بسم الله الرحمن الرحیم

In the name of God

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- Neonates, especially those cared for in the neonatal intensive care unit (NICU) setting, frequently experience painful procedures.
- Pain assessment and management is a routine part of neonatal care.

NEONATAL RESPONSES TO PAIN

- Both preterm and term infants experience pain and stress in response to noxious stimuli.
- By the middle of the second trimester, the human fetus has a highly differentiated and functional sensory system.
- Neonates respond to pain with:
- ١- autonomic responses (increases in heart rate and blood pressure)
- ٢-hormonal changes (release of cortisol and catecholamines)
- ٣-behavioral changes (eg, facial grimace, crying, hand and body movements)
- These responses form the basis of pain assessment tools used in neonates.

- in a systematic review that included six observational studies involving ١١٢٢ neonates managed in the NICU setting, neonates on average experienced ٨ to ٢٠ painful procedures per day during the first two weeks of their NICU hospitalization
- The most common painful procedures were:
- heel lance
- nasal or endotracheal suctioning
- venipuncture
- vascular catheter placement
- . In the largest study, specific analgesic therapy was provided for approximately ٢٠ percent of procedures .

LONG-TERM EFFECTS OF NEONATAL PAIN

- altered brain development
- dysregulation of the hypothalamic-pituitary-adrenal axis
- changes in how pain is experienced later in life
- The detrimental impact of cumulative procedural pain on neonatal brain development highlights the importance of recognizing and effectively managing pain in neonates

- **Short term effects –** Brain changes in the neonatal period included decreased total brain volume, decreased white matter, and decreased thalamic and basal ganglia volume and metabolism.
- ●**Long-term effects –** At school age, changes in the brain included decreased cortical thickness, decreased white matter maturation, and decreased volume of the amygdala, hippocampus, cerebellum, thalamus, and basal ganglia.

Altered pain response

- Several studies have reported that infants who are exposed to repetitive pain the neonatal period are at risk of subsequently developing increased pain sensitivity and/or chronic pain syndromes

PAIN ASSESSMENT

- **Routine standardized approach —** Pain assessment is a routine part of neonatal care.
- Healthcare facilities caring for neonates and young infants should establish standardized practices for pain assessment and management

- **Frequency of assessment** — For hospitalized neonates, pain assessments are performed using a validated tool at the following intervals:
- ●Routinely, at least every four hours.
- The pain score is measured and documented at the same time as routine vital sign measurements.
- ●After any painful procedure or intervention.
- ●Any time there is clinical concern for pain or if pain is likely to occur. As a general rule, anything that causes pain in older children also causes pain in neonates, regardless of gestational age (GA). Parental/caregiver concern that the neonate is experiencing pain should also prompt an assessment of the pain score.

pain assessment tools

- **Commonly used tools**
- The pain assessment tools that are commonly used in the neonatal intensive care unit (NICU) include
- ●BIIP (Behavioral Indicators of Infant Pain，

- ●BPSN (Bernese Pain Scale for Neonates)
- ●COMFORTneo
- ●COVERS (Crying, Oxygen requirement, Vital signs, Expression, Resting, Signaling distress)
- ●CRIES (Crying, Requires increased oxygen administration, Increased vital signs, Expression, Sleeplessness)
- ●DAN (Douleur Aiguë Nouveau-né) scale
- ●EDIN (Echelle de Douleur et d'Inconfort du Nouveau-né)
- ●NFCS (Neonatal Facial Coding System)
- ●NIPS (Neonatal Infant Pain Scale)
- ●N-PASS (Neonatal Pain Agitation and Sedation Scale)
- ●PAT (Pain Assessment Tool)
- ●PIPP-R (Premature Infant Pain Profile-Revised)

- the five that have been subjected to the most rigorous validation testing include:
- BIIP
- CRIES
- DAN
- N-PASS
- PIPP-R

Parameters evaluated

- Neonatal pain assessment tools assess the neonate's physiologic and behavioral responses to pain or noxious stimuli:
- ●**Physiologic parameters** :
- changes or variability in heart rate
- blood pressure
- respiratory rate
- and oxygen saturation.

- Other physiologic parameters that are occasionally considered include pupillary size, palmar sweating, and skin color. Some studies have used alteration in physiologic electroencephalographic (EEG) or electromyographic (EMG) patterns to assess pain; however, these methods are not widely available and their validity and reliability for assessing pain are not well established.

Behavioral responses

- crying patterns
- facial expressions
- hand and body movements
- muscle tone
- sleep patterns
- behavioral state changes
- consolability.
- In neonates, assessing for certain specific facial findings (brow bulge, eye squeeze, nasolabial furrow, and open mouth) helps to recognize acute and postoperative pain

For **acute pain**, including procedural or postoperative pain

- PIPP-R
- •NFCS
- •DAN
- •N-PASS

- For **prolonged pain** (eg, intubated neonates, prolonged pain after major surgery, indwelling chest tubes, painful chronic medical conditions [eg, necrotizing enterocolitis]):
- •N-PASS
- •COMFORTneo

MULTIMODAL APPROACH

- ●Nonpharmacologic measures:
- skin-to-skin contact
- breastfeeding
- non-nutritive sucking
- swaddling
- ●Topical or local anesthetics
- ●Systemic analgesic medications

Mildly painful

- ●**Example procedures**
- Heel lance or finger stick
- •Venipuncture or peripheral venous catheter insertion
- •Intramuscular (IM) or subcutaneous injection
- •Nasogastric (NG) tube insertion
- •Bladder catheterization
- •Dressing change/tape removal

Appropriate measures

- oral sucrose in combination with nonpharmacologic measures (eg, skin-to-skin contact, non-nutritive sucking)

- A topical anesthetic (eg, eutectic mixture of local anesthetics [EMLA]) can also be used for some procedures in this category (eg, intravenous [IV] catheter insertion, IM, or subcutaneous injection) but not others (eg, NG tube insertion, bladder catheterization, dressing change).
- EMLA is not routinely used for heel lance since it appears to be ineffective in this setting.

Moderately painful

- **Example procedures –** Examples of minor procedures that are associated with moderate pain include
- •Lumbar puncture (LP)
- •Peripheral arterial puncture or catheterization
- •Umbilical venous or arterial catheterization
- •Intraosseous (IO) cannulation

Appropriate measures for **Moderately painful**

- For neonates undergoing minor procedures associated with moderate pain, we use nonpharmacologic measures, oral sucrose, plus a topical anesthetic (eg, EMLA) when appropriate

More complex procedures

- More complex procedures are those that not only cause moderate pain, but also require that the neonate remain relatively still during the procedure.
- Examples of such procedures include
- Percutaneous central venous catheter (CVC) placement
- Placement of a peripherally inserted central catheter (PICC)
- ●Chest tube placement
- Circumcision
- ●Endotracheal intubation
- ●Retinopathy of prematurity (ROP) examination

Nonpharmacologic measures

- non-nutritive sucking
- facilitated tucking

- ●Oral sucrose
- ●Topical and/or local anesthetic when appropriate

- ●Acetaminophen
- ●A short-acting sedative or opioid agent (ketamine, fentanyl, sufentanil), if needed (see 'Ketamine' below and 'Fentanyl' below and 'Sufentanil' below)

- When opioids are used for these procedures, we prefer short-acting over longer-acting agents (ie, fentanyl or sufentanil rather than morphine) because these procedures are usually brief.
- The amount of opioid required can be reduced by using a local anesthetic and acetaminophen.
- In our experience, this combination often allows for a successful procedure.
- Opioids can cause respiratory depression in neonates, especially in preterm neonates, and these agents should be used with caution in nonintubated patients

Specific procedures

- **Circumcision —** Multimodal analgesia for neonatal circumcision includes oral sucrose, non-nutritive sucking, facilitated tucking, local anesthesia (eg, ring block or dorsal penile nerve block), and acetaminophen for postprocedure pain.
- Analgesia for neonatal circumcision is discussed in greater detail separately.

ROP screening examination

- For most neonates undergoing screening or follow-up ROP examination, we suggest the following measures :
- ●Nonpharmacologic measures (eg, non-nutritive sucking, facilitated tucking)
- ●Oral sucrose
- ●Topical anesthetic (eg, proparacaine), depending on ophthalmologist preference

Endotracheal intubation

- Commonly used agents for neonates undergoing elective tracheal intubation include :
- ●Ketamine (the preferred agent at the author's institution)
- ●Fentanyl or other short-acting opioid (eg, sufentanil, remifentanil)
- Though propofol is used in some centers for endotracheal intubation in neonates, it is not used at the author's institution given the high incidence of adverse hemodynamic effects.
- The combination of an opioid plus a benzodiazepine (eg, midazolam) is another alternative; however, this is associated with increased risk of adverse events and does not appear to improve the likelihood of successful intubation compared with an opioid alone

POSTOPERATIVE PAIN

- For most neonates undergoing major surgery, we use a multimodal approach to postoperative pain management including **all** of the following:
- ●Nonpharmacologic measures (eg, breastfeeding, skin-to-skin contact)
- ●Regularly scheduled acetaminophen, which reduces the need for opioid therapy
- ●Intermittent opioids as needed
- The available observational and clinical trial data suggest that intermittent opioid therapy is safe and effective for reducing postoperative pain in neonates and is equally effective when compared with continuous dosing [
- Higher doses of opioids, particularly when administered via continuous infusion, carry an increased risk of adverse effects (eg, apnea, increased ventilator requirement, hypotension)

PROLONGED OR CHRONIC PAIN

- ●Indwelling chest tube
- ●Ongoing medical condition associated with moderate to severe pain (eg, necrotizing enterocolitis, bacterial meningitis)
- ●Mechanical ventilation

- The distinction between the terms "prolonged" and "chronic" pain is not always clear. Despite ongoing efforts, consistent definitions for these terms in neonates have not been established
- We generally use the term "prolonged pain" when referring to pain that persists beyond a simple one-time procedure but that has a limited course (eg, pain associated with an indwelling chest tube or endotracheal tube);
- whereas we use "chronic pain" when referring to pain that is expected to last well beyond the neonatal period (eg, epidermolysis bullosa)

General approach

- For neonates with ongoing painful medical conditions and those who are receiving interventions that cause prolonged pain or discomfort, we use a multimodal approach to pain control that typically includes all of the following:
- ●Nonpharmacologic measures (eg, breastfeeding, skin-to-skin contact
- ●Acetaminophen as needed
- ●Intermittent as-needed opioids (eg, morphine, fentanyl)
- Most neonates are adequately managed with these measures. However, neonates with poorly controlled pain may require a continuous opioid infusion.
- We generally prefer intermittent rather than continuous dosing of opioids since intermittent dosing tends to result in a lower cumulative dose and lower risk of apnea and other adverse effects.
- Another advantage of intermittent dosing is that it necessitates regular pain assessments for these neonates.
- Other agents that are sometimes used in the management of infants with chronic pain include methadone, ketamine, or gabapentin
- Consultation with a pain specialist is often helpful for management of these patients.

- **Mechanical ventilation**
- ●**Approach** – For intubated neonates receiving ongoing invasive mechanical ventilation, we use a multimodal approach to pain and sedation management, including **all** of the following:
- •Intermittent doses of an opioid (eg, morphine, fentanyl, sufentanil)
- •Acetaminophen as needed
- •Nonpharmacologic measures
- Most neonates are adequately managed with these measures. However, neonates with poorly controlled pain or severe agitation may require continuous opioid infusion and/or the addition of a sedative agent (eg, midazolam or dexmedetomidine).

Nonpharmacologic measures

- **Breastfeeding or breast milk** — Breastfeeding is an effective analgesic measure.
- Supplemental breast milk is a reasonable option for providing neonatal analgesia, but less effective than breastfeeding or sucrose/glucose
- . Breastfeeding is a developmentally superior alternative to oral sucrose or glucose for pain control in infants.
- .

Benefits of breastfeeding

- maternal proximity and ventral skin-to-skin contact, which increase beta endorphin and oxytocin levels in newborns, and the effects of sugars, fats, and other nutrients in breast milk combined with nutritive sucking to reduce pain and divert the infant's attention away from the painful stimulus

breastfeeding

- A separate systematic review found that breastfeeding was more effective for reducing pain scores in full-term or preterm infants than :
- maternal holding, maternal skin-to-skin contact,
- topical anesthetics, oral sucrose, or music therapy
- , whereas expressed breast milk did not consistently reduce pain responses.

Non-nutritive sucking

- Although breastfeeding or oral sucrose are preferred to non-nutritive sucking for infants undergoing minor painful procedures, non-nutritive sucking is effective in reducing pain-related distress in both preterm and term infants.

- Clinical trial have shown that infants offered pacifiers during painful stimuli have less intense pain responses (less crying, lower heart rate) compared with those who received no intervention or swaddling or rocking alone .
- Infants who received pacifiers dipped in sucrose had greater pain relief compared with those who received a pacifier alone.

Swaddling or facilitated tucking

- In term and preterm infants, swaddling or facilitated tucking (defined as gently maintaining the arms and legs in a flexed position) is more effective than no intervention in reducing pain responses to invasive procedures (eg, endotracheal suctioning and heel stick)
- A multicenter randomized trial showed that facilitated tucking in combination with oral sucrose was more effective in relieving pain from repeated heel sticks compared with either intervention alone

- Gently keeping the infant's limbs flexed activates proprioceptive, tactile, and thermal systems;
- facilitates self-soothing behaviors (eg, hand-to-mouth movement, non-nutritive sucking) and is developmentally supportive.
- This can be achieved manually (facilitated tucking) or by swaddling in a blanket.
- Of note, tight swaddling should be avoided as this has been associated with an increased risk of developmental dysplasia of the hip.

Swaddling

Skin-to-skin contact (kangaroo care)

- which includes kangaroo care (with infant resting between the mother's breasts) stimulates ventral tactile and proprioceptive systems and reduces neonatal pain responses
- . A systematic review reported that skin-to-skin contact was effective and safe in reducing neonatal pain due to a single painful procedure (eg, heel lance or venipuncture).

Sensorial saturation

- Sensorial saturation refers to providing multimodal sensory inputs (eg, touch, massage, voice, smell) during a painful procedure.
- Several studies have shown pain reduction in infants receiving sensorial saturation (eg, radiant warmth or exposure to familiar scent) plus oral sucrose during painful procedures compared with oral sucrose alone.
- However, this approach is labor-intensive, and it can be challenging to define the right amount of stimulation (too much stimulation can cause distress and sensitize the infant to pain; too little stimulation may not be effective). This fine line changes across gestational ages.

Music

- – Music reduces pain responses and increases physiological stability during neonatal pain, although a systematic review found that the interventions and their therapeutic effects were inconsistent
- A subsequent randomized, controlled, blinded crossover clinical trial in neonates >٣٢ weeks gestation found that pain scores were significantly reduced at all time points when music was combined with sucrose compared with groups given music or sucrose alone, but there were no differences in scores between the music and sucrose groups .

Massage

Several studies have shown that massage has therapeutic benefits for acute pain (eg, heel lance, venipuncture) in term and preterm neonates

- ●**Unproven measures –** We suggest **not** routinely using the following modalities for treatment of acute pain in neonates since the available studies have not consistently demonstrated a benefit
- •Therapeutic touch
- •Warming
- •Osteopathic manipulation
- •Medical acupuncture


DAYTIME
CHICAGO

Oral sucrose and other sweet liquids

- Oral sucrose and other sweet-tasting liquids, such as glucose or dextrose, are effective analgesics in both term and preterm infants

- ●**Clinical uses –** At our institution, we use oral sucrose solution in combination with nonpharmacologic measures (eg, skin-to-skin contact, non-nutritive sucking) to reduce minor acute episodic procedural pain (eg, venipuncture, intramuscular [IM] injection

Sucrose

- may also be combined with local anesthesia and/or opioid agents as part of multimodal analgesia for more painful, prolonged and/or invasive procedures (eg, lumbar puncture [LP], circumcision, chest tube insertion, percutaneous central venous catheter insertion, or intraosseous access)

Dosing and administration sucrose

- – We use a ۲۴ percent sucrose solution with weight-based dosing as follows:
- •≤۱۰۰۰ g: ۰٫۰۵ to ۰٫۱ mL (one to two drops)
- •>۱۰۰۰ to ۱۵۰۰ g: ۰٫۱۵ to ۰٫۲ mL (three to four drops)
- •>۱۵۰۰ to ۲۰۰۰ g: ۰٫۲۵ to ۰٫۳۵ mL (five to seven drops)
- •>۲۰۰۰ g: ۰٫۴ to ۰٫۵ mL (۸ to ۱۰ drops)

- reported dosing regimens range from ۰٫۰۵ to ۱ mL of a ۲۴ percent sucrose solution Sucrose can be administered orally via a syringe or onto the tongue by allowing the infant to suck on a pacifier that has been previously dipped in a sucrose solution. For intubated infants, we place sucrose directly on the infant's tongue.

- **Timing** – We administer oral sucrose one to two minutes before a painful procedure, and repeat the dose as needed for pain relief. Multiple resources recommend an interval of two minutes after sucrose therapy before performing the procedure

- although one randomized trial suggested that it may not be necessary to wait after sucrose administration
- ●**Repeat doses** – If needed, we repeat sucrose doses during the procedure rather than waiting until after the procedure. In our experience, we have found that additional doses given during the procedure are beneficial
- .

topical anesthetics

- lidocaine-prilocaine (eg, EMLA [an acronym for "eutectic mixture of local anesthetics"]) and tetracaine (amethocaine) gel (eg, Ametop).

- EMLA is the topical anesthetic of choice in our center. It is the agent most widely used most extensively studied in neonates. Tetracaine gel is not available in the United States.
- •**Lidocaine-prilocaine cream (eg, EMLA)** – EMLA is a mixture of ۲٫۵% lidocaine and ۲٫۵% prilocaine in a cream base.
- It produces anesthesia within ۴۰ to ۶۰ minutes of its application, and the effects last for one to two hours.
- The term "eutectic" refers to a mixture of substances with a lower melting point than any of the individual constituents alone.
- EMLA is administered by applying ۰٫۵ to ۱ g to the site one hour prior to the procedure and covering with an occlusive dressing
- The lower end of this dose range is appropriate for preterm neonates <۳۷ weeks gestation. The maximum dose per ۲۴-hour period should not exceed ۱ g, and the application time should not exceed one hour.

- **Supporting evidence** – The evidence supporting EMLA and tetracaine (amethocaine) gel for minor dermal procedures in neonates comes from observational studies and several small randomized trials, which reached variable conclusions
- A systematic review identified seven small trials (n = ٥٧٤ neonates) comparing either EMLA or tetracaine gel to placebo
- For EMLA, two trials reported reduced pain scores during venipuncture or LP, whereas three trials found little to no difference in pain scores during heel lance . For tetracaine gel, one trial reported reduced pain scores during venipuncture, whereas a second trial found little to no difference in pain scores during intramuscular injection .
- ●**Adverse effects** – Topical anesthetics are generally well tolerated in neonates when used at appropriate doses. The most common adverse effects reported in the available trials were minor local skin reactions; no serious adverse events were reported
- Repeated or frequent doses should be avoided as this increases the risk for systemic absorption and toxicity. In addition, topical anesthetics should **not** be applied on open wounds or lacerations. A potential rare adverse effect of topical anesthetics is methemoglobinemia, which is discussed separately.

Acetaminophen

- ●**Clinical uses** – Acetaminophen (paracetamol) is a weak analgesic which is **not** effective enough to treat acute severe pain if used without other agents

- •For postoperative or postprocedural pain – We use acetaminophen in combination with opioids
- •For mild to moderate inflammatory pain (eg, enteropathy or necrotizing enterocolitis, skin wounds, bedsores, or nasal trauma due to noninvasive ventilation).
- •For musculoskeletal pain (eg, limb bruises, clavicle fractures, cephalohematoma following birth trauma).
- ●**Dosing and administration** – Oral, intravenous (IV), and rectal formulations of acetaminophen are available for use in neonates . We generally use oral dosing for neonates who can tolerate oral medication and IV dosing for those who cannot. We do not routinely use rectal acetaminophen at our center.
- •**Oral acetaminophen** – Oral dosing varies by GA:
- -<٣٢ weeks gestation – ١٥ mg/kg/dose every ١٢ hours
- -٣٢ to ٣٦ weeks gestation – ١٥ mg/kg/dose every eight hours
- -Term infants – ١٥ mg/kg/dose every six hours

- These doses and dosing intervals were primarily based upon antipyretic dose-response studies. In both preterm and term infants, the clearance of acetaminophen is slower than in older children, so repeat dosing is required less frequently.

- •**IV acetaminophen** – Data are limited for IV dosing of acetaminophen in neonates.
- We use the following dosing schedule for IV acetaminophen for infants with postmenstrual age (PMA) between ٣٢ and ٤٤ weeks:
- -Loading dose of ٢٠ mg/kg
- -Maintenance doses of ١٠ mg/kg starting six hours after the loading dose, and every six hours thereafter
- For neonates with PMA between ٢٨ to ٣١ weeks, the dosing interval for maintenance doses is increased to ١٢ hours

- **Rectal acetaminophen** – When acetaminophen is administered rectally, it is generally given at the same dose as for oral administration, though the optimal dosing is not established in neonates. As previously mentioned, we do not use rectal acetaminophen at our center.
- Other centers may use rectal acetaminophen for adjunctive analgesia in neonates who cannot receive oral therapy .
- We generally prefer IV acetaminophen for this purpose. In one study, rectal acetaminophen showed minimal opioid-sparing effects on postoperative pain in neonates and infants, possibly due to inadequate rectal absorption [١١٩].
- •**Total daily dose** – Recommended total daily doses are based on GA and postnatal age [١٢١]:
- -٢٤ to ٣٠ weeks GA – ٢٠ to ٣٠ mg/kg/day
- -٣١ to ٣٦ weeks GA – ٣٥ to ٥٠ mg/kg/day
- -٣٧ to ٤٢ weeks GA – ٥٠ to ٦٠ mg/kg/day
- -١ to ٣ months postnatal age– ٦٠ to ٧٥ mg/kg/day

- **Opioid-sparing effect** – For patients with postoperative pain, acetaminophen reduces the overall amount of opioid required (ie, it has an opioid-sparing effect) [١٢٠,١٢٢-١٢٥]. In a randomized trial involving ٧١ neonates who underwent noncardiac thoracic or abdominal surgery, those who received regularly scheduled IV acetaminophen required less total morphine during the first ٤٨ hours (median cumulative dose ١٢١ versus ٣٥٧ micrograms/kg) [١٢٢].
- ●**Adverse effects** – Acetaminophen is generally well-tolerated in neonates. Rare adverse events include hepatic or kidney toxicity [١٢٦,١٢٧]. While acetaminophen is effective for temperature reduction in febrile infants, the available evidence suggests it does **not** increase the risk of hypothermia in neonates who are normothermic [١٢٨].
- The long-term safety of IV acetaminophen was demonstrated in a five-year follow-up study of infants who required neonatal intensive care [١٢٩]. Rates of various childhood health conditions (eg, asthma, atopic dermatitis, inflammatory bowel disease, autism, speech disorders, or cerebral palsy) were similar in children exposed to IV acetaminophen in the neonatal period compared with those who were not exposed.

- **Nonsteroidal anti-inflammatory drugs (not recommended) —** Nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen, ketorolac, indomethacin) are **not** routinely used in the management of pain in neonates since safer and effective alternative agents are available. In infants <٣ months old, NSAIDs have an unacceptably high risk of adverse effects (eg, gastrointestinal bleeding, platelet dysfunction, postoperative bleeding, acute kidney injury) that precludes using these agents routinely for neonatal analgesia [١٣٠,١٣١].
- Use of NSAIDs in neonates is largely limited to treatment of patent ductus arteriosus, as discussed separately.

Opioids

- Opioids are highly effective for treating moderate to severe pain in patients of all ages.
- Opioids provide both analgesia and sedation, have a wide therapeutic window, and attenuate physiologic stress responses.
- However, the benefits of opioid therapy need to be balanced against the risk of serious adverse effects, including respiratory depression, hypotension, urinary retention, and reduced gastrointestinal motility.
- In neonates, opioids are most commonly used for postoperative pain control following major surgery, to facilitate mechanical ventilation, or for sedation/analgesia in neonates with hypoxic-ischemic encephalopathy

. Opioids are also used for procedural sedation and analgesia for invasive procedures such as CVC placement, tracheal intubation, or chest tube placement.

- In most situations, we use intermittent dosing of opioids rather than continuous IV infusions. This approach is in accordance with the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society (CPS) guidelines on pain in neonates

- **Opioid-sparing strategies** — Because neonates are at increased risk of experiencing adverse effects from opioids, especially respiratory depression, the pain management approach should utilize multimodal interventions aimed at minimizing the amount of opioid required. This includes:
- ●Concomitant use of acetaminophen.
- ●Use of oral sucrose and nonpharmacologic measures to address pain and discomfort (eg, non-nutritive sucking, swaddling).
- Limited data suggested that for neonates with postoperative pain, nurse-controlled analgesia may reduce opioid requirements compared with a continuous opioid infusion [

- Morphine and fentanyl are the most commonly used opioids in neonates
- [
- **Morphine —** Morphine is the prototypical opioid and is widely used for pain management in infants, children, and adults.
- The onset of analgesia after a single IV dose of morphine is rapid (within five minutes) with the peak effect occurring within ١٠ to ٢٠ minutes. The analgesic effect lasts for approximately four hours. The half-life of morphine is longer in neonates compared with older infants and children due to reduced protein binding.
- ●**Single or intermittent doses** – We start at the minimum dose possible and increase the dose, if needed, based on serial pain assessments. Initial dosing is based on GA, as follows:
- •<٣٢ weeks GA: ٥ micrograms (mcg)/kg per dose IV every four to eight hours, as needed based on pain assessment
- •≥٣٢ weeks GA: ١٠ mcg/kg per dose every four to eight hours, as needed based on pain assessment
- ●**Continuous infusion** – We start at the minimum dose and increase the dose, if needed, based on serial pain assessments. The initial dose for continuous IV morphine is based on GA is as follows:
- •GA <٣٢ weeks: ٥ mcg/kg per hour IV
- •GA ≥٣٢ weeks: ١٠ mcg/kg per hour IV

Fentanyl

- Fentanyl is a synthetic opioid that is ٥٠ to ١٠٠ times more potent than morphine. It has rapid onset (within two to three minutes) and relatively short duration of action (٣٠ to ٤٥ minutes), making it an attractive option for procedural sedation/analgesia.
- ●**Single or intermittent doses** – Fentanyl is given via slow IV push every two to four hours as needed based on pain assessment. Dosing is based on GA, as follows:
- •GA <٢٨ weeks – ١ to ٢ mcg/kg per dose
- •GA ٢٨ to ٣٢ weeks – ٢ to ٣ mcg/kg per dose
- •GA >٣٢ weeks – ٣ to ٤ mcg/kg per dose
- When using fentanyl for procedural sedation/analgesia, the procedurist should wait one to three minutes after administration prior to starting the procedure.
- ●**Continuous infusion** – Fentanyl infusion is started at ٠٫٥ to ١ mcg/kg per hour IV. The same dose is used for preterm and term neonates. We typically start at the lower dose and increase the dose if needed based on serial pain assessments.

- **Sufentanil** — Like fentanyl, sufentanil is a synthetic opioid that is substantially more potent than morphine. Sufentanil is approximately ١٠ times more potent than fentanyl. It has rapid onset (within two to three minutes) and short duration of action (٢٠ to ٣٠ minutes), making it an attractive option for procedural sedation/analgesia.
- ●**Single or intermittent doses** – Sufentanil is given via slow IV push every two to four hours as needed based on pain assessment. Dosing is based on GA, as follows:
- •<٢٨ weeks GA – ٠٫١ to ٠٫٢ mcg/kg per dose
- •≥٢٨ weeks GA – ٠٫٢ to ٠٫٣ mcg/kg per dose
- When using sufentanil for procedural sedation/analgesia, the procedurist should wait one to three minutes after administration prior to starting the procedure.

- **Continuous infusion** – Sufentanil infusion is started at ۰٫۰۵ to ۰٫۱ mcg/kg per hour IV. The same dose is used for preterm and term neonates. We typically start at the lower dose and increase the dose if needed based on serial pain assessments.
- **Supporting evidence** — The evidence supporting use of opioids in neonates in different clinical circumstances is summarized above:
- ●Procedural sedation/analgesia (see 'General approach' above)
- ●Elective endotracheal intubation (see 'Endotracheal intubation' above)
- ●Ongoing invasive mechanical ventilation (see 'Mechanical ventilation' above)
- ●Hypoxic-ischemic encephalopathy (see 'Hypoxic-ischemic encephalopathy' above)
- **Comparison of agents** — Most of the comparative studies on different opioid agents in neonates have compared morphine versus fentanyl. There are few data comparing these agents to other opioids (eg, sufentanil, remifentanil).
- ●**Analgesic effects** – In the available clinical trials, morphine and fentanyl were equally effective in reducing pain scores in intubated patients and in patients undergoing invasive procedures [۹٬۳۷٬۱۳۷].
- ●**Risk of adverse effects** – Some studies suggest that the risk of adverse effects (eg, apnea, hypotension, gastrointestinal dysmotility) is higher with morphine compared with fentanyl [۱۳۷٬۱۳۸]. (See 'Adverse effects' below.)
- ●**Risk of withdrawal** – In studies of neonates exposed to morphine or fentanyl for prolonged periods (eg, patients managed on extracorporeal membrane oxygenation), the risk of clinically significant opioid withdrawal was lower with morphine

- **Adverse effects** — Adverse effects associated with opioids include respiratory depression, hypotension, reduced gastrointestinal motility (which can delay establishment of enteral feeding), and urinary retention [١٣٢]. The risk of experiencing adverse effects increases with decreasing gestational age. Extremely preterm neonates <٢٦ weeks gestation are at particularly high risk of developing hypotension from opioid therapy [١٤١].
- ●**Respiratory depression** – When used for procedural sedation/analgesia, opioids can cause respiratory depression and apnea, particularly in preterm neonates [٩]. In mechanically ventilated neonates, use of continuous opioid infusions (eg, morphine, fentanyl) modestly prolongs duration of mechanical ventilation compared with no opioid analgesia [٣٧].
- ●**Hypotension** – All opioids can cause hypotension, particularly in at-risk neonates. However, synthetic opioids (fentanyl, sufentanil) cause less histamine release and therefore tend to cause less hemodynamic instability when compared with morphine [١٣٧]. Caution must be exercised if using opioid therapy (intermittent or continuous) in patients with hypotension at baseline and in extremely preterm neonates <٢٦ weeks gestation, since these neonates are prone to low blood pressure, which can be exacerbated by opioids [١٤١]. (See "Assessment and management of low blood pressure in extremely preterm infants".)
- ●**Feeding difficulties** – In mechanically ventilated neonates, use of continuous opioid infusions (eg, morphine, fentanyl) is associated with delayed establishment of full enteral feeding compared with no opioid analgesia [٣٧].
- ●**Dependence and withdrawal** – With prolonged exposure to opioids (≥٥ to ٧ days), patients begin to develop tolerance and chemical dependence, which can cause withdrawal symptoms upon discontinuation of therapy [١٤٠].
- ●**Chest wall rigidity (rare)** – Chest wall rigidity is a rare life-threatening complication of synthetic opioids (eg, fentanyl, sufentanil, remifentanil) [١٤٢]. (See "Pediatric procedural sedation: Pharmacologic agents", section on 'Fentanyl'.)
- ●**Long-term effects** – It is unclear if exposure to opioids in the neonatal period has any long-term effects of neurodevelopment. This issue is discussed separately. (See "Assessment of pain in neonates", section on 'Impact of analgesic and sedative therapy'.)

- **Sedatives** — Sedative drugs (eg, benzodiazepines, dexmedetomidine, ketamine, propofol) play a limited role in NICU practice.
- **Midazolam** — While midazolam is generally considered a short-acting benzodiazepine, its sedating effects tend to be prolonged in neonates, particularly critically ill preterm neonates.
- ●**Clinical uses** – Use of midazolam in the NICU setting is generally limited to the following circumstances:
- •Mechanically ventilated neonates with severe agitation that is refractory to other measures (eg, significant ventilator dyssynchrony not controlled by opioids). (See 'Mechanical ventilation' above.)
- •Mechanically ventilated neonates with severe pulmonary hypertension (eg, persistent pulmonary hypertension of the newborn [PPHN], congenital diaphragmatic hernia [CDH]).

Midazolam

- is **not** used for procedural sedation in nonintubated neonates because the risk of apnea and/or desaturation is unacceptably high.
- ●**Dosing** – We generally administer midazolam via continuous IV infusion. The initial dose is ٥ to ١٠ mcg/kg per hour. We start at the lower end of the dose range and increase if necessary to control agitation.
- ●**Data on efficacy and safety** – Midazolam is an effective sedative agent for mechanically ventilated neonates; data are mixed regarding its safety in this setting.

- Two small trials involving preterm neonates demonstrated that midazolam effectively increased sedation levels compared with placebo
-

- Accumulating data in newborn animal models suggests that midazolam induces apoptosis and/or necrosis of neurons and other brain cells in the developing brain [۱۴۷]. These data add to our concerns regarding the long-terms effects of routinely using midazolam for sedation in term and preterm newborns in NICU.

- **Ketamine —** Ketamine is widely used for procedural, operative, and postoperative analgesia and sedation in infants and children. It is an N-methyl-D-aspartate receptor antagonist, sometimes described as a "dissociative sedative". It has sedative, analgesic, and amnestic properties. A unique property of ketamine that distinguishes it from other sedatives and opioids is that it usually does not cause respiratory depression or hypotension. It also has bronchodilating effects. When given in the usual dosing range (۱ to ۲ mg/kg), ketamine produces mild increases in heart rate and blood pressure [۱۴۸]. However, higher doses can reduce heart rate and blood pressure [۱۴۹،۱۵۰].

- Because of its favorable cardiorespiratory side effect profile, ketamine is an attractive alternative to opioids for procedural sedation, particularly in neonates with hemodynamic instability.

- ●**Clinical uses** – At our institution, we use ketamine for neonates undergoing:

- •Elective endotracheal intubation (see 'Endotracheal intubation' above)

- •CVC placement (see 'More complex procedures' above)

- ●**Dosing** – Ketamine is given at a dose of ۱ to ۲ mg/kg per dose IV.

- ●**Data on efficacy and safety** – The safety and efficacy of ketamine in neonates is largely supported by observational data [۲۰،۲۳،۱۵۱]; there are limited clinical trial data [۱۵۲،۱۵۳]. A single small randomized trial compared ketamine versus fentanyl in infants undergoing laser therapy for retinopathy of prematurity (ROP) [۱۵۲]. However, the drug regimens provided insufficient analgesia for most infants in both arms, prompting the investigators to change the study protocol midway through the trial. Thus, it is difficult to interpret the results. Infants in the ketamine group less frequently experienced apnea during or after the procedure (۴ versus ۱۰ percent) and less frequently required supplemental oxygen during or after the procedure (۱۲ versus ۲۰ percent).

- In a single-center retrospective study of ۷۲ infants (mean gestational age ۳۲ weeks; mean postnatal age ۷ weeks) who received ketamine (۰٫۵ to ۲ mg/kg) plus fentanyl (۲ mcg/kg) for sedation for ultrasound-guided CVC placement, the procedural success rate was ۱۰۰ percent [۱۵۱]. Respiratory complications were uncommon and included need for supplemental oxygen (۱۵ percent) and apnea (۳ percent). Of the ۳۵ infants who were breathing spontaneously during the procedure, none required intubation. No infants experienced hypotension or other adverse hemodynamic effects.

- **Dexmedetomidine —** Dexmedetomidine is a selective alpha-۲ adrenergic receptor agonist that provides sedative and mild analgesic effects. Like ketamine, but unlike most other sedatives, it causes minimal respiratory depression. Unlike ketamine, it can cause clinically significant hemodynamic effects, especially bradycardia [۱۵۴،۱۵۵]. The risk of bradycardia is highest in extremely low birthweight (<۱۰۰۰ g) infants [۱۵۶].

- ●**Clinical uses** – We use dexmedetomidine as a second-line option for intubated neonates with the same clinical indications as for midazolam (ie, refractory agitation, ventilator dyssynchrony, PPHN, CDH). (See 'Mechanical ventilation' above and 'Midazolam' above.)

- Adjunctive dexmedetomidine is particularly advantageous in neonates requiring prolonged mechanical ventilation, as it may help reduce opioid withdrawal and facilitate extubation in this setting [۱۵۷،۱۵۸].

- ●**Dosing** – Dexmedetomidine is administered as a continuous IV infusion. Our suggested dosing for continuous infusion depends on GA:

- •GA <۳۷ weeks: Starting dose of ۰٫۲ mcg/kg per hour IV (maximum dose ۱٫۴ mcg/kg per hour).

- •GA ≥۳۷ weeks: Starting dose of ۰٫۴ mcg/kg per hour IV (maximum dose ۱٫۴ mcg/kg per hour).

- We typically do not administer a loading dose since it can cause bradycardia. However, other centers do start with a loading dose (۰٫۰۵ to ۰٫۲ mcg/kg); the risk of bradycardia can be reduced by administering the loading dose slowly (over ۲۰ to ۳۰ minutes). Rapid IV boluses should be **avoided**, as this can cause severe bradycardia.

- ●**Data on efficacy and safety** – There are limited data on the safety and efficacy of dexmedetomidine in neonates [۱۵۴،۱۵۸-۱۶۰]. In a small multicenter dose-finding clinical trial involving ۴۲ intubated preterm and term infants randomly assigned to different dosing regimens of dexmedetomidine, ۱۰ percent of patients required additional midazolam while on dexmedetomidine and ۴۰ percent required additional analgesic medications (fentanyl or morphine) [۱۵۹]. Serious adverse events related to dexmedetomidine occurred in ۵ percent of patients; none required discontinuation of the drug.

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- A systematic review identified six studies (the clinical trial described above, a small placebo-controlled trial, plus four observational studies) describing the use of dexmedetomidine in ۲۵۲ neonates [۱۵۸]. All six studies reported that dexmedetomidine provided adequate sedation in most neonates. Dexmedetomidine was associated with shorter duration of mechanical ventilation and lower requirement for adjunctive sedation compared with control or opioid analgesia alone. Three studies reported no major adverse events; one study reported bradycardia as an uncommon occurrence (۵ percent of patients); while one study reported that up to ۴۰ percent of patients treated with dexmedetomidine experienced bradycardia and/or hypotension. The differences in rates of adverse events in these studies may be explained by differences in the populations studied (bradycardia is more likely in more preterm neonates) and dosing regimens used (bradycardia is more likely with higher doses, particularly if a loading dose is given).
- **Propofol** — Propofol is a sedative hypnotic agent that produces deep sedation/anesthesia with amnesia. It does **not** provide analgesia. Thus, patients undergoing painful procedures under propofol sedation generally require additional medication(s) for pain control.
- In older infants and children, propofol is widely used by anesthesiologists as an induction agent for general anesthesia. It is also sometimes used by nonanesthesiologists (eg, emergency medicine specialists) for procedural sedation in children. (See "Pediatric procedural sedation: Pharmacologic agents", section on 'Propofol'.)

SUMMARY AND RECOMMENDATIONS

- ●**Multimodal approach** – A multimodal approach to neonatal pain management includes the following (see 'Multimodal approach' above):
- •Nonpharmacologic measures (eg, skin-to-skin contact, breastfeeding, non-nutritive sucking, swaddling) – In some cases, these measures alone may be sufficient. (See 'Nonpharmacologic measures' above.)
- •Topical or local anesthetics. (See 'Topical anesthetics' above and 'Local anesthesia' above.)
- •Systemic analgesic medications. (See 'Acetaminophen' above and 'Opioids' above.)
- ●**Procedural analgesia** – The need for specific analgesic drug therapy depends on the degree of anticipated procedural pain (table ↴). (See 'Procedural analgesia' above.)
- •**Simple procedures associated with mild pain** – For neonates undergoing brief painful procedures (table ↴), we suggest oral sucrose (or other sweet tasting liquid) in combination with nonpharmacologic measures rather than nonpharmacologic measures alone (**Grade ↴B**). We use weight-based dosing for sucrose and prescribe and track it as a medication. (See 'Mildly painful (heel lance, venipuncture, etc)' above and 'Oral sucrose and other sweet liquids' above and 'Nonpharmacologic measures' above.)
- •**Simple procedures associated with moderate pain** – For neonates undergoing procedures associated with moderate pain (table ↴), we suggest a topical anesthetic in addition to oral sucrose and nonpharmacologic measures (**Grade ↴C**). If the neonate does not achieve adequate analgesia from these measures, a low dose of a short-acting opioid (eg, fentanyl, sufentanil) may be required. (See 'Moderately painful (lumbar puncture, arterial puncture, etc)' above and 'Topical anesthetics' above.)
- •**More complex procedures** – For neonates undergoing more complex procedures associated with moderate pain and which require the neonate to remain still (eg, central venous catheter [CVC] placement, chest tube insertion) (table ↴), we suggest local anesthesia plus a short-acting sedative/analgesic (eg, ketamine, fentanyl, or sufentanil) rather than other agents or combinations (**Grade ↴C**). These measures are used in addition to acetaminophen and nonpharmacologic measures. (See 'More complex procedures' above and 'Opioids' above and 'Ketamine' above.)
- •**Sedation/analgesia for elective intubation** – For neonates undergoing elective endotracheal intubation, we suggest premedication with ketamine rather than other agents or drug combinations (**Grade ↴C**). A short-acting opioid (eg, fentanyl, sufentanil) is a reasonable alternative. (See 'Endotracheal intubation' above and 'Ketamine' above and 'Opioids' above.)
- ●**Postoperative pain** – Postoperative pain management is tailored to the specific surgical procedure. For most neonates undergoing major surgery, we suggest regularly scheduled acetaminophen (**Grade ↴B**) since it reduces the need for opioid therapy. Nonpharmacologic measures should also be used to reduce pain. Intermittent doses of an opioid (eg, morphine, fentanyl) may be required depending on the specific surgical procedure. (See 'Postoperative pain' above and 'Acetaminophen' above and 'Opioids' above.)

- **Prolonged pain/discomfort**
- •**Sedation/analgesia for mechanical ventilation** – For intubated neonates receiving ongoing mechanical ventilation, the typical sedation/analgesia regimen includes nonpharmacologic measures, as-needed acetaminophen, and intermittent doses of an opioid (eg, morphine, fentanyl, sufentanil). For patients receiving opioids, we suggest starting with intermittent dosing rather than a continuous opioid infusion or a combined opioid/benzodiazepine regimen (**Grade ٢C**). However, neonates with poorly controlled pain or severe agitation may require a continuous opioid infusion and/or the addition of a sedative agent (eg, midazolam or dexmedetomidine). (See 'Mechanical ventilation' above and 'Opioids' above and 'Sedatives' above.)
- •**Other painful conditions** – Acutely ill neonates with conditions associated with moderate to severe pain (eg, necrotizing enterocolitis, meningitis, indwelling chest tube) (table ٢) may require intermittent doses of an opioid (eg, morphine, fentanyl) in addition to acetaminophen, sucrose, and nonpharmacologic measures. (See 'General approach' above and 'Opioids' above and 'Acetaminophen'

Overview of procedural analgesia in neonates

Type of procedure	Suggested multimodal pain management regimen	Additional comments
Simple procedures associated with **mild** pain Examples: ▪ Heel lance or finger stick ▪ Venipuncture or peripheral IV catheter insertion ▪ IM or SubQ injection ▪ NG tube insertion ▪ Bladder catheterization ▪ Dressing change/tape removal	**Both** of the following: ▪ Nonpharmacologic measures (eg, skin-to-skin contact, non-nutritive sucking)* ▪ Oral sucrose	▪ A topical anesthetic (eg, EMLA) can also be used for some procedures in this category (eg, IV catheter insertion, IM or SubQ injection)¶ but not others (eg, NG tube insertion, bladder catheterization, dressing change). ▪ EMLA is not routinely used for heel lance since it appears to be ineffective in this setting.
Simple procedures associated with **moderate** pain Examples: ▪ LP ▪ Peripheral arterial puncture or catheterization ▪ Umbilical venous or arterial catheterization ▪ Intraosseous cannulation	**All** of the following: ▪ Nonpharmacologic measures (eg, skin-to-skin contact, non-nutritive sucking)* ▪ Oral sucrose ▪ Topical anesthetic (eg, EMLA), if appropriate¶	▪ In our experience, the combination of these 3 measures usually permits successful completion of the procedure. ▪ Rarely, neonates who do not achieve adequate analgesia from these measures may require a low-dose short-acting opioid (eg, fentanyl, sufentanil). ▪ Opioids should be used with caution in nonintubated patients.
More complex procedures△ Examples: ▪ Percutaneous CVC placement ▪ PICC placement ▪ Chest tube placement	**All** of the following: ▪ Nonpharmacologic measures (eg, non-nutritive sucking, facilitated tucking)* ▪ Topical and/or local anesthesia (eg, EMLA and/or lidocaine)¶ ▪ Acetaminophen ▪ Short-acting sedative/analgesic (eg, ketamine, fentanyl, sufentanil), if needed	▪ We prefer short-acting over longer-acting opioids in this setting because these procedures are usually brief. ▪ Opioids should be used with caution in nonintubated patients. ▪ Using a local anesthetic and acetaminophen reduces the amount of opioid required.
Specific procedures		
Circumcision◇	**All** of the following: ▪ Nonpharmacologic measures (eg, non-nutritive sucking, facilitated tucking)* ▪ Oral sucrose ▪ Local anesthesia (eg, ring block or dorsal penile nerve block) ▪ Acetaminophen for postprocedure pain control	▪ Local or topical analgesia is routinely provided for neonatal circumcision since it reduces procedural pain with minimal risk.
ROP examination	**All** of the following: ▪ Nonpharmacologic measures (eg, non-nutritive sucking, facilitated tucking)* ▪ Oral sucrose ▪ A topical anesthetic (eg, proparacaine), depending on the preference of the ophthalmologist	▪ The interventions listed are generally sufficient for routine screening or follow-up examination. ▪ Additional analgesia/sedation is required when ROP treatment is administered during the procedure (eg, laser therapy or anti-VEGF injection). We use a short-acting agent (eg, ketamine, fentanyl, sufentanil) for this purpose. ▪ Opioids should be used with caution in nonintubated patients.
Elective endotracheal intubation	Options include: ▪ Ketamine (preferred agent at the author's institution) **or** ▪ Short-acting opioid (eg, fentanyl, sufentanil, remifentanil)	▪ The combination of an opioid plus a benzodiazepine (eg, midazolam) is another alternative; however, this does not appear to improve intubation success rates compared with an opioid alone.

This table summarizes our suggested approach to procedural pain management in neonates. Suggested interventions for common neonatal procedures are summarized here; this is not intended to be a comprehensive list. The guidance in this table represents the general approach. Optimally, the pain management plan should be tailored to the individual neonate. Refer to UpToDate topics on neonatal pain for additional details, including a discussion of the evidence supporting our approach.

CVC: central venous catheter; EMLA: eutectic mixture of local anesthetics; IM: intramuscular; IV: intravenous; LP: lumbar puncture; NG: nasogastric; PICC: peripherally inserted central catheter; ROP: retinopathy of prematurity; SubQ: subcutaneous; VEGF: vascular endothelial growth factor.

* Nonpharmacologic measures include breastfeeding, non-nutritive sucking, swaddling or facilitated tucking, skin-to-skin contact, and sensorial saturation.

¶ Topical anesthetics should not be applied on open wounds or lacerations. Repeated or frequent doses should be avoided as this increases the risk for systemic absorption and toxicity.

△ These procedures not only cause moderate pain, but also require that the neonate remain relatively still during the procedure.

◇ Refer to separate UpToDate content on neonatal circumcision for a detailed discussion of pain management for the procedure.

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The premature infant pain profile: Revised

Infant indicator	Indicator score				Infant indicator score
	0	+1	+2	+3	
Change in heart rate (bpm) Baseline: _____	0 to 4	5 to 14	15 to 24	>24	
Decrease in oxygen saturation (%) Baseline: _____	0 to 2	3 to 5	6 to 8	>8 or increase in O_2	
Brow bulge (sec)	None (<3)	Minimal (3 to 10)	Moderate (11 to 20)	Maximal (>20)	
Eye squeeze (sec)	None (<3)	Minimal (3 to 10)	Moderate (11 to 20)	Maximal (>20)	
Naso-labial furrow (sec)	None (<3)	Minimal (3 to 10)	Moderate (11 to 20)	Maximal (>20)	
				Subtotal score:*	
Gestational age (weeks + days)	>36 weeks	32 to 35 weeks, 6 days	28 to 31 weeks, 6 days	<28 weeks	
Baseline behavioural state	Active and awake	Quiet and awake	Active and asleep	Quiet and asleep	
				Total score:¶	

Scoring instructions

Step 1: Observe infant for **15 seconds at rest** and assess vital sign indicators [highest heart rate (HR) and lowest O_2 saturation (O_2 SAT)] and behavioural state.

Step 2: Observe infant for **30 seconds after procedure** and assess **change** in vital sign indicators (maximal HR, lowest O_2 SAT and duration of facial actions observed).Δ

Step 3: Score for corrected gestational age (GA) and behavioural state (BS) if the subtotal score >0.

Step 4: Calculate total score by adding **subtotal score + BS score**.

PIPP-R: premature infant pain profile-revised; BS: behavioral state; GA: gestational age.

* Subtotal for physiological and facial indicators. If subtotal score >0, add GA and BS indicator scores

COMFORTneo scale

Instructions: The rater should observe the neonate for 2 minutes and then score each individual item for its most extreme manifestation observed during the 2-minute period.

Parameter		Points	Score
Alertness	Quiet sleep (eyes closed, facial movement absent)	1	
	Active sleep (eyes closed, facial movements present)	2	
	Quietly awake (eyes open, minimal facial movements)	3	
	Actively awake (eyes open, facial movements present)	4	
	Awake and hyperalert	5	
Calmness/agitation	Calm (appears lucid and serene)	1	
	Slightly anxious (shows slight anxiety)	2	
	Anxious (appears agitated but remains in control)	3	
	Very anxious (appears very agitated, just able to control)	4	
	Panicky (severe distress with loss of control)	5	
Respiratory response *(assess only in mechanically ventilated neonates)*	No spontaneous respiration	1	
	Spontaneous respiration on ventilator	2	
	Unrest or resistance to ventilator	3	
	Actively breathes against ventilator or coughs regularly	4	
	Fights ventilator	5	
Crying *(assess only in nonintubated neonates)*	No crying	1	
	Faint crying	2	
	Soft crying or moaning	3	
	Hard crying	4	
	Intense crying or screaming	5	
Body movement	No or minimal movement	1	
	≤3 slight arm/leg movements over 2 minutes	2	
	>3 slight arm/leg movements over 2 minutes	3	
	≤3 vigorous arm/leg movements over 2 minutes	4	
	>3 vigorous arm/leg movements over 2 minutes, or whole body is moving	5	
Facial tension	Facial muscles fully relaxed; relaxed open mouth	1	
	Normal facial tension	2	
	Intermittent eye squeeze and brow furrow	3	
	Continuous eye squeeze and brow furrow	4	
	Facial muscles contorted and grimacing (eye squeeze, brow furrow, open mouth, nasal-labial lines)	5	
Muscle tone *(observation only)*	Muscles fully relaxed (open hands, dribbling, open mouth)	1	
	Reduced muscle tone; less resistance than normal	2	
	Normal muscle tone	3	
	Increased muscle tone (clenched hands and/or clenched bent toes)	4	
	Extreme muscle tone (rigidity and flexion of the fingers and/or toes)	5	
	Total score (range 6-30)		

Adapted with permission from Wolters Kluwer Health, Inc.: van Dijk M, Roofthooft DW, Anand KJ, et al. Taking up the challenge of measuring prolonged pain in (premature) neonates: The COMFORTneo scale seems promising. Clin J Pain 2009; 25(7):607-16. Copyright © 2009 Lippincott Williams & Wilkins, Inc. https://journals.lww.com/clinicalpain/pages/default.aspx.

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