Pain Management in Neonates with Congenital Heart Disease

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Mednax and Sunrise Children’s Hospital
Do babies need pain meds before, during, or after heart surgery?
Unacceptable Outcomes
Dr Robert Gross, Boston Children’s
Aug 26, 1938

7yo Lorraine Sweeney, 4 mos POST OP

The operation took place on August 26th, 1938. An incision was made in the 3rd intercostal space on the left side, and the 3rd rib was retracted upward. The left lung collapsed, revealing a PDA that was 7–8 mm in diameter and 5–6 mm in length. Resting his finger on Lorraine’s heart, Gross described “a thrill of extreme magnety” felt over the pulmonary artery but disappearing over the aorta.

Anesthesia at this time was still in its early stages. Lorraine received cyclopropane by mask while lying on her side, breathing spontaneously during the surgery [1], [16], [17] and [18]. Betty Lank, the hospital’s chief nurse anesthetist, provided the anesthesia.
Dr Alfred Blalock, Johns Hopkins
Nov 29, 1944

OPERATION: Nov. 29, 1944

Dr. Alfred Blalock
Ether - Oxygen - Dr. Harral

ANASTOMOSIS OF LEFT PULMONARY ARTERY TO LEFT SUBCLAVIAN ARTERY
25 week 760 gm Apgar 3/7
IVH, Renal/Liver failure and Large PDA.
2 wks of life: Transferred for PDA ligation.
Signed informed consent for general anesthesia
Unstable on way to OR
Rx w/ Pancuronium and O₂
2 Days w/ hypertension and tachycardia
Died 3 weeks post op
The Committee on Fetus and Newborn, the Committee on Drugs, the Section on Anesthesiology, and the Section on Surgery believe that local or systemic pharmacologic agents now available permit relatively safe administration of anesthesia or analgesia to neonates undergoing surgical procedures and that such administration is indicated according to the usual guidelines for the administration of anesthesia to high-risk, potentially unstable patients. In occasional situations, physiologic instability will be so great that the anesthetic agents must be reduced or discontinued. However the decision to withhold such medication should be based on the same medical criteria used for older patients. The decision should not be based solely on the infant's age or perceived degree of cortical maturity.
Successful Outcomes!
The Drugs
Classes of Drugs Used in Neonates w/ CHD

- Opioids
- Benzodiazepines
- Central Alpha 2 Agonists
- IV General Anesthetics
Opioids

- Fentanyl
- Morphine
- Methadone
Fentanyl

- FDA: “Safety & efficacy in children <2 yrs has not been established”
- Dose: 1-2 mcg/kg IV
- $T_{1/2}$: 2.4 hrs
  - Neo <28 days (n=72): 1.3-16 hrs
- Duration of action: 30-60 min
Morphine

- FDA: "Safety & effectiveness < 18 yrs has not been established"
- Dose: 0.05-0.1 mg/kg IV/IM
- T<sub>1/2</sub>: 1.5-4 hrs
  - Neo 4-13 hrs
- Duration of action: 3-5 hrs
- Notable SE: hypotension, pruritis
Methadone

- FDA: “The pharmacokinetics have not been evaluated in the pediatrics”
- Dose: 0.05-0.1 mg/kg IV/PO
- $T_{1/2}$: 15-29 hrs
  - Neo: 41 hrs
- Duration of action: 22-48 hrs
Benzodiazepines

- Midazolam
- Lorazepam
- Diazepam
Midazolam

- FDA: “Safety and efficacy have been established in pediatric/neonatal pts”
- Dose: 0.05-0.2 mg/kg IV
- $T_{1/2}$: 0.8 – 3.3 hrs
  - 4- 12 hrs (critically ill neonates)
- Duration of action: 20-30 min
Lorazepam

- **FDA:** *Not for use in neonates (contains benzyl alcohol)*
- **Dose:** 0.05-0.1 mg/kg IV/PR
- **T\(_{1/2}\):** 4-12 hrs
  - **NEO:** 24-50 hrs
- **Duration of action:** 4-8 hrs
Diazepam

- FDA: “Contraindicated in pediatric pts <6 mos of age”
- Dose: 0.05-0.1 mg/kg IV/PO/PR
- $T_{1/2}$: 15-21 hrs
  - NEO: 40-50 hrs
  - Desmethyldiazepam: 50-100 hrs
Central Alpha 2 Agonists

- Clonodine
- Dexmedetomidine
Clonodine

- FDA: "Safety and effectiveness have not been established in pediatrics pts"
- Dose: PO/transdermal
- $T_{1/2}$: 12-16 hrs
- Patch delivers for 7 days
Dexmedetomidine

- FDA: “Safety and efficacy have not been established in pediatric pts”
- Dose: 1 mcg/kg IV Load
  - 0.2-1 mcg/kg/hr infusion
- T_{1/2}: 2 hrs
IV General Anesthetic Agents

- Propofol
Propofol

- FDA: “Not indicated in peds pts for ICU sedation… as safety and effectiveness have not been established”

- Dose: Load 1-2 mg/kg IV
  - 25-100 mcg/kg/min gtt

- $T_{1/2}$: 3.2-11 hrs

- Duration of action: 5-10 mins
The Data....
In a randomised controlled trial, preterm babies undergoing ligation of a patent ductus arteriosus were given nitrous oxide and d-tubocurarine, with (n = 8) or without (n = 8) fentanyl (10 micrograms/kg intravenously) to the anaesthetic regimen. Major hormonal responses to surgery, as indicated by changes in plasma adrenaline, noradrenaline, glucagon, aldosterone, corticosterone, 11-deoxycorticosterone, and 11-deoxycorticisol levels, in the insulin/glucagon, molar ratio and in blood glucose, lactate, and pyruvate concentrations were significantly greater in the non-fentanyl than in the fentanyl group. The urinary 3-methylhistidine/creatinine ratios were significantly greater in the non-fentanyl group on the second and third postoperative days. Compared with the fentanyl group, the non-fentanyl group had circulatory and metabolic complications postoperatively. The findings indicate that preterm babies mount a substantial stress response to surgery under anaesthesia with nitrous oxide and curare and that prevention of this response by fentanyl anaesthesia may be associated with an improved postoperative outcome.
HALOTHANE–MORPHINE COMPARED WITH HIGH-DOSE SUFENTANIL FOR ANESTHESIA AND POSTOPERATIVE ANALGESIA IN NEONATAL CARDIAC SURGERY

K.J.S. Anand, M.B., B.S., D.Phil., and P.R. Hickey, M.D.

Abstract  Background. Extreme hormonal and metabolic responses to stress are associated with increased morbidity and mortality in sick adults. We hypothesized that administering deep opioid anesthesia to critically ill neonates undergoing cardiac surgery would blunt their responses to stress and might improve clinical outcomes.

Methods. In a randomized trial, 30 neonates were assigned to receive deep intraoperative anesthesia with high doses of sufentanil and postoperative infusions of opiates for 24 hours; 15 neonates were assigned to receive lighter anesthesia with halothane and morphine followed postoperatively by intermittent morphine and diazepam. Hormonal and metabolic responses to surgery were evaluated by assay of arterial blood samples obtained before, during, and after the operations.

Results. The neonates who received deep anesthesia (with sufentanil) had significantly reduced responses of beta-endorphin, norepinephrine, epinephrine, glucagon, aldosterone, cortisol, and other steroid hormones; their insulin responses and ratios of insulin to glucagon were greater during the operation. The neonates who received lighter anesthesia (with halothane plus morphine) had more severe hyperglycemia and lactic acidemia during surgery and higher lactate and acetoacetate concentrations postoperatively (P<0.025). The group that received deep anesthesia had a decreased incidence of sepsis (P = 0.03), metabolic acidosis (P<0.01), and disseminated intravascular coagulation (P = 0.03) and fewer postoperative deaths (none of 30 given sufentanil vs. 4 of 15 given halothane plus morphine, P<0.01).

Conclusions. In neonates undergoing cardiac surgery, the physiologic responses to stress are attenuated by deep anesthesia and postoperative analgesia with high doses of opioids. Deep anesthesia continued postoperatively may reduce the vulnerability of these neonates to complications and may reduce mortality. (N Engl J Med 1992;326:1-9.)
Conclusion:

The group that received deep anesthesia had a decreased incidence of sepsis ($P = 0.03$), metabolic acidosis ($P < 0.01$), and disseminated intravascular coagulation ($P = 0.03$) and fewer postoperative deaths (none of 30 given sufentanil vs. 4 of 15 given halothane plus morphine. $P < 0.01$).
“Pain is not an inotrope”- KCK
But then....early extubation??

EARLY EXTUBATION AFTER CARDIAC OPERATIONS IN NEONATES AND YOUNG INFANTS

Jeffrey S. Heinle, MD
Laura K. Diaz, MD
Lawrence S. Fox, MD

Objective: This study was undertaken to determine the feasibility of early extubation of the neonate and young infant after surgical repair of congenital heart lesions. Methods: The records of all patients less than 90 days of age who had cardiac operations over a 1-year period were reviewed. During this time, all patients were managed as potential candidates for early extubation. Fifty-six patients are included with a mean age of 32 ± 31 days and a mean weight of 3.7 ± 0.9 kg. Results: Twenty-eight patients (50%) were extubated in the operating room or within 3 hours after arriving in the intensive care unit. This included 38% of patients less than 7 days of age, 50% of patients 8 to 30 days of age, 44% of patients 31 to 60 days of age, and 69% of patients 61 to 90 days of age. Three patients (11%) extubated early required reintubation. No deaths were related to early extubation. Only one

(J Thorac Cardiovasc Surg 1997;114:413-8)
New Concerns in 2016
FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women

**Safety Announcement**

[12-14-2016] The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains.

Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children’s brain development.

To better inform the public about this potential risk, we are requiring warnings to be added to the labels of general anesthetic and sedation drugs (see List of General Anesthetic and Sedation Drugs Affected by this Label Change). We will continue to monitor the use of these drugs in children and pregnant women and will update the public if additional information becomes available.
Neuronal apoptosis in neonatal rats

Loepke AW et al
Cincinnati Children’s
<table>
<thead>
<tr>
<th>Generic Name</th>
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<tbody>
<tr>
<td>desflurane</td>
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<tr>
<td>etomidate</td>
</tr>
<tr>
<td>halothane</td>
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<tr>
<td>isoflurane</td>
</tr>
<tr>
<td>ketamine</td>
</tr>
<tr>
<td>lorazepam injection</td>
</tr>
<tr>
<td>methohexital</td>
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<tr>
<td>midazolam injection, syrup</td>
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<tr>
<td>pentobarbital</td>
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<tr>
<td>propofol</td>
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<td>sevoflurane</td>
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The potential risk of negative cognitive or behavioral effects of anesthetic agents remains uncertain and must be placed in the context of the known risks and benefits of both the anesthetic and the related surgical or diagnostic procedure for which the anesthetic is required. Clinicians and parents are cautioned against the possible risk of delaying needed surgical or diagnostic procedures. Until additional information is available from ongoing studies, parents and providers should carefully weigh the risk and benefit of each contemplated procedure before proceeding.
So how do we do it?

- Dedicated Pediatric Cardiac Intensivists
- Committed Pediatric ICU Nursing
- Collaboration with Neonatology, Pediatric Cardiology & Pediatric Anesthesiology
- Exceptional Pediatric Cardiac Surgery
The Future of Neonatal Cardiac Intensive Care at SCH

Pediatric Cardiac ICU- Opening June 2018
The Chairman of the Committee on Fetus and Newborn of the American Academy of Pediatrics: "We did a small survey of neonatal units around the country about this issue. We found that there are still some units that regularly operate on the smallest, sickest premature infants using the same technique that your son experienced" (Poland, 1986).
# Levels of Sedation/Analgesia

<table>
<thead>
<tr>
<th></th>
<th>MINIMAL</th>
<th>MODERATE</th>
<th>DEEP</th>
<th>GENERAL</th>
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</thead>
<tbody>
<tr>
<td><strong>Responsiveness</strong></td>
<td>Normal response to verbal stimulation</td>
<td>Purposeful** response to verbal or tactile stimulation</td>
<td>Purposeful** response following repeated or painful stimulation</td>
<td>Unarousable even with painful stimulus</td>
</tr>
<tr>
<td><strong>Airway</strong></td>
<td>Unaffected</td>
<td>No intervention required</td>
<td>Intervention may be required</td>
<td>Intervention often required</td>
</tr>
<tr>
<td><strong>Spontaneous Ventilation</strong></td>
<td>Unaffected</td>
<td>Adequate</td>
<td>May be inadequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td><strong>Cardiovascular Function</strong></td>
<td>Unaffected</td>
<td>Usually maintained</td>
<td>Usually maintained</td>
<td>May be impaired</td>
</tr>
</tbody>
</table>

ASA Physical Status Classification

- Class I - A normally healthy patient.
- Class II - A patient with mild systemic disease
- Class III - A patient with severe systemic disease
- Class IV - A patient with severe systemic disease that is a constant threat to life
- Class V - A moribund patient who is not expected to survive without the operation
Goals of sedation

- Analgesia = pain control
- Amnesia = loss of memory
- Anxiolysis = diminishing anxiety
- Induce sleep like state
- Control movement/behavior
- Any or all of the above
Classes of Drugs No Longer in General Use

- Antihistamines
- Chloral hydrate
- Barbiturates
- Phenothiazines
RESULTS: The median minimum dexmedetomidine dose was similar between infants and neonates at 0.2 mcg/kg/hr (IQR, 0.17-0.3) versus 0.29 mcg/kg/hr (IQR, 0.2-0.31), p = 0.35. The median maximum dose was higher for infants than neonates (0.6 mcg/kg/hr [IQR, 0.4-0.8] vs. 0.4 mcg/kg/hr [IQR, 0.26-0.6], p < 0.01). Additional sedative use was more common in infants than neonates (75/99 [76%] vs. 15/28 [54%], p = 0.02). At least 1 episode of hypotension was noted in 34/127 (27%) patients and was similar between groups. An episode of bradycardia was identified more frequently in infants than neonates (55/99 [56%] vs. 2/28 [7%], p < 0.01). Significant reduction in heart rate and systolic blood pressure was noted when comparing baseline vital signs to lowest heart rate and systolic blood pressure during infusion (p < 0.01).
Ketamine

- FDA
- Dose: 1-3 mg/kg IV/IM
- $T_{1/2}$: ###hrs
- Duration of action: ###hrs
- SE: hypertension, tachycardia
Propofol

<table>
<thead>
<tr>
<th>Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients</th>
<th>Adults only</th>
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<tr>
<td>Safety, effectiveness and dosing guidelines for DIPRIVAN have not been established for MAC Sedation in the pediatric population; therefore, it is not recommended for this use (see PRECAUTIONS, Pediatric Use).</td>
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<tr>
<td>DIPRIVAN is not recommended for induction of anesthesia below the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations.</td>
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</tr>
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</table>

DIPRIVAN is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established (see PRECAUTIONS, Pediatric Use).

DIPRIVAN is not indicated for use in pediatric patients for ICU sedation or for MAC sedation for surgical, nonsurgical or diagnostic procedures as safety and effectiveness have not been established.
New Drugs

- Ketoralac
- Acetaminophen IV
FDA Drug Safety Communication: FDA approves label changes for use of general anesthetic and sedation drugs in young children

Safety Announcement

[4-27-2017] The U.S. Food and Drug Administration (FDA) is notifying the public that we have approved previously announced label changes regarding the use of general anesthetic and sedation medicines in children younger than 3 years. These changes include:

- A new Warning stating that exposure to these medicines for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years.

- Addition of information to the sections of the labels about pregnancy and pediatric use to describe studies in young animals and pregnant animals that showed exposure to general anesthetic and sedation drugs for more than 3 hours can cause widespread loss of nerve cells in the developing brain; and studies in young animals suggested these changes resulted in long-term negative effects on the animals’ behavior or learning.
Pain in Infants

Immediate effects
- Irritability.
- Fear.
- Disturbance of sleep and wakefulness state.
- Increased oxygen consumption.
- Ventilation-perfusion mismatch.
- Diminished nutrient intake.
- Increased gastric acidity.

Short term effects
- Enhanced catabolism.
- Altered immunological function.
- Delayed healing.
- Impaired emotional bonding.

Long term effects
- Memory of pain.
- Developmental retardation.
- Alteration in response to subsequent painful experience.