Neonatal Pain Management

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Declarations

• I have no financial interest in any product discussed and will not be discussing off-label use of medications unless specified.
Learning Objectives

- Recognize neonates, particularly those in the NICU, undergo painful procedures in the days to weeks after birth.
- Recognize that neonatal pain predispose to heightened future pain responses
- Recognize that clinically-validated tools have been developed to grade pain in premature and term neonates
- Describe non-pharmacologic and pharmacologic interventional to palliate neonatal pain

Birth can be rough ..... 

- The noggin
  - Molding
  - Significant caput
  - Cephalohematoma
  - Foreceps injury, skull fracture
- Fractured clavicle or arm injury
Newborn Nursery

- Vitamin K
- Hepatitis B immunization
- Glucose checks
- Cold Stress
- Hip exams

NICU

- IV placement, repeated heel sticks for labs, venipuncture, ABGs, peripheral arterial lines, PICC line placement
- CPAP, endotracheal intubation, oral airway, suctioning (endotracheal or naso/oropharyngeal)
- Needle thoracentesis, chest tube
- Catheterization, tape removal
- Inability to rest, bright lights, noise, daily weights
- Swaddling may not be possible
Procedures

• Circumcision
• Frenulumectomy
• Surgery for congenital abnormalities
• Thermal stress (therapeutic hypothermia for asphyxia)
• Lumbar puncture

Congenital Anomalies & Pain

• Arthrogryposis and need for physical therapy or joint manipulation
• Epidermolysis Bullosa and dressing changes
• Osteogenesis imperfecta
• Palliative care team and others (anesthesia, clinical pharmacy support) can be helpful
Epidemiology of painful procedures performed in neonates: A systematic review of observational studies

• Synthesis of multiple studies examining number of painful NICU procedures in first 14 days
• 7.5 to 17.3 painful procedures/neonate/day
• Heel stick, suctioning, venipuncture, PIV most common
• % Receiving pain management: 0 to 85%

Prevention and Management of Procedural Pain in the Neonate: An Update
COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE
• February, 2016

• “Despite recommendations from the AAP and other experts, neonatal pain continues to be inconsistently assessed and inadequately managed.”
**Why treat pain?**

- Compassionate care
- Pain alters physiology (tachycardia, increased O2 desaturations, rapid irregular breathing)
- Neonatal brain appears to be at a vulnerable period in which repeated noxious stimuli affect brain plasticity, neurodevelopment, and long term pain sensation.

**What is Pain?**

- Defined as a ....

- “complex constellation of unpleasant sensory, emotional and cognitive experiences provoked by real or perceived tissue damage and manifested by certain autonomic, psychological, and behavioral reactions.”
  - *Bonica’s Management of Pain, 2003*
You know it when you feel it...

- Many manifestations
  - Sharp
  - Hot
  - Cold
  - Achy
  - Colicky
  - Quality/intensity modified by psychological state
- Pain fibers activate at higher thresholds than other sensory fibers

Nociception

- Physiologic processes involved in pain perception
- Peripheral fibers $\rightarrow$ dorsal horn of SC $\rightarrow$ Brain

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Aδ (Aδ)</th>
<th>C (Unmyelinated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Thibly myelinated</td>
<td>Unmyelinated</td>
</tr>
<tr>
<td>Source of pain</td>
<td>Cutaneous pressure, touch</td>
<td>Mechanoreceptive, pressure, temperature</td>
</tr>
<tr>
<td>Diameter</td>
<td>6-12 µm</td>
<td>1.5 µm</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>19.6 ± 1.3 m/s</td>
<td>5.9 ± 0.9 m/s</td>
</tr>
<tr>
<td>Threshold for stimulus intensity</td>
<td>0.6 ± 0.2 mA</td>
<td>0.6 ± 0.1 m/s</td>
</tr>
<tr>
<td>Duration of action potential</td>
<td>0.28 ± 0.01 ms</td>
<td>3.1 ± 0.5 m/s</td>
</tr>
<tr>
<td>Sensory quality of pain mediated</td>
<td>Non-mechanoeptive: inhibits the effects of firing by Aδ and C fibers</td>
<td>Mechanoreceptive: pain, temperature, chemical, thermal</td>
</tr>
</tbody>
</table>

### Peripheral Nerve Anatomy

- Peripheral nerve fibers functional by 20 wk.
- Number and types of nociceptors equal to adult levels by 20-24 wk (so density of fibers may be higher than adults).
- $\alpha$ fibers may also transmit noxious stimuli to dorsal horn of spinal cord (transmit light touch and proprioception later).

### Nociceptor Activation

- Cellular and blood vessel damage causes release of inflammatory mediators and substances (calcium, potassium, bradykinin, Substance $P$, prostaglandins) activate $\alpha$ and $C$ fibers.
- Wheal and flare response.
- Substance $P$ and prostaglandins also initiate localized inflammation.
Spinal Cord Pathways

- Ascending pathways appear to communicate with thalamus, subplate zone and sensory cortex by 22 to 24 wk
- Limb withdrawal reflex mediated through spinal cord can be elicited at 25 wk
  - Ipsilateral flexor activation, extensor inhibition
  - Contralateral extensor activation
- Impulse spreads to adjacent dermatomes

Secondary Effects

- Primary Hyperalgesia
  - Pain threshold lowered due to localized nociceptor sprouting
- Allodynia
  - Stimulus produces pain that usually would be non-painful
- Windup
  - Increased sensitivity of adjacent dermatomes due to spread of NT in spinal cord
Ascending

- Aδ impulses
  - Spinothalamic tract to VPL thalamic nuclei and somatosensory cortex
- C Fibers
  - Spinoreticular tract
  - Connect to thalamic nuclei and

Endogenous Anesthesia

- Descending fibers release dopamine, serotonin, NE that inhibit ascending pathways
- Poorly developed in premature infants
Pain Modulation Deficient in Babies

- At < 36 to 40 wk, spinal cord has low levels of dopamine, serotonin, and norepinephrine
- Descending inhibitory pathways do not release neurotransmitters until 46 to 48 wk EGA

Supraspinal Connections

- Thalamus—major relay center
  - Thalamo-cortical connections by 20-24 wk
  - Somatosensory area of parietal lobe
  - Hippocampus
- Periaqueductal Gray
  - Autonomic changes
    - 20-22 wk
  - Facial expression
    - 25 wk
- RAS
  - Alerting response to pain
Neonatal Pain—Long Term Effect

- Altered neurodevelopment
  - Pain and stress promote excitatory cell death in the CNS in animal studies
- Stimulated areas of premature brain proliferate, underused areas have heightened apoptosis
- Heightened response to future pain
- Neonatal tissue damage results in increased innervation that lasts into adulthood

Assessment of Neonatal Pain

- Difficult due to inability of neonates to vocalize
- Use other signs to assess pain
- AAP and international bodies strongly recommend use of pain scales to assess and manage neonatal pain
- Many pain scales available (at least 16 in latest statement by COFN)
COFN Recommended Pain Scales

- Neonatal Facial Coding System (NCFS)
- Premature Infant Pain Profile (PIPP)
- Neonatal Pain and Sedation Scale (N-PASS)
- Behavioral Indicators of Infant Pain (BIIP)
- Douleur Aigue du Nouveau-ne (Acute Newborn Pain)

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Premature Infant Pain Profile (PIPP)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA in weeks</td>
<td>≥ 36 weeks</td>
<td>32 to 35 weeks and 6 days</td>
<td>28 to 31 weeks and 6 days</td>
<td>&lt; 28 weeks</td>
</tr>
<tr>
<td>Observe the NB for 15 sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alertness</td>
<td>Active awake</td>
<td>Quiet awake</td>
<td>Active sleep</td>
<td>Quiet sleeping</td>
</tr>
<tr>
<td></td>
<td>Opened eyes</td>
<td>No facial movements</td>
<td>Closed eyes</td>
<td>Closed eyes</td>
</tr>
<tr>
<td></td>
<td>Facial movements present</td>
<td>No facial movements</td>
<td>Facial movements present</td>
<td>No facial movements</td>
</tr>
<tr>
<td>Record HR and SpO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal HR</td>
<td>↑ 0 to 4 bpm</td>
<td>↑ 5 to 14 bpm</td>
<td>↑ 15 to 24 bpm</td>
<td>↑ ≥ 25 bpm</td>
</tr>
<tr>
<td>Minimal Saturation</td>
<td>↓ 0 to 2.4%</td>
<td>↓ 2.5 to 4.9%</td>
<td>↓ 5 to 7.4%</td>
<td>↓ ≥ 7.5%</td>
</tr>
<tr>
<td>Observe NB for 30 sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frowned forehead</td>
<td>Absent</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Maximal</td>
</tr>
<tr>
<td>Eyes squeezed</td>
<td>Absent</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Maximal</td>
</tr>
<tr>
<td>Nasolabial frown</td>
<td>Absent</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Maximal</td>
</tr>
</tbody>
</table>

Absent is defined as 0 to 9% of the observation time; minimal, 10% to 29% of the time; moderate, 40% to 69% of the time; and maximal as 70% or more of the observation time. In this scale, scores vary from zero to 21 points. Scores equal or lower than 6 indicate absence of pain or minimal pain; scores above 12 indicate the presence of moderate to severe pain.

GA = Gestational Age, NB = Newborn.
The Premature Infant Pain Profile: Revised

<table>
<thead>
<tr>
<th>Infant Indicator</th>
<th>Infant Indicators Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Heart Rate (Bpm) Baseline</td>
<td>0&lt;24 ≤3 ≥4 1&gt;4</td>
</tr>
<tr>
<td>Oxygen-Saturation (%) Baseline</td>
<td>0&lt;2 ≤3 ≥4 1&gt;4</td>
</tr>
<tr>
<td>Blood Glucose (mg/dL) Baseline</td>
<td>None (≤5) Minimal (6–10) Moderate (11–20) Maximal (≥20)</td>
</tr>
<tr>
<td>Eye Squinting (Sec) Baseline</td>
<td>None (≤3) Minimal (4–8) Moderate (9–20) Maximal (≥20)</td>
</tr>
<tr>
<td>Nasal-Transmission Delay (Sec) Baseline</td>
<td>None (≤3) Minimal (4–8) Moderate (9–20) Maximal (≥20)</td>
</tr>
</tbody>
</table>

Gestational Age (Wks + Days)

- >36 wks: 32 wks - 35 wks: 6d 28 wks - 31wks, 6d =<28wks

Baseline Functional State

- Active and Awake
- Quiet and Awake
- Active and Asleep
- Quiet and Asleep

**Total Score:** Subtotal score + GA score + BS score

- *Sub-total for physiological and facial indicators. If subtotal score > 0, add GA and BS indicator scores.
- **Total Score:** Subtotal score + GA score + BS score

Scoring Instructions

1. Observe infant for 10 seconds at rest and assess vital sign indicators.
2. Observe infant for 10 seconds after procedure and score change in vital sign indicators.
3. Score for corrected gestational age (GA) and behavioral state (BS) if the subtotal score ≥ 1.
4. Calculate total score by adding Sub-total Score + BS Score.

**FIGURE 1.** Premature Infant Pain Profile-Revised (PIPP-R): Initial Validation and Feasibility. Shewan, Barry, RN, PhD; Gibbons, Sharyn, RN, PhD; Yamada, Janet, RN, PhD; Donmez, Kimberly; EN, MN; Lee, Grace; RN, MS; Johnston, Celeste, RN, OCN; Taddio, Arora.


**N-PASS**

<table>
<thead>
<tr>
<th>Assessment Criteria</th>
<th>Sedation</th>
<th>Normal</th>
<th>Pain / Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>-1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Crying / Irritability</td>
<td>No cry with painful stimuli</td>
<td>Means or cries minimally with painful stimuli</td>
<td>Appropriate crying Not irritable</td>
</tr>
<tr>
<td>Behavior State</td>
<td>No arousal to any stimuli No spontaneous movement</td>
<td>Arouses minimally to stimulus Little spontaneous movement</td>
<td>Appropriate for gestational age</td>
</tr>
<tr>
<td>Facial Expression</td>
<td>Mouth is lax No expression</td>
<td>Minimal expression with stimulus</td>
<td>Relaxed</td>
</tr>
<tr>
<td>Extremities Tone</td>
<td>No grasp reflex Flaccid tone</td>
<td>Weak grasp reflex ↓ muscle tone</td>
<td>Relaxed hands and feet Normal tone</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>
</tbody>
</table>

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N-PASS Scoring

- Can assess both pain and sedation
- Pain: Scored from 0 to 10 when checking VS
  - Adjusted for prematurity (< 28 wk +3, 28-31 wk +2, 32-35 wk +1)
  - Goal score 3 or less
  - Treat/Intervene if > 3
  - If known painful stimulus, may pre-treat
- Sedation score from 0 to -10
  - Heavy sedation -5 to -10
  - Light sedation -5 to -2

Behavioral Indicators of Infant Pain
Douleur Aigue du Nouveau-ne

| REPONSES FACIALES | 
|-------------------|------------------|
| Calme             | 0                |
| Pleurnichée avec alternance de fermeture et ouverture douce des yeux | 1 |
| Déterminer l'intensité d'un ou plusieurs des signes suivants : contraction des paupières, froncement des sourcils, ou accentuation des sillons naso-labiaux : | |
| Légers, intermittents avec retour au calme | 2 |
| Modérés           | 3                |
| Très marqués, permanents | 4 |

| MOUVEMENTS DES MEMBRES | 
|------------------------|------------------|
| Calmes ou mouvements doux | 0 |
| Déterminer l'intensité d'un ou plusieurs des signes suivants : pédalage, écartement des orteils, membres inférieurs raidis ou surelevés, agitation des bras, réaction de retrait. | |
| Légers, intermittents avec retour au calme | 1 |
| Modérés | 2 |
| Très marqués, permanents | 3 |

| EXPRESSION VOCALE DE LA DOULEUR | 
|-------------------------------|------------------|
| Absence de plainte             | 0 |
| Gémit brièvement. Pour l'enfant intubé, semble inquiet | 1 |
| Cris intermittents. Pour l'enfant intubé, mimique de cris intermittents | 2 |
| Cris de longue durée, hurllement constant. Pour l'enfant intubé, mimique de cris constants | 3 |

TOTAL

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Treatment of Pain

- Try to avoid painful procedures when possible
- Group blood draws when possible
- Coordinate cares (suctioning, diaper changes, etc) and handling
- Quiet soothing environment
- Non-pharmacologic interventions
- Pharmacologic Interventions
Non-pharmacologic Strategies

• Swaddling and Positioning—chronic pain relief
• Facilitated Tucking
• Non-nutritive sucking (pacifier, “Rec BF”)
• Massage
• Skin to Skin +/- simultaneous sucrose/glucose
• BF during heelstick or venipuncture
• Sensorial Stimulation

Facilitated Tucking

• Position hand and legs in flexed position along midline
• Different hand positions for suctioning vs heel stick
• Takes a few minutes for to accommodate
Sensorial Stimulation

• Simultaneous gentle stimulation
  – Tactile—massage face or back
  – Taste—sweet solution by pacifier
  – Auditory—gently talk to infant
  – Visual—looking into infant’s face
• Review of 16 studies showed that Sensorial Stimulation was better than sugar solution alone if all 4 elements were used

Breast Feeding & Pain

• 2012 Cochrane Review of 20 RCT
  – Breast feeding during heel stick or venipuncture
  – Lower Pain expression in term neonates
    • ↓ crying time
    • Attenuated rise in heart rate
  – Breast milk could also be provided by pacifier or syringe with similar effectiveness to glucose/sucrose in term neonates
Skin to Skin

- During heelstick or venipuncture
  - Review of 19 studies showed improvement in overall pain scores, but did not show improvement in physiologic measurements
  - Others have reported preterm infants have lower cortisol levels and improvement in autonomic measurements

Neonatal Analgesics

- Sweet solutions: Glucose or Sucrose
- Opioids
- NSAIDS
- Acetaminophen
- Topical (EMLA)
- Lidocaine
Sucrose and Glucose

- Typically 20-30% solutions
- Volume 0.1 to 1 ml
- Give 2 min before procedure
- Effect lasts about 4 min
- Not useful for chronic pain or prolonged procedures
- Unclear developmental effects
- Overall felt to be efficacious in decreasing pain scores, probably by endogenous endorphins
- But, one small RCT showed no difference in EEG readings or leg withdrawal versus placebo

Sucrose and Glucose

- Sucrose: Meta-analysis of 57 studies with 4730 patients showed benefit in patients from 25 to 44 wk
- Avoid sucrose in Hereditary Fructose Intolerance
  - Sucrose = Glucose linked to Fructose
- Glucose: Meta-analysis of 38 studies with 3785 patients showed decreased crying time and pain scores versus placebo or no intervention.
Opioids

- Morphine—medium duration, frequently used, often used for intubated patients
- Fentanyl—shorter acting, associated with chest wall rigidity
- Methadone—not designed for treatment of acute pain, long acting

Morphine

- IV dose typically 0.05 to 0.1 mg/kg/dose, variable duration of action
- Can be given PO
- Side Effects
  - Respiratory Depression
  - Hypotension
  - Urinary retention
  - Decreased intestinal mobility
  - Concern for short and long term development, increase in duration of mechanical ventilation
- Tolerance develops. Long term use often requires tapering dose
Fentanyl

- IV medication, initial dose 1 to 2 mcg/kg
- Often given as a drip, tolerance develops requiring escalating dose
- Shorter duration of action than morphine
- Similar side effect profile to morphine, but higher association with chest wall rigidity
- Reversal of chest wall rigidity requires either naloxone or paralytic (Vecuronium)

NSAIDS: Ibuprofen, Indomethacin

- Use in neonates is primarily limited to pharmacologic closure of PDA
- No clear analgesic role in premature or term newborns
- Side effect profile concerning
  - GI
  - Pulmonary hypertension—real concern
  - Urinary retention
  - Platelet dysfunction
  - Unclear developmental effects (prostaglandins are involved in CNS, cardiac, and renal development)
- Animal data suggests decreased COX 1 activity in spinal cord
Acetaminophen

• Used fairly often for neonatal pain control
• Efficacy seems best in post-surgical care
• Can be given PO or IV:
  • IV form not FDA approved for neonates
  • IV form is very expensive
• May have increased role for closure of PDA

Acetaminophen: Cochrane Review

• October 2016
• 9 Trials examining acetaminophen use for pain following heel stick, assisted vaginal delivery, ROP (eye) exams, or post operative care
• Studies could not be combined
• Overall poor evidence for analgesic effect
• No benefit for heel stick or pain following assisted VD
• May potentiate pain scores and cause longer crying after heel stick when given following assisted VD
• May decrease post operative cumulative morphine need (but this study included babies up to 1 year)
EMLA

• Eutectic Mixture of Local Anesthetics (2.5% lidocaine, 2.5% prilocaine)
• Demonstrated benefit in:
• Side Effect: methemoglobinemia
• Must leave in place for 30 min to 1 hr for good effect, questionable benefit in deeper tissues

Lidocaine

• Surprisingly little documented benefit
• Some documented benefit for tracheal anesthesia when given as spray
• Bupivicaine superior to lidocaine for dorsal penile nerve block (Stolik Dollber OC, BMC Pediatr 2005)
• Frequently used for lumber punctures
• Very important: toxic dose is > 4.5 mg/kg
• Lidocaine 1% = ______ mg/mL
• Other Side Effect: methemoglobinemia
Summary

• Premature and term neonates are very susceptible to pain
• Pain may have long term developmental, behavioral, and nociceptor effects
• Several neonatal pain scales are available and are strongly recommended for use by AAP
• Non-pharmacologic and pharmacologic interventions have proven benefit to limit physiologic and behavioral signs of neonatal pain
• Therapy should be tailored to the clinical situation bearing in mind potential side effects