ASSESSMENT AND MANAGEMENT OF PAIN IN CRITICALLY ILL NEONATES

Sandeep K Chilukala
PGY-3 Pediatrics

PAIN- A Universal Disorder

"Were we to imagine ourselves suspended in timeless space over an abyss out of which the sounds of revolving earth rose to our ears, We would hear naught but an elemental roar of pain uttered as with one voice by suffering mankind."

Fulop-Mueller, R.

MYTH 1: The neural and endocrine systems of the newborn infant are not developed to the stage that allows for transmission of painful stimuli (i.e. that they can't feel pain)

MYTH 2: Newborn infants cannot "remember" pain and, therefore, there can be no sequelae of pain

MYTH 3: Pain cannot be assessed in the newborn infant

MYTH 4: Newborn infants are easily comforted without analgesics

MYTH 5: Pain is a subjective experience that cannot be communicated in neonates.

DISCLAIMER

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Infants, regardless of age, feel pain. The youngest premature infant has the anatomic and physiologic components to perceive pain or "nociception" and demonstrate a severe stress response to painful stimuli. Anything that causes pain in an adult may cause pain in infant's – pain may be more intense than the adult. Unrelieved pain in infants can permanently change their nervous system and may "prime" them for having chronic pain. By 29 wks of gestation, pain pathways and cortical and sub-cortical centers involved in the perception of pain are well developed, as are the Neurological systems for the transmission and modulation of pain sensation.

Repetitive pain alters subsequent processing of pain. Animal models show increased cell death in the immature brain at the cortical and sub-cortical level. Long-term sequelae:
- Altered pain processing: hyperalgesia, hypoesthesia.
- Behavioral problems: ADHD, poor cognition.
- Physiological changes: high blood pressure.

What is Pain?

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. (Note: Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life.)
Some Definitions

- **STRESS**: A mentally or emotionally disruptive condition occurring in response to adverse external influences and capable of affecting physical health, or a stimulus which leads to such a condition.

- **STRESS RESPONSE**: The physiologic response, including motor, visceral, humoral, and behavioral responses of the neonate to stress.

- **DISCOMFORT**: Something that would ordinarily be considered to disturb one's comfort or cause annoyance.

PAIN Vs AGITATION

**PAIN**
- Decreased respiratory effort (guarding)
- BP & HR increase/decrease
- Diaphoresis
- Palmar sweating
- Metabolic changes

**AGITATION**
- Increased respiratory effort
- Increased HR & RR with activity only
- No diaphoresis
- No Palmar sweating
- No metabolic changes

Sources of Neonatal Pain

- **Acute Pain**: diagnostic and therapeutic procedures, minor surgery, suctioning oral/nasal/tracheal.
- **Established Pain**: Postoperative pain, inflammatory pain, thermal/chemical burns.
- **Prolonged or disease-related pain**: Meningitis, NEC, phlebitis, inflammation from heelsticks.

Classification of Procedures (Clinicians' Opinion)

- **No pain**: head u/s, chest x-ray, diaper change.
- **Discomfort**: nasal prongs, eye exam, nasal/oral suction, NG tube, extubation.
- **Real pain**: tracheal suction, umbilical cath, bladder cath, S/Q injection, remove CVL/art line.
- **More pain**: heel stick, I/M injection, venipuncture, peripheral IV, remove chest tube.
- **Lots of pain**: arterial puncture, tracheal intubation, arterial catheter, CVL catheter.
- **Unbearable pain**: circumcision, lumbar puncture, chest tube placement, bone marrow biopsy.
EPIDEMIOLOGY

- Newborns in the hospital setting are routinely subjected to painful procedures from very early in their lives.
- All newborns will experience iatrogenic pain in the first days of life, commencing with vitamin K injection and blood collection for metabolic screening tests before discharge from the hospital.
- Additional painful procedures are undertaken in selected populations as warranted by their clinical conditions.
- 1.2 million circumcisions and >200000 other operations are performed on infants <1 year of age in the United States, in 1 year.

PAIN MECHANICS IN NEWBORN

- Peripheral and spinal structures for pain transmission are present and functional between the 1st and 2nd trimester.
- A-Delta Myelinated fibres and C-unmyelinated fibres are responsible for pain impulse transmission- NOCICEPTION.
- Surrounding neurons in the periphery and spinal chord can either amplify or attenuate the pain signals. (A-Beta fibres and inflammatory mediators).
- Nociceptive sensory input reaches the thalamus by 2nd order neurons and widely distributed through out the brain.
The perception, emotional interpretation and cognitive meaning of the stimuli occurs within a distributive neuromatrix.

No single pain center exists.

The sensory-discriminative, affective-emotional and evaluative dimensions of pain perception are mediated by past experience and the context of painful event.

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**Neurodevelopment of Pain Perception**

- 7 - Skin receptors and sensory nerves around the mouth.
- 8-10 - Cortex begins to form.
- 13 - Maturation of neurons in the dorsal horn of spinal cord.
- 15 - Subplate zone of cortex formed (Signaling Station).
- 16 - Nonthalamic fibres reach cortex.
- 18 - Thalamic fibres reach the cortex.
- 19 - First EEG signals recorded.
- 20 - Thalamic fibres completely penetrate the cortex. Responses to light, sound, touch and taste recorded.
- 32 - Appearance of inhibitory mechanisms.

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Functional maturation of fetal cerebral cortex has been demonstrated by:

1. EEG Recordings
2. Cerebral glucose Utilization
3. Periods of sleep and wakefulness regulated by cortical functioning from 28 wks.
4. Newborn infants possess well-developed hypothalamo-pituitary-adrenal axes and can mount fight-or-flight responses with the release of catecholamine and cortisol. Cortisol and endorphin levels have been shown to increase during intrahepatic transfusion in 23- to 34-week-old fetuses.
Difference Between Infants and Adults

Young infants may perceive pain more intensely than older children or adults because

1) pain impulse transmission in neonates occurs primarily along non myelinated C fibers rather than myelinated A-delta fibers.
2) Less precision in pain signal transmission exists in the spinal cord.
3) Descending inhibitory neurotransmitters are lacking in infants.

ASSESSMENT OF PAIN

- Accurate pain assessments in the neonate remains challenging because of the inability of the infant to self-report.
- Pain assessment tools are either unidimensional (evaluating one parameter) or multidimensional (evaluating physiologic, behavioral and contextual parameters).
- Several tools are used in NICU, based upon physiologic and behavioral and metabolic indicators readily assessed at the bedside.

PHYSIOLOGIC PARAMETERS:
- Increased heart rate.
- Increased blood pressure.
- Change in respirations.
- Duskiness/color change.
- Decreased oxygen saturation.
- Palmar sweating.

METABOLIC:
- Catecholamines (Epinephrine, Norepinephrine).
- Cortisol (blood, saliva, or urine can be used).
- Beta-Endorphin.
- Growth hormone, glucose, glucagon, renin, aldosterone, and lactate have also been noted to increase with pain.
- Insulin secretion is usually suppressed.

BEHAVIORAL:
- Crying “Cry face”.
- Gross motor movements.
- Limp/flaccid/decreased activity.
- Fussiness.
- Grinace.
- Rigid posturing.
- Clenched hands.
- Flushed face.
- Fisting extremities.
- Tensing muscles.
- Sleeplessness.
- Restlessness/irritability.
- Decreased periods of alertness.
- Hand splaying.
TOOLS

- **PIPP** - Premature Infant Pain Profile.
- **N-PASS** - Neonatal Pain Agitation and Sedation Scale.
- **NIPS** - Neonatal Infant Pain Scale.
- **CRIES** - Crying, Requires oxygen, Increased Vital signs, Expression, Sleeplessness.

**PIPP**

<table>
<thead>
<tr>
<th>Neonates:</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>Breaths</td>
<td>Active</td>
<td>Closed</td>
</tr>
<tr>
<td>Valsalva</td>
<td>3-5</td>
<td>5-7</td>
<td>7-10</td>
</tr>
<tr>
<td>NIFN</td>
<td>T 1-3</td>
<td>T 1-3+</td>
<td>T 3+</td>
</tr>
<tr>
<td>NIFSM</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NIFSS</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
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**N-PASS** - Neonatal Pain, Agitation, and Sedation Scale.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Crying</th>
<th>Behavior</th>
<th>Eyes</th>
<th>NOSE</th>
<th>Mouth</th>
<th>SessionTime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Noisy</td>
<td>Not noticeable</td>
<td>Closed</td>
<td>widens</td>
<td>still</td>
<td>2</td>
</tr>
<tr>
<td>Crying</td>
<td>Yes</td>
<td>Not noticeable</td>
<td>Open</td>
<td>widens</td>
<td>squint</td>
<td>2</td>
</tr>
<tr>
<td>Behavior</td>
<td>No</td>
<td>Somewhat noticeable</td>
<td>Open</td>
<td>primates</td>
<td>squint</td>
<td>2</td>
</tr>
<tr>
<td>Eyes</td>
<td>No</td>
<td>Noticeable</td>
<td>Open</td>
<td>Jet black</td>
<td>squint</td>
<td>2</td>
</tr>
<tr>
<td>NOSE</td>
<td>Yes</td>
<td>Noticeable</td>
<td>Receding</td>
<td>May be wet</td>
<td>Fluttering</td>
<td>2</td>
</tr>
<tr>
<td>Mouth</td>
<td>Yes</td>
<td>Noticeable</td>
<td>Open</td>
<td>Still</td>
<td>squint</td>
<td>2</td>
</tr>
<tr>
<td>SessionTime</td>
<td>No</td>
<td>Noticeable</td>
<td>Open</td>
<td>Jet black</td>
<td>Fluttering</td>
<td>2</td>
</tr>
</tbody>
</table>
**LIMITATIONS**

The inability to select a single assessment tool is based in part upon the following limitations.

- Most tools were developed and validated for neonates undergoing acute pain.
- Many signs require the subjective evaluation by observers. So there is significant interobserver variability.
- Requiring specialized equipment.
- Some measures are not available in real time.
- Responses to pain may be decreased in neurologically impaired neonates and absent in those with paralytics.
- Because of the limited ability to detect and quantify pain in neonates, especially preterm infants, it is suggested that pain control measures be administered preemptively to prevent or reduce pain due to known noxious stimuli.

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**MANAGEMENT OF PAIN**

<table>
<thead>
<tr>
<th>Non-Pharmacological Methods</th>
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<tr>
<td>- Non nutritive Sucking</td>
<td>- Local Anesthesia</td>
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<tr>
<td>- Swaddling</td>
<td>- Systemic Anesthesia</td>
</tr>
<tr>
<td>- Skin-to-Skin contact</td>
<td>- Opiods</td>
</tr>
<tr>
<td>- NIDCAP approach</td>
<td>- NSAIDS</td>
</tr>
<tr>
<td>- Sucrose Therapy</td>
<td>- Other Drugs</td>
</tr>
<tr>
<td>- Ketamine</td>
<td>- Acetaminophen</td>
</tr>
<tr>
<td>- NSAIDS</td>
<td>- Local Anesthetics</td>
</tr>
<tr>
<td>- Other Drugs</td>
<td>- Topical Anesthetics</td>
</tr>
</tbody>
</table>

- **Non Nutritive Sucking**
  - Mediated via orotactile and oral mechanoreceptors
  - Reduces pain in heel lance, circumcision, immunizations
  - Effective in preterm infants
  - More effective when pacifiers dipped in sucrose

- **Swaddling**
  - Can be achieved by swaddling in a blanket or facilitated tucking.
  - Stimulation of proprioceptive, tactile, thermal systems and facilitates self soothing behavior
  - Studies inconclusive in preterm infants

- **Skin-to-Skin Contact**
  - Kangaroo care.
  - Decreases HR, crying and grimacing after heel lance.
  - Decrease light and noise
  - Positioning with “nests”
  - Respect sleep-wake cycles

- **NIDCAP Approach**
  - Cluster tests and exams
  - Decrease light and noise
  - Positioning with “nests”
  - Kangaroo care.
  - Decreases HR and emotional stress after heel lance.
  - Non nutritive sucking
  - Decrease lachrymation and grimacing
  - Use sucrose

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*References: Gray et al., Pediatrics, 2000.*
**SUCROSE THERAPY:**
Oral sucrose and sweet tasting liquids like saccharin are effective analgesics in both term and preterm infants. Acts by activating the endogenous opioid mechanisms in the brainstem. It also suppresses the neurophysiological responses to pain.

- **Dose:**
  - 27 to 31 weeks: 0.5ml
  - 32 to 36 weeks: 1ml
  - >37 Weeks: 2 ml

Give 2 min pre procedure. Not effective after 3 months of age.

**LOCAL ANESTHETICS**
- Includes topical anesthetics and injectable.

**TOPICAL**
- EMLA Cream (Lidocaine + Prilocaine)
- Ametop (4% Tetracaine)
- L.M.X-4 (4% Liposomal Lidocaine)
- S-caine (Tetracaine + Lidocaine)

**INJECTABLE**
- Lidocaine

**SYSTEMIC ANALGESIA**
- Non Opioids - Acetaminophen.
- NSAIDS
- Opioids - Morphone, Fentanyl.
- Sedatives - Midazolam.

**MORPHINE**
- Provides sedation AND analgesia.
- Do NOT provide amnesia.
- Relatively slow onset of action.
- Ceiling effect noted with higher doses.
- Longer duration due to lower lipid solubility, especially in premature infants.
- Metabolized in liver to active compounds:
  - M6G: Potent analgesic, T1/2 > Morphone
  - M3G: opioid antagonist, high levels may cause seizures.
- Histamine release:
  - Hypotension, especially with hypovolemia.
  - Bronchospasm - caution in asthma, BPD.
- Greater effects on GI motility, biliary spasm
- Less risk of dependence/withdrawal than fentanyl.
**N.E.O.P.A.I.N.** Trial (NEurologic Outcomes & Preemptive Analgesia In Neonates)

**HYPOTHESIS:** Ventilated preterm neonates treated with morphine infusions may have a decreased incidence of poor neurologic outcomes as compared to a placebo control group.

(Poor Neurologic Outcomes: Death at <28 days without NICU discharge; Severe IVH (grade III or grade IV); Periventricular leukomalacia).

- Randomized (N=898) Morphine (N=449), Placebo (N=449).

**CONCLUSIONS:**
Continuous morphine infusions do not alter the neurologic outcomes of preterm neonates (23-32 wks GA). Additional, intermittent IV boluses of morphine were required for neonates with severe IVH and/or PVL. Side effects of morphine include hypotension, prolonged ventilation, decreased GI motility.

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**FENTANYL**

- Rapid onset (2-3min).
- Prolonged elimination with infusion.
- Minimal hemodynamic effects.
- Chest wall rigidity may occur with bolus doses.
- Metabolized in liver to inactive compounds, but not significantly altered in liver disease.
- Tolerance develops rapidly (infusion>bolus).
- Risk of dependence is greater than Morphine.

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**KETAMINE**

- IV anesthetic agent; procedural pain.
- Produces “dissociative state” via NMDA receptor blockade, intense sedation, analgesia and amnesia; increased muscle tone.
- Maintains hemodynamic stability, respiratory drive, causes bronchodilation.
- Usual doses:
  - 0.5-2 mg/kg IV
  - 2-4 mg/kg IM
  - 5-8 mg/kg orally.

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**ROUTINE ONGOING ANALGESIA.**

- Swaddling, containment or facilitated tucking.
- Reduction of acoustic, thermal & other stresses.
- Use a pacifier, consider sucrose therapy.
- Establish a Kangaroo care program.
- Consider low-dose morphine/fentanyl infusions for ventilated neonates.
- Use of midazolam is not recommended.
- Consider acetaminophen and ibuprofen [safety or efficacy of repeated doses is unknown].
**CAPILLARY BLOOD SAMPLING.**
- Use a pacifier with sucrose (concentration 12–24%) given 2 minutes prior to the procedure.
- Swaddling, containment or facilitated tucking.
- Consider skin-to-skin contact with the mother.
- Use a mechanical spring-loaded lance, less painful than manual lance.
- Consider the use of venepuncture (less painful, more efficient and requires less re-sampling)
- EMLA, acetaminophen and warming the heel are ineffective; squeezing for blood is the most painful.

**LUMBAR PUNCTURE.**
- Use a pacifier with sucrose.
- Apply Topical Anesthetic to the site.
- Subcutaneous infiltration of lidocaine.
- Containment & careful physical handling.

**CONCLUSIONS**
- Golden Rule: What is painful to an adult is painful for infants unless proven otherwise.
- Babies do experience and remember pain.
- Exposure to repetitive pain occurs commonly in newborn infants.
- Long-term sequelae:
  - Altered pain processing: hyperalgesia, hypoesthesia.
  - Behavioral problems: ADHD, poor cognition.
  - Physiological Changes: High Blood Pressure.
- Assessment methods only for acute pain.
- Limited evidence for some analgesic therapies: sucrose, local/topical anesthesia, morphine.

**Some Final Thoughts**
- Research on long-term outcomes is essential.
- Is neonatal pain relief by itself an adequate and distinct outcome, in the absence of other benefits or adverse effects?
- If opioids are safe and effective and have equivalent long term outcomes, is it ethical to tolerate a small increase in short-term side effects (e.g. bowel dysmotility or prolongation of ventilation) for improved pain relief?
- Future research must define:
  - Efficacy of specific therapeutic approaches.
  - Applicability to specific neonatal populations.
  - Combination approaches.
  - Comparative studies between analgesic drugs.
Questions, Comments, Concerns.