
- 6 hr
- 6 hr
- 6 hr
- 8 hr
Egg Allergy and Propofol

• Propofol is emulsified with Egg Lecithin
• Vast majority of allergic rxn is against Egg White proteins, not egg yolk proteins
• Trace contamination is possible
  – approx 5ug in an intubating dose. 200ug is threshold for immunogenic run
• Soybean Oil contains 1.4 ppm soy proteins
• Propofol is safe unless pt has anaphylaxis to baked egg or known anaphylaxis to propofol
Upper Respiratory Infections

Clinically Significant Cofactors:
- Copious Secretions
- Nasal Congestion
- Parental Smoking
- Hx RAD
- Airway Surgery/Intubation
- Productive Cough
- ExPremature

Can increase Risk of:
- Laryngospasm
- Airway obstruction
- Croup
- Hypoxemia
- Bronchospasm
- Stridor
- Breath holding
Child with URTI symptoms:
- If surgery urgent?
  - Yes: Proceed
  - No: Severe symptoms
- If severe symptoms?
  - Yes: General anaesthesia?
    - Yes: Risk factors
      - Hx of asthma
      - Use of TT
      - Copious secretions
      - Nasal congestion
      - Parental smoking
      - Surgery of airway
      - Hx of prematurity
      - Risk/Benefit?
        - Good: Proceed
        - Poor: Postpone 4 weeks
  - No or recent URTI: Proceed
- If infectious aetiology?
  - Yes: Postpone 4 weeks
  - No: Proceed
- Other factors?
  - Need for expediency
  - Parents travelled far
  - Surgery cancelled previously

Management:
- Avoid TT
- Consider LMA
- Pulse Oximetry
- Hydration
- Humidification?
- Anticholinergics?
Ideal Anesthetic for Common Surgical Procedures

- Optimize Surgical Outcome
- Minimize Physiologic Stress, derangements
- Minimize Pain, Vomiting
- Optimize Post-procedure Discharge
- Avoid Iatrogenic Complications
- Respond to Untoward events/ Crisis Management
General Approach to Pedi Anesthesia in USA

- Preop Anxiolysis
- Parent Present Inhalational Induction by Mask
- ETT/ LMA/ Mask
- Sevoflurane has replaced Halothane
- Morphine Based Analgesia
- NSAIDs   PONV Prophylaxis
- Ambulatory Discharge...
“Criteria” for Overnight Observation
(eg: Tonsillectomy)

- OSA
- Sleep Disturbance
- < 3y
- Craniofacial Dx
- Lives > 1hr away
- Extreme Obesity
- Postoperative complications

From Coté Practice of Anesth Infants Children
5th Ed. Table 31-5
Overnight Admission Variability

• Younger age, Complex Medical Conditions, OSA
• >94% age under 2y with OSA
• <14% age over 5y ASA PS 1-2
• Extreme variability between hospitals
  – 3-5y: Some hospitals admit 5% others 90%

• Estimated Cost to prevent 1 post-op Apneic death ~ $15M

Goyal Laryngoscope (2013) 123
Is Tonsillectomy an Effective Surgery?

• Randomized trials for OSA? Tonsillitis?
• Is surgical technique “Routine”?
• Is Anesthesia Care “Routine”?
• Are the risks outweighed by the Benefits?
Why are we still doing Tonsillectomy?

- *Sore Throats*

- Paradise Criteria
- £154 cost for each sore throat saved (7-9 saved per year) Wilson Oto HNS (2012) 146(1)
- Most often Adolescent Females

- Tonsillitis
- 3 less Sore Throats
- Surgery has a “Modest effect” Burton 2009
OSA

• 1 study
• “lack of strong evidence to support (T&A)”
• Poor diagnostic criteria for OSA

Lim 2009
CHAT trial

- 464 children 5-9y multi center single blinded
- OSA diagnosed by PSG
- Excluded AHI 30+, SpO2 Nadir <90%, Obesity, Recurrent Tonsillitis, ADHD
- (8) Cognitive/ Behavioral Tools

CHAT trial (2)

• Primary endpoint was negative (attention and executive function scores)
• Both cohorts improved Baseline attention and executive function (p= 0.16)
• Restless-Impulsive/ Emotional Lability Improved more after Tonsillectomy (caregiver p=0.01, teacher p=0.04)
• Executive Function improved for Caregiver, not Teachers (p<0.001 vs 0.22)

CHAT trial (3)

- Symptoms of OSA improved after surgery (p<0.001)
- AHI decreased after surgery (p<0.001) though both groups improved after 7 months
- 46% of PSG normalized after watchful waiting (79% after surgery)

Neurotoxicity
Study Finds Possible Link Between Anesthesia and ADHD

A new study found an association multiple procedures requiring anesthesia in young children and the development of ADHD later. (Keith Brofsky/Getty Images)

By Linda Thrasy

updated 2/2/2012 4:59:3

Children who go hyperactivity disc

By KIM CAROLLO (@kimcarollo)

Feb. 2, 2012

Young children who undergo multiple procedures requiring anesthe...
Jevtovic-Todorovic et al. (2003)

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

Vesna Jevtovic-Todorovic,1 Richard E. Hartman,2 Yukitoshi Izumi,3 Nicholas D. Benshoff,3 Krikor Dikranian,3 Charles F. Zorumski,3 John W. Olney,3 and David F. Wozniak3

1Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia 22908, and Departments of 2Neurology and 3Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110

- Model: Neonatal Rat (PND 7), 6 hours of anesthesia.
- Anesthetic Regimen: cocktail of nitrous oxide, oxygen, isoflurane and midazolam.
- Endpoints: Histopathology, behavioral testing over 160 days, and electrophysiology testing in hippocampal slices (P29-p33)

J. Neuroscience 23(3): 876-882
Triple anesthetic cocktail induces apoptotic neurodegeneration.

Figure 1.

- a–l, h–j show light micrographic scenes from various brain regions of either a control rat (a–c, d–e, f–g), a rat exposed to the triple anesthetic cocktail (h–j, k), or a rat exposed to air alone (l). The regions illustrated are the posterior cingulate/retrosplenial cortex (a–c), lateral dorsal (d–e), medial dorsal (f–g), anterodorsal (h), anteromedial (i), anteroventral (j), laterodorsal (k), and parietal cortex (l). Some sections are stained with cupric silver (a–e, g) or activated caspase-3 (f, h–j) to evaluate the neurodegenerative reaction in experimental brains compared with controls were mutually compared.

- m, n show electron micrographic scenes depicting the ultrastructural appearance of neurons undergoing apoptosis. The cell in the laterodorsal (m) displays a very early stage of apoptosis in which the entire cell is condensed, the nuclear membrane is absent, and there is intermixing of nuclear and cytoplasmic constituents. These changes are hallmark characteristics of neuronal apoptosis as it occurs in the mammalian brain. The two histological methods used (activated caspase-3 ICC staining and silver staining) to evaluate the neurodegenerative reaction in specific regions, where the rate of degeneration was at least 15-fold greater in the triple cocktail (Fig. 1a–l, h–j) compared with the baseline rate in the same region of control brains (Fig. 1a–l, h–j). The most vulnerable brain regions were the thalamus, the hippocampal subiculum, and the lateral and medial geniculate nuclei, where even the lowest isoflurane concentration (0.75%) caused a significant reaction entailing more severe damage in the thalamus and hippocampal subiculum compared with this concentration of isoflurane alone. Under this condition the most vulnerable areas were the thalamus, the hippocampal subiculum, and the lateral and medial geniculate nuclei, where even the lowest isoflurane concentration (0.75%) caused a significant reaction entailing more severe damage in the thalamus and hippocampal subiculum compared with this concentration of isoflurane alone.

- The parietal cortex (layer II) was also affected in an apparently dose-dependent manner, although the damage was significantly greater than controls at only the high concentration of isoflurane (1.5 vol%). When a nontoxic dose of midazolam (9 mg/kg, i.p.) was followed by 6 hr of a double cocktail (isoflurane plus N₂O at a low/nontoxic concentration (75 vol%) was added to transient hyperventilation caused by carboxic puncture. In vehicle-treated animals (10% DMSO plus air), both cupric silver and activated caspase-3 ICC staining revealed a sparsely scattered pattern of baseline physiological cell death that occurs naturally in the developing brain.)
FDA Conclusion in 2007

“surgery that is truly elective should be postponed until after 6 months of age”

“there are not adequate data to extrapolate animal findings to humans”
DATE: February 8, 2011

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the March 10, 2011 ALSDAC Meeting to Discuss the Neurotoxicity of Anesthetic and Sedative Drugs in Juvenile Animals
<table>
<thead>
<tr>
<th>Key Nonclinical Finding</th>
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<tr>
<td>2. Anesthesia exposure during early brain development results in alterations in synaptic architecture (Tan, et al., 2009; De Roo, et al., 2009; Briner, et al., 2010; Lunardi, et al., 2010).</td>
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<td>3. Anesthesia exposure during early brain development results in decreased neurogenesis (Stefovska, et al., 2008; Stratmann, et al., 2009; Zhu, et al., 2010).</td>
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<td>4. Exposure to anesthetic agents (inhaled isoflurane or spinal ketamine) during early brain development results in apoptosis of the dorsal horn of the spinal column; whereas, spinal morphine did not (Sanders, et al., 2008; Westin, et al., 2010; Walker, et al., 2010).</td>
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<td>5. An analgesic dose of ketamine protects against pain-induced neuroapoptosis in the rat inflammatory pain model (Anand, et al., 2007; Rovnaghi, et al., 2008).</td>
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<td>6. Several drugs have been reported to not result in increased neuroapoptosis:</td>
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<td>• fentanyl (Rizzi, et al., 2008),</td>
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<td>• morphine (Black, et al., 2008), and</td>
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<td>• dexmedetomidine (Sanders, et al., 2009; Sanders, et al., 2010)</td>
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<td>7. A growing number of nonclinical reports suggest that the following drugs or approaches could either ameliorate or prevent anesthesia-induced neuroapoptosis in vivo:</td>
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<td>• β-estradiol (Bittigau, et al., 2002; Asimiadou, et al., 2005; Lu, et al., 2006),</td>
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<td>• erythropoietin (Dzietko, et al., 2004; Shang, et al., 2007),</td>
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<td>• melatonin (Yon, et al., 2006),</td>
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<td>• xenon (Ma, et al., 2007; Cattano, et al., 2008; Shu, et al., 2010),</td>
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<td>• L-carnitine (Zou, et al., 2008),</td>
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<td>• lithium (Xia, et al., 2008),</td>
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<td>• dexmedetomidine (Sanders, et al., 2009; Sanders, et al., 2010) and</td>
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<td>• hypothermia (Creeley and Olney, 2010)</td>
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Cognitive and Behavioral Outcomes After Early Exposure to Anesthesia and Surgery

AUTHORS: Randall P. Flick, MD, MPH,a Slavica K. Katusic, MD,b Robert C. Colligan, PhD,c Robert T. Wilder, MD, PhD,a Robert G. Voigt, MD,d Michael D. Olson, PhD,e Juraj Sprung, MD, PhD,a Amy L. Weaver, MS,f Darrell R. Schroeder, MS,f and David O. Warner, MDa

aDepartment of Anesthesiology, bDivision of Epidemiology, Department of Health Sciences Research, cDepartment of Psychiatry and Psychology, dDivision of Biomedical Statistics and Informatics, Department of Health Sciences Research, and eDepartment of Pediatrics and Adolescent Medicine, and fMayo Clinic Mayo Medical School, College of Medicine, Mayo Clinic, Rochester, Minnesota

ABBREVIATIONS

WHAT’S KNOWN ON THIS SUBJECT: Exposure to virtually all anesthetic drugs has been shown to cause neurodegeneration in young animals. Studies of learning and cognition in children exposed to anesthesia and surgery have been few, have relied on single outcome measures, and have not controlled for comorbidity.

WHAT THIS STUDY ADDS: In this study of children exposed to anesthesia/surgery before the age of 2, multiple group and individual measures of learning and behavior are examined by using a matched design with adjustment for comorbidity using 2 separate methods.
“The risk of being subsequently diagnosed with developmental and behavioral disorders in children....who had surgery when they were younger than 3 years was 60% greater than that of a similar group of siblings who did not undergo surgery”
Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia

Juraj Sprung, MD, PhD; Randall P. Flick, MD, MPH; Slavica K. Katusic, MD; Robert C. Colligan, PhD; William J. Barbaresi, MD; Katarina Bojanić, MD; Tasha L. Welch, MD; Michael D. Olson, PA-C; Andrew C. Hanson, BS; Darrell R. Schroeder, MS; Robert T. Wilder, MD, PhD; and David O. Warner, MD

Reprogramming of the Infant Brain by Surgery With General Anesthesia
Study Subjects

- 8548 Births 1/76- 12/82 in one school district
- 5357 enrolled
- 341 ADHD cases by age 19y
- 350 had 1 or more GA before age 2y
- 286 had 1 GA
- 64 had 2 or more GA's
- Halothane/ N2O

ADHD rates
- No GA: 7.3%
- 1 GA: 10.7%
- 2 or more: 17.9%
FIGURE. Cumulative percentage of attention-deficit/hyperactivity disorder diagnosis by age shown separately for those that had 0, 1, or multiple procedures performed with general anesthesia under the age of 2 years. The number of individuals at risk at 5, 10, and 15 years of age is 4995, 4009, and 3576 for those with no exposure; 284, 230, and 214 for those with 1 exposure; and 64, 50, and 44 for those with 2 or more exposures.
(1) learning, speech, and language are affected by early exposure to anesthesia whereas behavior seems to be unaffected; (2) single anesthetics do not seem to have an effect, whereas repeated anesthetic exposures consistently show an effect; and (3) these effects persist despite adjustment for comorbidity.

As evidenced by recent findings, a very reliable link between the animal and human data is rapidly emerging. At a minimum, physicians should strive to minimize the length of time a child is sedated, as well as the number of trips to the operating room. If a surgery can be deferred until after the child is 4 years old, without causing serious harm to the child, the deferral may be warranted.
Ketamine is most toxic for the fetus

Isoflurane is most toxic for the neonate.

Propofol is least toxic at either age.
...while the abundant laboratory findings should not be easily dismissed, the main concern for pediatric anesthesiologists remains the prevention of respiratory and cardiovascular complications. C.G. Ward, A.W. Loepke / Pharmacological Research 65 (2012) 271–274
Summary of current research...

- 25 Studies in Mice
- 70 Studies in Rats
- 15 Studies in Non-Human Primates
- Observed Neurotoxicity in All studied Species
- Threshold and Dose Dependent effect
- Timing of Exposure changes region of CNS effected and subsequent possible functional effect
Summary of current research...

- Effects seem to be permanent
- Effect ameliorated by many approaches
- Effect worsened when associated with tissue damage (Surgery)
- Sex differences
- Functional effects may increase with age
Conundrum of Routine Surgery in Children...

- Common Routine Pediatric Surgeries/Procedures
  - Tonsillectomy
  - Myringotomy
  - Hernia
  - EUA
  - Dental
  - Orthopedic
  - MRI/CT
  - Skin
  - Circumcision
  - NLD Probe
Post-test (T/F)

• A perfect prep evaluation will decrease risk of perioperative complications?
• Anesthetics cause neuronal apoptosis in young mammalian brains?
• Severe egg allergy is a contraindication to propofol administration?
• Tonsillectomy is the best treatment for pediatric OSA?