



USC University of  
Southern California

# Effects of Anesthesia and Pain Management on the Very Young: 2018 update



We Treat Kids



USC University of  
Southern California

**Anesthesia!**

Lydia (aka

dras MD

Assistant Professor Anesthesiology  
CHLA



# Disclosures

- a. Grants/Research Support
- b. Consultant
- c. Stock/Shareholder
- d. Speakers' Bureau
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Lydia Andras MD - Eli Lilly (c); Nuvasive, Biomet & Medtronic (d); SRS, POSNA, JPO (e); Orthobullets (f)



# Goals

- Briefly review the concerns about the neurotoxicity of anesthesia in the very young
- Look at the most recent data
- Opioids in Children



## December 14<sup>th</sup> 2016

- FDA- “Today, based on the FDA’s comprehensive analysis of the latest published scientific studies, we are issuing a Drug Safety Communication to inform health care providers, parents and caregivers of children younger than three years, and pregnant women in their third trimester, that the repeated or lengthy (more than three hours) use of general anesthetic and sedation drugs may adversely affect children’s developing brains. To better inform the public of the risks, we are requiring warnings to be added to the labels of these drugs. We recognize that in many cases these exposures may be medically necessary and these new data regarding the potential harms must be carefully weighed against the risk of not performing a specific medical procedure.”

# Publicity

- “Anesthesia might pose a risk to children!”
- “Anesthesia drugs can be dangerous for children’s brains!”







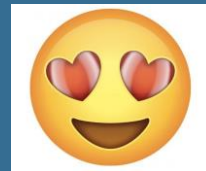






# Anesthetic/Sedation Drug Classification

- Inhalation Gas
  - Nitrous Oxide\*
  - Halothane\*
  - Desflurane\*
  - Isoflurane\*
  - Sevoflurane\*
- Barbituates
  - Thiopental\*
  - Methohexital\*
- Dissociative Anesthesia
  - Ketamine\*
- Benzodiazepines
  - Midazolam\*
  - Lorazepam\*
  - Diazepam\*
- Others
  - Propofol\*
  - Etomidate\*
  - Dexmedetomidine / Precedex
- Opioids
  - Fentanyl
  - Morphine
  - Hydromorphone



\*=neurotoxic



# Pediatric Anesthesia Neuro-Development Assessment (PANDA)

- Prospective sibling matched cohort study, 105 sibling pairs. 1 with general anesthesia at less than 36 months
- Subjects/Siblings ranged in age 8-15, given comprehensive battery of neuropsychological assessments and full scale IQ score
- Average duration of anesthesia 84 minutes
- 86% white; middle to upper middle class, well educated families
- Primary outcome: WASI IQ, no significant difference
- Statistical Difference in: internalizing behavior

JAMA 2016

# The General Anesthesia compared to Spinal anesthesia (GAS) trial

- 722 infants, < 60 weeks gestation age for inguinal hernia surgery
- Randomized to GA with sevo vs awake spinal anesthesia
- Measured neurodevelopmental outcomes
  - Secondary outcome was cognitive score at age 2 years—no difference
  - Primary outcome of study is full-scale IQ at age 5 years—pending
  - First fully prospective, randomized controlled trial

Lancet 2016

## Mayo Anesthesia Safety in Kids (MASK)

- Unexposed (411), single exposure (380) and multiple exposure (206): 997 children
- Neuropsychological testing at age 8-12, or 15-20
- Primary outcome: Intelligence quotient- did not differ significantly (1.3 points lower in multiple, and 0.5 points lower in single exposure)
- Secondary Outcome- processing speed and fine motor were decreased in multiple exposed children

# Influence of Surgical Procedures and General Anesthesia on Child Development Before Primary School Entry Among Matched Sibling Pairs

- Retrospective sibling matched cohort pairs 10,897 with Early Development Instrument
- Any anesthetic before age 5-6
- No significant differences found between exposed and unexposed

JAMA 2018



## Summary of Clinical Studies

### Increased Risk

Wilder et al.  
Flick et al.  
Sprung et al.  
DiMaggio et al.  
Andropoulos et al.  
Ing et al.  
Block et al.  
Naumann et al.  
Guerra et al.  
Bong et al.  
Stratmann et al.

### No Increased Risk

Wilder et al.  
Hansen et al.  
Bartels et al.  
Bong et al.  
Williams et al.  
Ing et al.  
Davidson et al. (GAS trial)  
Sun et al. (PANDA)  
O'Leary et al.  
Graham et al.  
Warner et al. (MASK)

# A family case study



One anesthetic as child	>1 anesthetic
Meeting Co-Chair	Meeting attendee
>40 publications	<10 publications
Orthopedist	Anesthesiologist

←?→





# Future Research

- Dexmedetomidine
  - Hypnosis and anxiolysis; Causes analgesia/sedation via presynaptic  $\alpha$ -2 receptors in CNS; Not FDA labeled for patients < 18 years of age
  - Neonatal rats exposed to dexmedetomidine at various concentrations don't display neuroapoptosis; dose dependent reduction; Increasing evidence in fetal/neonatal primates—no clinical neurodegenerative changes
  - Reduces neurotoxicity caused by GA such as isoflurane, propofol, and ketamine
  - Human studies are ongoing
- Bio markers
- Follow up on GAS (age 5 outcome)



- Public-private partnership studying the safety use of anesthetics and sedatives in children
- Consensus statement
- Funding
- Most current updates/research
- Resources

# Opioid Epidemic

- Opioid Prescribing for the Treatment of Acute Pain in Children on Hospital Discharge- C. Monitto et al Dec 2017
  - Parents of 343 patients given a scripted 10 min interview (<48 hrs, and 10-14 days)
- Orthopedic or Nuss procedure= 25.42 more doses (median number of doses for all was 43)
- 19% of families were instructed on safe disposal (only 4% did)



- Opioid Disposal:
  - EPA- DO NOT FLUSH
  - DEA- FLUSH
  - Opioids and detergent



# Summary

- Single, brief anesthetic: likely no detrimental effects
- Repeated, longer anesthetic exposure: potentially small detrimental effect of unclear cause, potentially reversible
- Concerns should NOT cause practitioners to delay necessary care
- Opioids should be a component of a multi-modal post-operative pain plan and should be disposed of properly