Pain Management in the Neonate

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Neonatal Outreach Educator

Attitudes

▪ Wide variation in medical personnel’s beliefs and knowledge about pain
▪ Parents have anxiety around the use of opiates and sedatives (narcotics)
▪ General public concern over “addiction” to pain medications
Attitudes

- Attitudes of nurses, physicians, parents and ancillary staff must be evaluated to identify current beliefs.
- Attitudes can be a barrier to successful implementation of this program as with any other multifaceted program.
- Have you had an experience where provider attitudes were conflicting?

Misconceptions

- The pain pathways in neonates are unmyelinated or otherwise immature and cannot transmit painful stimuli to the brain.
- Pain perception is located only in the cortex, and thalamocortical connections must be fully developed in order to allow pain perception.
- The human infant does not have the psychological context in order to identify any experiences as painful and this does not develop until two years or later.
- Newborn infants are at greater risk for developing the adverse effects of analgesic or sedative agents, or these drugs have adverse long-term effects on brain development and behavior.
Personal Experience

▪ What is your own experience of pain?
▪ What pain medications or sedatives have you taken?
▪ Have you had good or bad feeling when given a sedative or opiate?
▪ Have you had a patient with an adverse effect that led to a serious consequence?

Definitions

▪ Pain
▪ Stress
▪ Stress or pain response
▪ Analgesia
▪ Pain control
▪ Types of pain: acute, established, chronic

(Anand et al, 2006)
Physiology of Pain

- Fetal Development
- Neonatal vs adult pain
- Developmental responses
- Pain Pathways
  - Ascending
  - Descending

"Behind the Heel Lance" Minyan Wang, 2012

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Epidemiology and treatment of painful procedures in neonates in intensive care units (Carbajal et al., 2008)
- Large, prospective study of 430 infants
- All painful, stressful procedures for first 14 days recorded
- 70,000 first attempt procedures
- 11,500 supplemental attempts
- Median of 115 procedures
- Of the 42,413 painful procedures, analgesia was provided in **20.8 percent** of patients (34 percent received concurrent analgesia)
  - nonpharmacologic therapy (18 percent)
  - only pharmacologic therapy (2 percent)
  - both nonpharmacologic and pharmacologic therapy (0.4 percent)
### Effects of inadequate analgesia

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Cardiovascular</th>
<th>Pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓’d gut motility</td>
<td>↑’d heart rate</td>
<td>↓’d tidal volume</td>
</tr>
<tr>
<td>Delay in return of bowel function</td>
<td>↑’d blood pressure</td>
<td>↓’d cough</td>
</tr>
<tr>
<td></td>
<td>↑’d cardiac output</td>
<td>↑’d splinting</td>
</tr>
<tr>
<td></td>
<td>hyper coagulation</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
<td>Atelectasis</td>
</tr>
<tr>
<td>↓’d urine output</td>
<td></td>
<td></td>
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<tr>
<td>Urinary retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential for fluid overload</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Immune System
- Impaired immune function
- Exaggerated stress response

### Metabolic
- Hyper metabolism
- Decreased insulin secretion
- Protein catabolism
- Metabolic acidosis
- ↓’d glucose stores (especially neonates)
### Pain Signs

- Elevated HR
- HR lower than baseline
- Loss of HR variability
- Elevated CO2
- Increased respiratory rate
- Lower saturations
- Elevated temperature
- Knees drawn up
- Cries with handling
- Limbs stiff
- Jumpy/jittery
- Crying volume louder
- Increased crying
- Elevated BP
- Metabolic Acidosis
- Grimace with handling
- Grimace undisturbed
- Furrowed brow
- Restless while sleeping
- Stiffens with handling
- Whimpering
- Hypoventilation
- Clenched hands/feet
- Pale/mottled/cyanotic
- Reduced movement
- Lack of quiet alert state
- Cool skin/Temp ok
- Higher pitched cry
- Unusual silence
- Disturbed sleep
- Excessive sleep
- Elevated blood glucose
- Curled toes
- Stiff body

### “Pain Signs Survey”
Rating of signs to Assess Pain in Neonates

- **Physiologic indicators** - rated as #1 Used Often
  - Increased HR - 85%
  - Increased BP - 88%

- **Behavioral Indicators** - rated as #1 Used often
  - Curled toes - 65%
  - Clenched hand and feet - 68%
  - Facial grimace with handling - 79%
Physiologic Responses to Pain
Clinical J Pain, 26 (9) 2010

- Change in respirations
- Increase/decrease blood pressure
- Increase/decrease in heart rate
- **Loss of HR variability**
- Color change
- Decreased skin perfusion-pallor and mottling
- Decrease in oxygen saturation
- Palmar sweating

Effects of inadequately treated pain

- Altered pain response
  - May lead to increased pain sensitivity and/or chronic pain syndromes
- Neurodevelopmental outcome
  - Frequent exposure to pain-related stress has been correlated with impaired:
    - Cognitive development, altered neurocognitive processing, decreased cortical thickness, dysregulation of the hypothalmic-pituitary-adrenal (HPA) axis

Pain Assessment Tools

- Multiple tools exist
- Some use only behavioral indicators such as cry or tone
- Others use physiologic indicators such as HR and blood pressure
- Some use a combination of both
- In a setting with monitoring, use a tool with physiologic indicators

Barriers to Assessment

- Non-verbal population
- Lack of consensus in health care providers
- Physiologic changes that are compatible with condition/disease as well as pain-THINK PAIN
- Parents less likely to have knowledge of infant’s pain behaviors
- Prolonged effect of neuromuscular blockade
- Extreme prematurity or critically ill patients
- Persistent or prolonged pain
Pain Tools

- FLACC - one dimensional
- NIPS - behavior, state, tone, pattern of respiration
- CRIES - behavior /physiologic-Term Post-op
- N-PASS - behavioral, physiologic, credit for immaturity, allows sedation assessment
- COMFORT - behavior and physiologic-nonverbal post-op critical care
- PIPP - gestational based, state, facial expression, saturation change

<table>
<thead>
<tr>
<th>Measure</th>
<th>Variables included</th>
<th>Type of pain</th>
<th>Psychometric testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPP (Premature Infant Pain Profile)</td>
<td>Heart rate, oxygen saturation, facial actions, takes state and gestational age into account</td>
<td>Procedural, postoperative (minor)</td>
<td>Reliability, validity, clinical utility well established</td>
</tr>
<tr>
<td>NIPS (Neonatal Infant Pain Score)</td>
<td>Facial expression, crying, breathing patterns, arm and leg movements, arousal</td>
<td>Procedural</td>
<td>Reliability, validity</td>
</tr>
<tr>
<td>NFCS (Neonatal Facial Coding System)</td>
<td>Facial actions</td>
<td>Procedural</td>
<td>Reliability, validity</td>
</tr>
<tr>
<td>N-PASS (Neonatal Pain, Agitation, and Sedation Scale)</td>
<td>Crying, irritability, behavioral state, facial expression, extremitry tone, vital signs</td>
<td>Postoperative, procedural, ventilated</td>
<td>Reliability, validity, includes sedation end of scale, does not distinguish pain from agitation</td>
</tr>
<tr>
<td>CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness)</td>
<td>Crying, facial expression, sleeplessness, requires oxygen to stay at &gt;55% saturation, increased vital signs</td>
<td>Postoperative</td>
<td>Reliability, validity</td>
</tr>
<tr>
<td>COMFORT scale</td>
<td>Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure</td>
<td>Postoperative, critical care, if developed for sedation, recently validated for postoperative pain in 0 to 3 year-old infants</td>
<td>Reliability, validity, clinical utility</td>
</tr>
<tr>
<td>Douleur Aiguë Nouveau-né scale</td>
<td>Facial and limb movements, vocal expression</td>
<td>Procedural pain</td>
<td>Reliability, validity</td>
</tr>
<tr>
<td>Behavioral Infant Pain Profile</td>
<td>Behavioral state, facial expression and hand movements</td>
<td>Acute pain</td>
<td>Reliability, validity</td>
</tr>
</tbody>
</table>

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**FLACC**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Face</td>
<td>No particular expression or smile</td>
</tr>
<tr>
<td>Legs</td>
<td>Normal position or relaxed</td>
</tr>
<tr>
<td>Activity</td>
<td>Lying quietly, normal</td>
</tr>
<tr>
<td>Cry</td>
<td>No cry (awake or asleep)</td>
</tr>
<tr>
<td>Consolability</td>
<td>Content, relaxed</td>
</tr>
</tbody>
</table>

**Neonatal/Infant Pain Scale (NIPS)**

(Recommended for children less than 1 year old) A score greater than 3 indicates pain.

<table>
<thead>
<tr>
<th>Pain Assessment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial Expression</strong></td>
<td></td>
</tr>
<tr>
<td>0 - Relaxed Muscles</td>
<td>Restful face, neutral expression</td>
</tr>
<tr>
<td>1 - Grimace</td>
<td>Tight facial muscles; furrowed brow, chin, jaw (negative facial expression – nose, mouth brow)</td>
</tr>
<tr>
<td><strong>Cry</strong></td>
<td></td>
</tr>
<tr>
<td>0 - No cry</td>
<td>Quiet, not crying</td>
</tr>
<tr>
<td>1 - Whimper</td>
<td>Mild moaning, intermittent</td>
</tr>
<tr>
<td>2 - Vigorous cry</td>
<td>Loud scream; rising, shrill, continuous (Note: Silent cry may be scored if baby is intubated as evidenced by obvious mouth and facial movement)</td>
</tr>
<tr>
<td><strong>Breathing Pattern</strong></td>
<td></td>
</tr>
<tr>
<td>0 - Relaxed</td>
<td>Usual pattern for this infant</td>
</tr>
<tr>
<td>1 - Change in breathing</td>
<td>Indrawing, irregular, faster than usual; gagging, breath holding</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td></td>
</tr>
<tr>
<td>0 - Relaxed/Restrainted</td>
<td>No Muscular rigidity; occasional random movements of arms</td>
</tr>
<tr>
<td>1 - Flexed/Extended</td>
<td>Tense, straight arms; rigid and/or rapid extension, flexion</td>
</tr>
<tr>
<td><strong>Legs</strong></td>
<td></td>
</tr>
<tr>
<td>0 - Relaxed/Restrainted</td>
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</tr>
<tr>
<td><strong>State of Arousal</strong></td>
<td></td>
</tr>
<tr>
<td>0 - Sleeping/Awake</td>
<td>Quiet, peaceful, sleeping or alert, random leg movements</td>
</tr>
<tr>
<td>1 - Fussy</td>
<td>Alert, restless and thrashing</td>
</tr>
</tbody>
</table>

(Reference: Hudson-Barr et al., 2002)
CRIES Scale

**DATE/TIME**

- **Crying** - Characteristic cry of pain is high pitched.
  - 0 - No cry or cry that is not high-pitched
  - 1 - High pitched but baby is easily consolable
  - 2 - Crying high pitched but baby is inconsolable

- **Requires O₂ for SaO₂ < 95%** - Babies experiencing pain manifest decreased oxygenation. Consider other causes of hypoxemia, e.g., oversedation, atelectasis, pneumothorax.
  - 0 - No oxygen required
  - 1 - < 30% oxygen required
  - 2 - > 30% oxygen required

- **Increased vital signs (BP* and HR*)** - Take BP last as this may awaken child making other assessments difficult.
  - 0 - Both HR and BP unchanged or less than baseline
  - 1 - HR or BP increased but increase in < 20% of baseline
  - 2 - HR or BP is increased > 20% over baseline

- **Expression** - The facial expression most often associated with pain is a grimace. A grimace may be characterized by brow lowering, eyes squeezed shut, deepening naso-labial furrow, or open lips and mouth.
  - 0 - No grimace present
  - 1 - Grimace alone is present
  - 2 - Grimace and non-verbalization grimace is present

- **Sleepless** - Scored based upon the infant's state during the hour preceding this recorded score.
  - 0 - Child has been continuously asleep
  - 1 - Child has awakened at frequent intervals
  - 2 - Child has been awake constantly

**TOTAL SCORE**

(KRECHEL, & Bildner, 1995)

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**N-PASS:** Neocrotal Pain, Agitation, & Sedation Scale

**Assessment Criteria**

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Normal</th>
<th>Pain / Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crying</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Externals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pressure Assessment**

- 3 if 28 weeks gestation / corrected age
- 5 if > 32 weeks gestation / corrected age

**Assessment of Pain/Agitation**

- Pain assessment is the FIFTH vital sign - assessment for pain should be included in every vital sign assessment.
- Pain is scored from 0 to 2 for each behavioral and physiologic criterion, then added.
- If the infant is under 32 weeks gestation, the score is divided by 2.5 to get the pain index.
- Pain index of 0 or 1 is normal.
- Pain index of 2 or 3 indicates pain.

**N-PASS**

Paradox/Paralytic

- It is imperative to behavioral evaluate a paralyzed infant for pain.
- Increases in heart rate and blood pressure may be the only indicator of an need for more analgesia.
- Analgesia should be administered continuously by drip or around-the-clock dosing.
- Higher, more frequent doses may be required if the infant is intubated, has a chest tube, or other pathology (such as NEC) that would otherwise increase the infant's stress levels.
- Opioid doses should be increased by 10% every 3-5 days as tolerance will occur without symptoms of inadequate pain relief.
**N-PASS**

- Select a box that describes the infant for each category in the pain section
- Range is 0-10
- Cannot be used if infant paralyzed
- Credit given for very immature infants
- Limits - no category for “shut down”

<table>
<thead>
<tr>
<th>Assessment Criteria</th>
<th>Sedation</th>
<th>Normal</th>
<th>Pain/Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Crying Irritability</td>
<td>No cry with painful stimuli</td>
<td>Moans or cries minimally with painful stimuli</td>
<td>Appropriate crying Not irritable</td>
</tr>
<tr>
<td></td>
<td>Irritable or crying at intervals Consolable</td>
<td>High-pitched or silent continuous cry Inconsolable</td>
<td></td>
</tr>
<tr>
<td>Behavior State</td>
<td>No arousal to any stimuli No spontaneous movement</td>
<td>Arouses minimally to stimuli Little spontaneous movement</td>
<td>Appropriate for gestational age</td>
</tr>
<tr>
<td></td>
<td>Restless, squirming Awakens frequently</td>
<td>Arching, kicking Constantly awake or arouses minimally/no movement/not sedated</td>
<td></td>
</tr>
<tr>
<td>Facial Expression</td>
<td>Mouth is lax No expression</td>
<td>Minimal expression with stimuli</td>
<td>Relaxed Appropriate</td>
</tr>
<tr>
<td></td>
<td>Any pain expression intermittent</td>
<td>Any pain expression continual</td>
<td></td>
</tr>
<tr>
<td>Extremities Tone</td>
<td>No grasp reflex Flaccid tone</td>
<td>Weak grasp Decrease muscle tone</td>
<td>Relaxed hands and feet Normal tone</td>
</tr>
<tr>
<td></td>
<td>Intermittent clenched toes, fist, or finger splay Body is not tense</td>
<td>Continual clenched toes, fist, or finger splay Body is tense</td>
<td></td>
</tr>
<tr>
<td>Vital Signs HR, RR, BP, SaO2</td>
<td>No variability with stimuli Hypoventilation or apnea</td>
<td>&lt;10% variability from baseline with stimuli</td>
<td>Within baseline or normal for gestational age</td>
</tr>
<tr>
<td></td>
<td>Increase 10-20% from baseline SaO2 76-85% with stimulation- quick increase</td>
<td>Increase &gt;20% from baseline SaO2 &lt; 75% with stimulation- slow increase Out of sync with vent</td>
<td></td>
</tr>
</tbody>
</table>
COMFORT pain scale

- Useful for post-procedural pain
- Ages 0-18 yrs

PIPP scale
Pain Assessment in Neonates

**Classic Pain Faces**

- Eye squeeze
- Broaden nose and bulging
- Nasolabial furrow
- Mouth open
- Brow bulge

**Shutdown**

- All infants move and have tone
- Severe pain is associated with a patient who does not move, has decreased tone and does not have “social contact”

Assessment of Functional Capacity

- Very few Pain Tools incorporate the concept of “Shutdown” in assessment
Evaluation of Treatment

- Dependent on skill, and attitude of caretaker
- Adequacy of a tool to improve objectivity
- Evaluation time may cross over two caretakers (shift change)
- What drug and dose was right for last week may not be adequate for this week and this circumstance

“Pain Assessment should be comprehensive and multidimensional, including contextual, behavioral and physiological indicators”
“Think outside the Tool”

▪ Use all the information that is available to you
▪ If there is a clear pain source, treat it
▪ Do not wait for the score to be high, preempting pain will require less drug

“We rule out sepsis, why can’t we rule out pain?”
What is painful?

Commonly Performed Procedures:
Mild Invasiveness

- Physical exam
- Insertion of gavage tube
- UAC/UVC placement
- Cultures
- Bladder catheterization
- Eye culture
- Hearing screen

Commonly Performed Procedures: Moderate Invasiveness

- Arterial Puncture
- Venipuncture
- Heel stick
- Tracheal Suctioning
- Intubation
- Intramuscular Injection
- CVL removal
- Thoracentesis
- Surfactant Administration
- Suture removal
- Extubation
- Ventricular Tap


Commonly Performed Procedures: Severe Invasiveness

- Arterial/venous cutdown
- Arterial Catheterization
- Circumcision
- Lumbar Puncture
- Eye exam for ROP
- Bronchoscopy or Endoscopy
- Suprapubic Bladder Tap
- CVL placement
- Chest Tube Placement

Pain Management Analgesia

- Nonpharmacological measures
- Pharmacological measures
  - Topical Anesthetics
  - Oral, IV or rectal acetaminophen
  - Slow IV infusion of opioids
  - Subcutaneous lidocaine or nerve blocks
  - Deep sedation or general anesthesia

Principles of Pain Management

- Environmental, behavioral, non-pharmacologic interventions are the foundation of pain management
- Pharmacologic pain intervention is additive
- Combination of non-pharmacologic with pharmacologic measures minimizes pain/stress & maximizes self-regulatory capacities
Nonpharmacological measures

▪ Breastfeeding
▪ Non-nutritive sucking
▪ Swaddled or facilitated tucking
▪ Skin-to-skin contact
▪ Sensorial saturation
▪ Massage
▪ Environmental

Pharmacological measures

▪ Oral Sucrose or Glucose
  ▪ Reduced crying time
  ▪ Dampened physiologic responses
  ▪ Reduced facial expression
  ▪ Lower pain scores
Oral Sucrose & Glucose

• Proposed mode of action
• Clinical use
• Dosing and administration
  • Onset of action is 10 seconds
  • Peak action is 2 minutes
  • Duration of action is 10 minutes

Sucrose for Procedural Pain
Linda Franck, Children’s Medical Ventures Educational Booklet, Vol1,N0.1,2000.

• Analgesic effects-primarily mediated through opioid pathways
• Efficacy-supported in many studies over the past decade AAP/CPS support
• Safety-No adverse effects reported except choking in very low birth weight infants
• 24% solution is hyperosmolar but has been shown to not grow bacteria, or fungus
Sucrose for Procedural Pain

- Dose and mode of delivery-varies
- NG administration is not effective
- Felt to be synergistic with non-nutritive sucking
- Drops as needed-repeat during procedure
- Heel stick, venipuncture, immunization, tape removal, NG insertion, dressing changes, bladder catheterizations etc.
- Non-procedural use- Pain behaviors that cannot be managed with interventions such as diaper change etc.
Topical Anesthetics

• Pain behaviors reduced as an adjunct to nerve block in circumcision
• Reduced pain in venipuncture and arterial puncture
• No effect on heel stick
• Reduced pain in spinal tap
• Mild transient skin irritation is rare
• Application requires occlusion-LMX 20 minutes, EMLA 60 minutes
• Level of anesthesia for 45-60 minutes

Non-Opiate Therapy

• Acetaminophen-10-15 mg/kg PO q4-8 hr.
• Acetaminophen-15-20 mg/kg PR q4-8 hr.
• Acetaminophen 15 mg/kg IV q 4-6 hr.
(All acetaminophen should be ordered based on a daily max safe dose)
• Ketorolac (not much data)-0.5 mg/kg/dose, 2-4 doses a day
Pain Management IV Tylenol

- Current dosing recommendation:
  - Load with 20 mg/kg IV over ~15 minutes
  - 10 mg/kg IV every 6 hours - longer interval in premature infants
- New FDA approval in the US, used in Europe for over a decade
- Not much published compatibility data
- Does not mask fever
- No reports of hepatic injury when used for post-operative pain management

Effect of IV Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery

Ceelie, She, et al, JAMA, 2013; 309 (2)

- 71 Neonates in an Intensive Care Unit
- Loaded with morphine 30 minutes before the end of surgery
- Randomized to continuous morphine or intermittent IV Tylenol for 48 hours after surgery
  - Cumulative morphine dose in Tylenol group was 121 (99-264 mcg/kg)
  - Cumulative morphine dose in the non Tylenol group was 357 (220-605 mcg/kg)

- P<.001 between groups
Lidocaine-1%

- Local instillation effective for:
  - Venipuncture or arterial puncture
  - Circumcision
  - Infiltration of incision site preoperatively
  - Chest tube insertion
  - Tap procedures for fluid-peritoneal or pleural
  - Toxicity can occur if used in high doses and multiple sites

Morphine and Related Opioids

- Morphine remains the standard against which new analgesics are measured
- The drug is still obtained from opium or extracted from poppy straw
- Morphine produces its major effect on the CNS by acting as agonists to mu receptors
- There is no upper limit
  - However, hyperanalgesia can occur
Morphine Pharmacokinetics

- Respiratory depression-direct effect on brainstem respiratory centers
- **Therapeutic doses rarely effect blood pressure, cardiac rate and rhythm**
- Histamine release may lead to hypotension-rare in young infants
- Blunts reflex vasoconstriction caused by increased PCO2

Pharmacokinetics “The Moving Target”

- Opiates and sedatives are cleared slower in an immature infant
- Clearance improves with post conceptual age, reaches adult levels at about 1 month
- Amount of drug needed to achieve goal increases with time (tolerance)
- There are significant individual differences
Single Dose Morphine Pharmacokinetics in Prematures

- 20 infants studied, 26-40 Weeks
- Given a single dose of Morphine 0.1mg/kg
- Distribution half-life: Preterm vs Term
  - 50+-35 minutes/19 +- 8 minutes
- Elimination half-life: Preterm vs Term 10+- 3.7 hours/6.7+-4.8 hours

Morphine Clearance in Post-Op Infants

- 26 non-cardiac/major surgery, > 36 Wk.
- Continuous post-op infusions, levels checked once steady state achieved
- Clearance mean in:
  - 1-7 day olds 9.2 mL/min/kg,
  - 31-90 days 25.3 mL/min/kg,
  - 91-180 49.9 mL/min/kg
Morphine Clearance in Infants

• Conclusions:
  • Adult clearance values were reached by 1 month of age
  • Clearance was faster than previous studies looking at post-op cardiac surgical infants

Hemodynamic Effects of IV Morphine
• 30 ventilated Infants 27-31 wk., 800-1680 grams
• Loaded 100 mcg/kg/h for 2 hours
• No change in cerebral or cardiac Doppler parameters
• MAP 44 +/- 6 mmHg fell to 42+-4
  • down 4%
• HR 148+-12 fell to 140 +-16
  • down 5%
Hemodynamic Effects of IV MS

• Summary: A loading dose of morphine over 2 hours did not have any significant effect on MABP or cerebral and cardiac hemodynamics
• No Adverse effects were noted that could be attributed to morphine therapy

Neonatal Dosing
• Morphine-.05-.1 mg/kg/dose IV
  • Repeat every 4 hours as needed
• Continuous infusion:
  • Loading 0.1 mg/kg infused slowly (1hour)
  • Continuous drip 0.015-.02 mg/kg/hour
• There is no limit
• Doses will need to be adjusted based on effect, age, duration of drug and maturity
Practical Tips/Morphine Use

- Use lower dose in non-ventilated infants
- Have Narcan available
- Increase pressers or give volume if blood pressure falls
- Give the dose slowing the first time, prepare for but do not assume adverse reaction

Fentanyl Pharmacokinetics in Infants
Koentop, D. et al.

- Total body clearance 17 +/- 4.3 ml/kg/min
- Elimination half-life 317+/-70 minutes
- Highly variable in all infants
- Dosing
  - 0.5-2 mcg/kg/dose IV
  - Repeat every 1-2 hours
  - Adjunct to anesthesia
  - Infusion- 1mcg load and 0.5 mcg/kg/hr-.4 mcg/kg increase to effect
  - Doses will need to be varied based on age
Practical Tips/Fentanyl

- Start with low doses in more at risk infants
- Use for shorter duration of procedure
- If chest wall rigidity occurs, reverse with Narcan/paralytic
- Consider in hypotensive infants or those who have histamine effect with morphine

“Sedatives and Opiates are unique in that their adverse effects can be reversed rapidly.”
Naloxone

- Specific Opioid antagonist, nonselective
- Reverses desired and undesired effects
- Half life shorter than morphine, may need to be repeated
- Intermittent small doses .05-.1 mg/kg to reverse unacceptable effects with little change in desired effects

Flumazenil

- Romazicon- 10 mcg/kg IV
- Reverses CNS effects with 2 minutes
- Sedative antagonist
What do we know about sedatives?

- Midazolam
  - Short acting benzodiazepine
  - Increased sedation
  - Increase in poor neurological outcomes in preterm infants
- Lorazepam
- Ketamine


Procedural Pain

- Review and reduce need for noxious procedures
- Use pharmacologic agents for the ones that cause pain—chest tubes, LP's
- Nonpharmacologic measures for minor procedures
- Topical analgesics—EMLA/J-tip
- Combination of therapies
Procedural Pain Management

- Develop consensus
- Write treatment protocol including premedication, dose, monitoring, assessment
- Plan ahead

IV Start/Venipuncture

- Oral sucrose
- Containment
- Vein selection-hands more painful than antecubital
- When frequent blood draws are required consider a short term access such as an umbilical catheter or peripheral arterial line-Risk/Benefit discussion
- Batching of all lab draws-coordination of orders to reduce sticks
PICC Insertion

- Topical Lidocaine
- Low dose opiate
- Containment
- Oral sucrose

Spinal Tap/Lumbar Puncture

- Topical Lidocaine
- Lidocaine instillation
- Low dose opiate
- Low dose sedative

- Goals are patient comfort and ease of positioning to improve success of procedure
Chest Tube Insertion

- Lidocaine instillation-0.5 ml-1% solution without epinephrine no more than 3-5 mg/kg
- Opiate IV-lower dose if not intubated
- Consider more opiate for chest tube removal
- Some pain source during duration of indwelling tube during handling and breathing

ROP Laser


- Topical anesthetic (proparacaine), oral sucrose and comfort care (containment) show minimal or no effects on pain behaviors
- Deep sedation recommended with short acting drugs like midazolam and fentanyl are most effective
- Consider orders for Romazicon and Narcan after the procedure is completed if sedation leads to apnea, bradycardia or desaturations
- Doses will need to be repeated due to the half life of the reversal agents compared to the drugs
Intubation
AAP Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine, 2010

- Recommend premedication for nonemergency intubation in neonates
  - Number of attempts reduced
  - Time to intubation reduced
  - Minimizes airway trauma
  - Improved physiologic homeostasis - less bradycardia, desaturations, less increased in intracranial pressure

Intubation - Premedication

- Initial medication:
  - Fast acting opiate: Fentanyl 2 mcg/kg given by slow IV push to avoid chest wall rigidity

- Second medication:
  - Atropine 20 mcg/kg IV, wait for a 20 bpm risk in heart rate, blunts the vagal response and reduces secretions

- Last medication:
  - Fast acting neuromuscular blockade agent - Rocuronium 1 mg/kg or Succinylcholine 2 mg/kg IV push-given when ready to insert tube (in hand/positioned) - duration 1 hr.-4-6 minutes
Other Procedures

➢ ETT Suctioning
➢ NG insertion
➢ Bladder catheterization
➢ Dressing changes
➢ Heel sticks
➢ Eye exams
➢ IM or SQ injections
➢ Imaging procedures
➢ Reduce number of events with no routines

Proposed steps for neonatal analgesia

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
<th>Step 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Pacifier, sucrose, kangaroo care, massage, sensorial saturation</td>
<td>Topical anesthetic cream or gel</td>
<td>Slow intravenous infusion of opioids</td>
<td>Local anesthetics, subcutaneous infiltration of nerve blocks</td>
<td>Deep sedation/analgesia or general anesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Agents used (examples)

- Fentanyl, morphine, ketamine, alfentanil, anesthetics, or sedatives
- Lidocaine, bupivacaine, ropivacaine
- Ketamine, morphine, alfentanil, remifentanil
- Articaine, prilocaine, epinephrine
- Lidocaine-epinephrine, ropivacaine-lidocaine, bupivicaine, lidocaine

This figure depicts the stepwise approach to providing preemptive analgesia in neonates undergoing procedures that may cause pain or discomfort. The level of analgesia provided is based upon the degree of anticipated procedural pain. However, with the escalation of intervention with increasing pain, it is important to remember that interventions from earlier steps should still be provided. For example, when a central line is placed, the neonate should receive subcutaneous administration of local anesthetic (Step 5), along with oral sucrose (Step 1), and topical anesthetic for the skin (Step 2).

**Analgesia for specific neonatal procedures**

### Stepwise interventions with increasing analgesia as the degree of anticipated procedural pain increases

- **Step 1**: Non-pharmacologic measures (palpate, oral sucrose, swaddling, kangaroo care, skin-to-skin contact with the mother), sensorial saturation
- **Step 2**: Topical anesthetics (topical lidocaine, lidocaine-prilocaine cream, ketamine gel)
- **Step 3**: Avertin: intramuscular (10 to 15 mg/kg once), or rectally (15 to 25 mg/kg once), or intravenous (10 to 20 mg/kg once); maintenance doses may be repeated as needed for post-procedural analgesia (see tip&tricks topic on prevention and treatment of neonatal pain for dosing)
- **Step 4**: Opioids: slow intravenous infusion of fentanyl (0.5 to 3 mcg/kg) or morphine (10 to 30 mcg/kg) as single dose only for pain control
- **Step 5**: Lignocaine: subcutaneous infiltration 0.5 mL/kg of 1% (20 mg/mL), lidocaine solution at 0.2% (20 mg/mL) lidocaine solution up to a maximum dose of 3 to 5 mg/kg or 3% as nerve block
- **Step 6**: Deep sedation/analgesia using fentanyl (2 to 4 mcg/kg up to 60 mcg/kg once) or morphine (50 to 100 mcg/kg once), combined with propofol (1 to 2 mg/kg once, use with caution if hypotensive), or ketamine (2 to 8 mg/kg once) for brief procedures, use remifentanil as preferred opioid (1 to 3 mg/kg once, infuse slowly to avoid chest wall rigidity), or ketamine (2 to 8 mg/kg once)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Stepwise Interventions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheal aspiration</td>
<td>Step 1: consider pharmacologic therapy using lidocaine 1% (0.3 mg/kg intratracheal tube or low-dose IV fentanyl (0.5 mcg/kg))</td>
<td>Perform rapidly, brief catheter insertion to the tip of the endotracheal tube only</td>
</tr>
<tr>
<td>Heelstick</td>
<td>Step 1 &amp; use mechanical lance</td>
<td>Venipuncture is more efficient, less painful: Steps 2, 3, &amp; heel wakening are ineffective</td>
</tr>
<tr>
<td>Adhesive removal</td>
<td>Use esSENTial esSENTial to sEE if adhesive is on; consider Step 1</td>
<td></td>
</tr>
<tr>
<td>Gastric tube insertion</td>
<td>Step 1: consider Step 2</td>
<td>Perform rapidly, use lubricant, avoid injury</td>
</tr>
<tr>
<td>Venipuncture</td>
<td>Steps 1 &amp; 2</td>
<td>Requires less time &amp; less resampling than heelstick</td>
</tr>
<tr>
<td>Arterial puncture</td>
<td>Steps 1 &amp; 2; consider Step 5</td>
<td>More painful than venipuncture</td>
</tr>
<tr>
<td>Intravenous cannulation</td>
<td>Steps 1 &amp; 2</td>
<td></td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>Gentle positioning; consider Step 4 if a chest tube is present</td>
<td>Avoid areas of injured or inflamed skin, drains, or catheters</td>
</tr>
<tr>
<td>Removal of intravenous catheter</td>
<td>Use esSENTial esSENTial to sEE if adhesive is on; consider Step 1</td>
<td></td>
</tr>
<tr>
<td>Wound treatment</td>
<td>Step 1: consider Steps 2, 3, 5, or 6 depending upon the extent of the wound</td>
<td>See also “dressing changes”</td>
</tr>
<tr>
<td>Brief tracheal intubation (eg, for surfactant administration)</td>
<td>Step 4: in some cases, consider a small dose of IV lidocaine (0.5 mg/kg once), or IV dexamethasone (0.2 mg/kg once), or IV remifentanil (2 mcg/kg once); atropine (0.02 mg/kg IV) may be given before intubation to avoid reflex bradycardia due to vagal stimulation. Short-acting muscle relaxant may be considered if an experienced diniaon is present</td>
<td>Superiority of a specific drug regimen over the others has not been investigated</td>
</tr>
</tbody>
</table>

### Prolonged tracheal intubation (for mechanical ventilation)

- **Step 5**: If an experienced diniaon is present, muscle relaxant is strongly advised to avoid traumatic intubations; may give atracurium (0.5-0.6 mg/kg IV)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Prolonged tracheal intubation (for mechanical ventilation)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central line placement</td>
<td>Steps 1, 2, 3; consider Step 6</td>
<td>Some centers prefer using general anesthesia</td>
</tr>
<tr>
<td>Finger stick</td>
<td>Step 1 &amp; use mechanical lance</td>
<td>Venipuncture is more efficient, less painful: Steps 2 &amp; 3 are ineffective</td>
</tr>
<tr>
<td>Umbilical catheterization</td>
<td>Steps 1, 2, 3, 5, 7</td>
<td>Cord tissue is not innervated, avoid injury to skin</td>
</tr>
<tr>
<td>Bladder compression</td>
<td>Consider Steps 1, 2, or 4</td>
<td></td>
</tr>
<tr>
<td>Tracheal extubation</td>
<td>Use esSENTial esSENTial to sEE if adhesive is on; consider Steps 1, 3</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous injection</td>
<td>Avoid if possible, use Steps 1 &amp; 2 if cannot avoid procedure</td>
<td></td>
</tr>
<tr>
<td>Intramuscular injection</td>
<td>Avoid if possible, use Steps 1 &amp; 2 if cannot avoid procedure</td>
<td></td>
</tr>
<tr>
<td>Dressing change</td>
<td>Step 1: consider Step 3, 4, or 6 if extensive</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Steps 1, 2, 3, 4, with careful positioning</td>
<td>Consider Step 4 if patient is intubated/ventilated</td>
</tr>
<tr>
<td>Peripheral arterial line</td>
<td>Steps 1 &amp; 2; consider Steps 4, 5</td>
<td></td>
</tr>
<tr>
<td>Cutdown</td>
<td>Steps 1, 2, 3; consider Step 4 pre-procedure and Step 3 pre- and post-procedure</td>
<td></td>
</tr>
<tr>
<td>Suprapubic bladder aspiration</td>
<td>Steps 1 &amp; 2; consider Steps 4, 5</td>
<td></td>
</tr>
<tr>
<td>Arterial or venous cutdown</td>
<td>Steps 1, 2, 3, 4, 5; consider Step 6</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Peripheral insertion of central catheter (PICC line placement)</td>
<td>Steps 1 &amp; 2; consider Steps 3, 4, &amp; 5</td>
<td></td>
</tr>
<tr>
<td>Eye examination for retinopathy of prematurity</td>
<td>Step 4, 5, 6; if step 6 is used, combination therapy with propofol and ketamine may be considered</td>
<td>Deep sedation with short-acting drugs like propofol and remifentanil</td>
</tr>
</tbody>
</table>

*The medication doses listed in this table are for term neonates; preterm and low birth weight neonates may require adjustment of dose and/or interval. Some agents listed in this table are not recommended in preterm neonates (eg, remifentanil). Refer to accompanying text and Lexicomp pediatric drug monographs for additional recommendations.

*The frequency of these procedures can be reduced without sacrificing the quality of neonatal care.

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Examining the New Research - Efficacy and Safety

NOPAIN Trial
Arch Pediatr Adolesc Med, 1999: 331-338

▪ To define the incidence of clinical outcomes in the target study population, and adverse effects associated with analgesia and sedation, and to calculate the sample size or a definitive test of this hypothesis

▪ 67 infants 24-32 weeks from 9 centers

▪ Ventilated infants

▪ Randomized to:
  ▪ Continuous infusions of morphine sulfate
  ▪ Continuous infusions of Midazolam
  ▪ Continuous infusions of 10% dextrose
NOPAIN Trial

- Monitored for:
  - Level of sedation (Comfort Score)
  - Responses to pain-PIPP
  - Cranial ultrasounds
  - Examined for poor neurologic outcomes:
    - Death
    - Severe IVH (III or IV)
    - Periventricular leukomalacia

NOPAIN Trial Results

- Death-1 in Midazolam and placebo group
- Poor outcomes:
  - 24% in placebo group
  - 32% in Midazolam group
  - 4% in morphine group
  - PIPP scores reduced in the morphine group
NOPAIN Trial Results

• Analgesia given by continuous low-dose morphine infusion may reduce the incidence of poor neurologic outcomes in preterm neonates who require ventilatory support

• Cannot be recommended for all infants (uptodate.com, 2017)

NEOPAIN Study

Neurologic Outcomes and Pre-emptive Analgesia in Neonates
NEOPAIN Randomized Trial

- 898 infants, randomly assigned to placebo or morphine infusions
- Loading dose of morphine 0.1 mg/kg then:
  - 0.01 mg/kg/hr 23-26 weeks
  - 0.02 mg/kg/hr 27-29 weeks
  - 0.03 mg/kg/hr 30-32 weeks
- Continued as long as clinically justified, max of 14 days

NEOPAIN Randomized Study

- Open label morphine could be given on clinical judgment
  - 242/443 in morphine group
  - 202/446 in placebo group
- Similar death rates - 11% vs 13%
- Severe IVH 11% vs 13%
- PVL 9% vs 7%
NEOPAIN Study

- Placebo-group neonates receiving open label morphine had worse rates of composite outcome that those not receiving open label morphine p<0.0001

- Morphine group neonates receiving open-label morphine were more likely to develop severe IVH 19% vs 9% p=0.0024

Morphine, Hypotension, and IVH in Ventilated Premature Infants

Objective:
- To provide secondary data analysis from the NEOPAIN trial
- Identify clinical factors associated with hypotension
- Examine the contributions of morphine treatment or hypotension in severe IVH
Secondary Data Analysis NEOPAIN Study

- Hypotension was associated with:
  - 23-26 weeks of gestation
  - Morphine infusions
  - Severity of illness
  - Additional morphine doses
  - Prior hypotension
- Morphine infusions were not a significant factor in logistic models for severe IVH, any IVH or death

Outcome at 5-6 years of prematurely born children who received morphine as neonates

- 87 children were assessed at age 5-6 years who had been previously less than 34 weeks and randomly assigned to receive morphine or non-morphine treatment as neonates
- No differences in the groups with trend “towards better performance” in all three tests in the morphine group
Measuring preterm cumulative stressors within the NICU: the Neonatal Infant Stressor Scale (Newnham CA1, Inder TE, Milgrom J., 2009)

- Aimed to quantify the severity of common stressors for preterm infants
- Created tool to manage presumed accumulated infant stress
- If a baby had a score of 6 in a 2 hour period, no one could touch the baby

Appendix A

NICU Infant Stressor Record Sheet (<28 weeks)

<table>
<thead>
<tr>
<th>Acute items</th>
<th>(score 4)</th>
<th>(score 3)</th>
<th>(score 2)</th>
<th>(score 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely stressful</td>
<td>Table entries</td>
<td>Upper-lower-ventilator</td>
<td>Feeding/iv</td>
<td>In-line catheter</td>
</tr>
<tr>
<td>Very stressful</td>
<td>Table entries</td>
<td>Upper-lower-ventilator</td>
<td>Feeding/iv</td>
<td>In-line catheter</td>
</tr>
<tr>
<td>Moderately stressful</td>
<td>Table entries</td>
<td>Upper-lower-ventilator</td>
<td>Feeding/iv</td>
<td>In-line catheter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic items</th>
<th>(score 5)</th>
<th>(score 4)</th>
<th>(score 3)</th>
<th>(score 2)</th>
<th>(score 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely stressful</td>
<td>Table entries</td>
<td>Upper-lower-ventilator</td>
<td>Feeding/iv</td>
<td>In-line catheter</td>
<td>Head/eye exam</td>
</tr>
<tr>
<td>Very stressful</td>
<td>Table entries</td>
<td>Upper-lower-ventilator</td>
<td>Feeding/iv</td>
<td>In-line catheter</td>
<td>Head/eye exam</td>
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<tr>
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<td>Feeding/iv</td>
<td>In-line catheter</td>
<td>Head/eye exam</td>
</tr>
</tbody>
</table>

INSTRUCTIONS: Enter the time that the procedure was performed (eg: 9:15 am)
NISS scores


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Pre-emptive Analgesia in the NICU
Grunau, R.E. et al, Seminars in Fetal and Neonatal Medicine 2006

“It is very challenging to study effects of morphine or other analgesics or sedatives used pre-emptively in the NICU, even in RCT’s, because humane care of infants currently requires physicians to treat those thought to be in pain, despite the knowledge gaps of long-term risks and benefits of these medications.”
Summary Proceedings From the Neonatal Pain Control Group

- Pain control measures are adopted infrequently because of unresolved scientific issues and lack of appreciation for the need for control of pain and its long-term sequelae during the critical phases of neurologic maturation in the preterm and newborn infant.

Offsetting stress & pain with POSITIVE experiences
- Stressful experiences in NICU are inevitable
- How do we provide positive experiences?
  - Tactile
  - Vestibular
  - Gustatory
  - Olfactory
  - Auditory
  - Visual
- How do we document this?
Summary

• Sick, premature infants undergo multiple painful procedures
• Pain management during invasive procedures and post-operatively should be a **standard** in neonatal care
• Routine use of sedatives and or opiates in the absence of a painful procedure is not currently recommended
• Study design will remain problematic due to difficulties in control and the clear obligation to treat pain in infants

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Summary

• There is no clear evidence that the use of opiates in neonates causes adverse neurodevelopmental outcomes
• All sedative and opiate use should be carefully considered in light of the behavior in the infant and the source of the behavior
• It is our professional duty to treat pain behaviors and preempt procedural and postoperative pain
“Treating Pain in neonates is the right thing to do and is our job. We may not have all the answers but we can begin by advocating for every infant in our care and work towards a consensus and safe practice.”

References


Questions?

Thank you!!

Tanya.Hatfield@ucsf.edu