CHAPTER

53

Pain Assessment and Management

Neonates admitted to NICU undergo several painful procedures per day, and they communicate their pain and stress through various autonomic, motor, and behavioral cues. The caregivers in NICU must recognize these cues and modify the environment to reduce stress and pain and facilitate self-regulatory mechanisms to promote the infant's comfort.

Four subsystems need continuous positive environmental influence and synchronized functioning to optimize well-being and growth in neonates. Table 53.1a to d lists the subsystems and the associated organized and disorganized behavior.

Pain prevention is essential from a humanitarian perspective because pain is associated with long-term neurobehavioral consequences. Every healthcare facility caring for neonates should implement a comprehensive pain prevention program, including routine assessment of pain, minimizing procedures that can cause pain, effective use of nonpharmacological and pharmacological techniques to prevent pain during common procedures, and complete pain relief during major surgeries.[1]

Table 53.1a: Organized and disorganized behavior in autonomic and visceral subsystem

Parameter	*Organized behavior*	*Disorganized behavior*
Respiratory rate	Stable	Very fast/very slow or with pauses
Heart rate	Stable	Very fast or very slow
Skin color	Pink	Blanching
Oxygen saturation	Normal	Gasping/ cyanosis
Other signs	Absent	Yawning, startles, tremors, twitches, sneezing, coughing drooling, spitting, vomiting, gagging, straining as if passing bowel

Table 53.1b: Organized and disorganized behavior in motor subsystem		
Parameter	*Organized behavior*	*Disorganized behavior*
Tone	Normal	Flaccidity in trunk, extremities, stiffening or arching and hyperextension
Posture	Maintains flexed posture	All limbs are extended
Movement	Slow regulated, controlled smooth movements	Jerky movements/ very slow movements, flailing movements of the arms and legs
Other signs	Nil	Arching body, finger splay, foot splay, fisting of hands, salute, high arm guard, sitting on air, tongue protrusion

Table 53.1c: Organized and disorganized behavior in attention and interactive sub-system	
Organized behavior	*Disorganized behavior*
Neonate is in deep sleep or quiet and alert, maintains eye contact, mouth pursing, cooing, smiling, consolable	Neonate is in a diffused sleep state, twitching, fussy, frowning, grimacing, irritable, crying, eyes rolling upwards, averting eye gaze, gaping, sleepless

Table 53.1d: Behavior in self-regulatory subsystem*	
Organized behavior	*Disorganized behavior*
This system helps the preterm infant to calm and soothe themselves in stressful situations. An infant who can self-regulate will have a longer duration of undisturbed sleep; have better-organized learning and coping mechanisms during different painful experiences. *Self-regulatory signs are finger clasping, clasping of blanket or sheet, fingers in the mouth with or without sucking, foot clasp, and feet against the bassinet for support.*	Neonate will be fussy, irritable, and unable to interact with the environment positively.

**Observing an infant over a period is crucial. These cues indicate whether the infant is ready for the activity, needs to be calmed before the activity is continued, or is unprepared to engage. The older the infant, the more they use self-calming or self-regulatory techniques to organize themselves.*

PAIN ASSESSMENT

- Use Premature Infant Pain Profile: Revised (PIPP-R; Table 53.2) for assessment of acute pain.[2]
- ComfortNeo pain scale may be used to assess the degree of prolonged pain and its response to analgesics.[3]

Table 53.2: Premature Infant Pain Profile: Revised (PIPP-R)

S.N.	*Parameters*	*Score*			
		0	*+1*	*+2*	*+3*
1.	Change in heart rate (bpm) from baseline	0–4	5–14	15–24	>24
2.	Decrease in oxygen saturation (%) from baseline	0–2	3–5	6–8	>8 or increase in O_2
3.	Brow bulge (sec)	None (<3)	Minimal (3–10)	Moderate (11–20)	Maximal (>20)
4.	Eye squeeze (sec)	None (<3)	Minimal (3–10)	Moderate (11–20)	Maximal (>20)
5.	Naso-labial furrow (sec)	None (<3)	Minimal (3–10)	Moderate (11–20)	Maximal (>20)
	Subtotal score: (1 + 2 + 3 + 4 + 5)				
6.	Gestational age (weeks)	>36 weeks	32 – 35 + 6 weeks	28 – 31 + 6 weeks	<28 weeks
7.	Baseline behavioral state	Active and awake	Quiet and awake	Active and asleep	Quiet and asleep
	Total score:				

Instructions:

- Observe the infant for 15 sec at rest to determine baseline vital signs.
- Observe the infant for 30 sec after the procedure to assess changes in the vital parameters.
- If infants require an increase in FiO_2 during a procedure, give a score of 3 in the O_2 saturation score.
- If the subtotal score > 0, add gestational age and behavioral state scores.
- Total score = Sub-total score + GA score + BS score
- Maximum score = 21
- Score 7–12: non-pharmacological measures; score >12: pharmacological analgesia

PREVENTING OR REDUCING PAIN

General Measures

Pain is managed most effectively by preventing, limiting, or avoiding noxious stimuli. The following measures in combination are followed to minimize pain:

- Keep ambient light and sound levels minimum; avoid strong perfumes and pungent odours.
- Close incubator doors gently and optimize alarm limits and alarm sounds.
- Limit the number of painful procedures and handling by clustering the care activities.
- Encourage parental involvement and interaction.
- 'Sensorial stimulation': gently stimulate audiovisual, gustatory, and tactile systems simultaneously.
- Swaddling, facilitated tucking, distraction measures like talking, music, etc.

Nonpharmacological Measures

The nonpharmacological measures include sucrose (24% solution), dextrose (20–30% solution), breastfeeding or breastmilk through pacifiers, skin-to-skin contact, and sensorial stimulation. These measures have been best studied for acute mild-to-moderate procedural pain, including pain during heel lance, venipuncture, adhesive removal, intramuscular injections, etc. These measures are more effective when used simultaneously. No significant adverse effects have been described, though the long-term effects have yet to be well-studied. Table 53.3 summarizes the evidence supporting nonpharmacologic analgesics.

The sucrose/dextrose solution is given orally by a syringe/pacifier 2–3 min before the procedure and may be repeated 1–2 min afterward. The effect lasts around 4–6 minutes. Intragastric administration has no analgesic effect. The usual dose is 0.1–0.5 ml for preterm (<32 weeks neonates) and 0.2–1 ml for late preterm and term neonates.

Pharmacological Measures

The pharmacological measures can be broadly divided into:

- Local anesthetic agents
- Systemic agents: opioids, paracetamol

Table 53.3: Evidence supporting nonpharmacological analgesic measures in neonates

Agent	*Evidence*	*Major findings and conclusions*
Sucrose (24%)	Cochrane meta-analysis[4] (74 studies, 7049 infants)	• Reduction in pain scores (PIPP) during heel lance, venipuncture, and intramuscular injections, in both preterm and term infants. • Inconclusive benefits during other painful procedures. • No major adverse effects. • Combination of sucrose with other nonpharmacological measures may augment the analgesic effect.
Dextrose (20–30%)	Systematic review and meta-analysis[5] (38 studies, 3785 infants)	• Reduction in pain scores during heel lance and venipuncture.
Breast milk and breastfeeding	Cochrane meta-analysis[6] (20 studies)	• Breastfeeding reduces pain during heel lance and venipuncture. • Supplemental breastmilk has uncertain benefits. • Glucose/sucrose have similar effectiveness as breastfeeding.
Skin-to-skin contact	Cochrane meta-analysis[7] (25 studies, 2001 infants)	• Reduction in composite pain indicators (both physiological and behavioral). • Insufficient evidence regarding additive effect with other interventions.

Nonsteroidal anti-inflammatory agents (NSAIDs) are generally not used as analgesics in newborns.

Local Anesthetics

Local anesthesia is helpful for the management of acute procedure-related pain. It can be either topically applied on intact skin or injected subcutaneously. The common preparations include EMLA (eutectic mixture of local anesthetics), lidocaine (2%) injection, and tetracaine (4%). Proparacaine eye drops are used for topical anesthesia during ROP examination.

The dose of EMLA is 0.5–2 g with a contact period of 30 min to 1 hour. Apply the cream over a 2–3 cm^2 area with 1–2 mm thickness

and cover with transparent (Tegaderm) dressing. For maximal analgesic effect, topical anesthetics should be combined with other nonpharmacological measures like sucrose analgesia or breast milk supplementation. The clinical effect of EMLA is modest, with good efficacy for lumbar puncture and no or minimal benefit for heel lance and venipuncture. The major drawback is the delayed onset of action and a contact period of at least 1 hour before the procedure, making it unsuitable for emergent procedures. Though EMLA is approved for use in only infants older than three months, it has been used off-label in neonates.[8] There is a possible risk of methemoglobinemia with EMLA cream; it is recommended to test for MetHb levels if multiple doses of EMLA are used.

For emergent procedures (e.g. chest drain insertion), subcutaneous local anesthetic injection (2% lidocaine hydrochloride) is preferred over topical creams.

Opioids

Opioid drugs are the mainstay in managing severe pain, including mechanical ventilation, endotracheal intubation, and post-surgical pain in neonates. The two most used agents are morphine and fentanyl. The common adverse effects of opioids include respiratory depression, hypotension, urinary retention, reduced intestinal motility, bronchospasm, and chest wall rigidity (fentanyl). Also, their pharmacokinetics have not been well-described in preterm neonates, underscoring the need for cautious use. Tolerance and withdrawal are common with prolonged use. Fentanyl is the preferred opioid among neonates. Short-acting opioids like Sufentanil, Remifentanil, etc. have been used for brief procedures like endotracheal intubation and short surgeries.

Special considerations for fentanyl and morphine:

- Avoid morphine (and prefer fentanyl) in case of hypotension, gestation <27 weeks, acute kidney injury, and reduced gastrointestinal motility.[9]
- Avoid fentanyl in neonates who have undergone abdominal surgery or are at risk of increased intraabdominal pressure and during ECMO (circuit sequestration of fentanyl).[10,11]

Analgesia for Specific Procedures

Table 53.4 enumerates the recommended analgesia measures in routine bedside procedures.

Table 53.4: Analgesia measures for routine bedside procedures				
Procedure	*Analgesia measure recommended*			
	General measures	*Sucrose analgesia*[*]	*Breast milk*[*]	*Skin-to-skin contact/sensorial stimulation*
Venipuncture Sampling[#]	+	+	+	+
Heel prick[#]	+	+	+	+
Subcutaneous/IM injection	+	+	+	+
Adhesive tape removal[$]	+	±	±	+
IV cannulation	+	+	+	+
Urinary catheterization	+	+	+	–
Echocardiography	+	+	+	–

[*]Either sucrose analgesia or breastfeeding can be adopted depending on the availability and feasibility; for slightly longer procedures, sucrose analgesia is preferred over breast milk/breastfeeding
[#]Venipuncture should be the preferred mode of blood sampling as heel lance is more painful; automated lancets are superior to conventional lancets for the heel prick
[$]Use adhesive removal solution

NON-EMERGENCY INTUBATION

Endotracheal intubation is a stressful procedure and may be associated with bradycardia, hypoxia, hypertension (both systemic and pulmonary), and increased intracranial pressure. In all non-emergent intubations, premedications are recommended to blunt the stress response, decrease the risk of adverse events, and facilitate successful intubation. These drug regimens generally consist of the following:

A. A sedative-analgesic (e.g. fentanyl, morphine) to decrease pain and stress.
B. A vagolytic (e.g. atropine, glycopyrrolate) to counter bradycardia and decrease secretions.
C. A muscle relaxant (e.g. vecuronium, rocuronium) to allow adequate visualization (Table 53.5).

The AAP recommends the following for all non-emergency neonatal intubations:[12]

- Analgesic agents or anesthetic doses of a hypnotic drug should be given.
- Vagolytic agents and rapid-onset muscle relaxants should be considered.

Table 53.5: Analgesia-sedation for non-emergency intubation*			
S.No.	*Drug*	*Dose*	*Timing*
1	Inj Fentanyl	1–4 µg/kg IV	Slowly over 3–5 minutes
2	Inj Atropine	0.02 mg/kg IV (minimum dose 0.1 mg)	1–2 min prior to intubation
3	Inj Vecuronium#	0.1 mg/kg IV	2–3 minutes prior to intubation

*Preferred regimen includes the above three-drug combination.
#Avoid using paralytic agents (vecuronium) if an experienced person is unavailable for intubation.

- Use of sedatives alone, such as benzodiazepines without analgesic agents, should be avoided.
- A muscle relaxant without an analgesic agent should not be used.

Mechanical Ventilation

Mechanical ventilation is a painful and uncomfortable experience that may adversely affect the course of acute illness and long-term neurodevelopment.

- There is no role for routine opioids in mechanically ventilated neonates. Consider opioids only in the following situations:
  1. Chest tube insertion, post-surgery, planned intubation/reintubation.
  2. Significant ventilator dyssynchrony that is not attributable to improper/inadequate ventilator settings or secretions. Note that inadequate ventilatory setting is a more common cause of ventilator dyssynchrony than lack of sedation-analgesia.
  3. Documented pain (document PIPP-R pain score at baseline and 30 minutes after dose)
  4. PPHN requiring mechanical ventilation and not improving with environmental measures alone.
- Assess the requirement of opioids daily and document the same in case records.
- Consider early de-escalation.
- In neonates with expected short duration of mechanical ventilation (e.g. preterm infants with respiratory distress syndrome), use intermittent boluses of opioids only if required to ensure lower cumulative doses:
  - **Fentanyl:** 1–2 µg/kg IV slowly over 5 minutes.
  - **Morphine:** 10–50 µg/kg IV over 15–30 minutes.

- Emergency intubation and resuscitation kit (including IV naloxone: 0.1 mg/kg/dose) should be ready bedside while administering a bolus dose of opioids.
- In neonates with an expected longer duration of ventilation, continuous infusion of opioids is preferred over intermittent boluses, but only in defined indications cited above.
- Avoid opioids in extremely preterm neonates due to uncertain safety and pharmacokinetic profile.

Analgesia/sedation in ventilated neonates: what is the evidence?

A Cochrane review (2021), including 23 studies and 2023 neonates (both term and preterm), examined the role of opioids during mechanical ventilation in neonates. It found no significant benefit of using opioids over placebo in terms of PIPP score 12–48 hours after starting the infusion, duration of mechanical ventilation, IVH, BPD, neurodevelopmental impairment at 18–24 months and 5–6 years, and mortality. The authors recommended selective use of opioids in neonates based on pain assessment using validated tools.[14]

Table 53.6 enlists the recommended analgesia measures for other procedures in the NICU.

Table 53.6: Analgesic measures for specific procedures[13]

Procedure	*Measures*
Arterial puncture/ cannulation Lumbar puncture PICC line placement	• Sucrose/dextrose analgesia • EMLA cream locally (esp for LP) • General measures
Chest tube placement	• Inj Fentanyl* 0.5–1 µg/kg 2–3 min prior • Local infiltration with lignocaine 2% • Sucrose/ dextrose analgesia
Chest drain removal	• Sucrose/dextrose analgesia • General measures
ROP screening	• Local anesthetic eye drops • Sucrose/dextrose analgesia • General measures
Laser photocoagulation for ROP**	• Inj Fentanyl 2 µg/kg bolus followed by 2–5 µg/kg/hr infusion till the procedure lasts • Local anesthetic eye drops • Sucrose analgesia • General measures • Post-procedure paracetamol 15 mg/kg q 6 hourly for 1–2 days

(*Contd.*)

Table 53.6: Analgesic measures for specific procedures[13] (*Contd.*)	
Procedure	*Measures*
CT/ MRI for sedation	**Intubated:** • Inj Fentanyl 0.5–1 µg/kg IV 2–3 min prior • Inj Midazolam 0.1–0.2 mg/kg IV **Non-intubated:** • Oral Trichlophos 20–30 mg/kg or chloral hydrate 50–100 mg/kg, 20–30 min prior • Inj Midazolam 0.1–0.2 mg/kg

**In non-ventilated babies while using opioids, watch for apnea/respiratory depression; IV Naloxone should be kept ready and used in case of respiratory depression or apnea (0.1 mg/kg or 0.25 ml/kg IV)*

***Even ventilated patients on opioid infusion during procedures need additional analgesic measures*

Table 53.7 depicts the dosages and common adverse effects of different analgesic agents used in the NICU.

Opioid Tolerance

- Tolerance leads to reduced efficacy of the drug and may require dose escalation. Tolerance is rare, with a duration of therapy of less than 4 days. Other causes of increased pain, such as worsening primary disease, opioid-related hyperalgesia, and ventilator asynchrony, must be considered and ruled out.
- Consider escalating the dose after about 4 days of fentanyl infusion or 14 days of morphine infusion, based on pain scores.
- Opioid rotation, i.e. switching to an equianalgesic dose of a different opioid, may help counter tolerance and decrease the need for dose escalation.
- While switching from one opioid to another, reduce the equianalgesic dose of the new opioid by 20–30% to adjust for a probable lack of cross-tolerance.
- To convert intravenous fentanyl to an equivalent intravenous morphine dose, multiply the fentanyl dose (in µg/kg/hour) by 10–20, reduce it by 25%, and continue that dose as morphine infusion (in µg/kg/hour).
- When very high doses of opioid analgesics are required or sedation is desirable, adding agents like midazolam (to be used cautiously in preterm infants), dexmedetomidine, or ketamine may help decrease the opioid doses.

Table 53.7: Drugs and dosages of analgesic/sedative medications commonly used in NICU

Drug	*Dose*	*Preparation/administration*	*Pharmacology*	*Adverse effects*
Morphine	Bolus: 25–100 µg/kg slow IV Infusion: 7–50 µg/kg/hour IV	1 ml = 15 mg Dilute in NS/10D/5D to make a maximum concentration of 5 mg/ml Incompatible with phenytoin, phenobarbitone	Narcotic analgesic Onset: 5–15 min Duration of action: 3–5 hours Not recommended in neonates <28 weeks	Respiratory depression, bradycardia, hypotension ileus, urinary retention; naloxone can reverse effects
Fentanyl	Bolus 1–4 µg/kg IV slow over 3–5 minutes Infusion: 1–4 µg/kg/hour (≥32 weeks); start at 0.5 µg/kg/hour in neonates <32 weeks during 1st week of life	1 ml = 50 µg Dilute in NS/5D/10D Incompatible with phenytoin, phenobarbitone	50–100 times more potent than morphine Onset: immediate Duration of action 30–60 min	Respiratory depression, chest wall rigidity (esp with rapid push), urinary retention, hypotension; naloxone can reverse effects
Midazolam	• Bolus: 0.05–0.1 mg/kg slow IV • IV Infusion: 0.25–1 µg/kg/min • Intranasal: 0.2–0.3 mg/kg may also be used	1 ml = 1 mg Dilute in NS/ 5D/10D Incompatible with $NaHCO_3$, fat emulsion	Short acting benzodiazepine Sedation only, no analgesic effect Onset: 1–5 min (iv), Duration of action: 20–30 min (iv) Not recommended in preterm neonates	Apnea, CNS depression, myoclonic jerks, hypotension; flumazenil can reverse effects

(*Contd.*)

Table 53.7: Drugs and dosages of analgesic/sedative medications commonly used in NICU

Drug	*Dose*	*Preparation/administration*	*Pharmacology*	*Adverse effects*
Paracetamol	10–15 mg/kg/dose PO 6–8 hourly 30 mg/kg/ dose per rectal	Syrup 5 ml = 125 mg Drops 1 ml = 100 mg Suppositories 80 mg	Rectal route has an erratic absorption	Avoid in hepatic dysfunction
EMLA cream	0.5–2 g for 30–60 minutes	Lidocaine (2.5%) and prilocaine (2.5%) in 1:1 ratio (e.g. Oint Prilox available in India) 5 g/30 g with transparent dressing	Onset: 30–60 min Duration of action: 2–4 hours	Methemoglobinemia

Withdrawal and Opioid Tapering

- Withdrawal symptoms may be seen with rapid tapering of opioids and present with features similar to those seen in neonatal abstinence syndrome, such as irritability, poor sleep, diarrhea, vomiting, jitteriness, tremors, tachycardia, sweating, fever, mottling, seizures, excessive sucking. Certain factors like prematurity, male gender, longer duration of therapy, lower initial dose of opioids, use for post-operative pain, and concomitant use of sedatives have been associated with a higher risk of opioid withdrawal.[14]
- Assess the need for opioids daily, and start de-escalating the dose as early as possible.
- If the neonate has received opioids for less than 5 days, initially decrease the original dose by 30–50% and then by 20–30% every 6–8 hours.
- If the neonate has received opioids for 5 or more days, decrease the original dose by 20% and then by 10% every 12 hours.[14]
- Document modified Finnegan score before starting tapering and then every 4 hours subsequently.

If the score is 8 or more, pause the tapering. Increase the dose to the previous higher dose if the score is 12 or more.

In case of a prolonged tapering regimen, switching from IV fentanyl or morphine to oral morphine may help obviate the need for IV access (Table 53.8).

Table 53.8: Algorithm for converting IV dose of opioid to equianalgesic oral dose of opioids

Current intravenous agent	*Usual maintenance infusion rate*	*Equivalent oral opioid dose*
IV fentanyl	1–5 µg/kg/hour	Multiply hourly fentanyl dose (in µg/kg/hour) by 0.1; Administer as oral morphine (in mg/kg/dose) q 4 hours
IV fentanyl	1–5 µg/kg/hour	Multiply hourly fentanyl dose (in µg/kg/hour) by 0.05–0.1; Administer as oral methadone (mg/kg/dose) q 6 hours
IV morphine	7–50 µg/kg/hour	Multiply hourly morphine dose (in µg/kg/hour) by 0.01; Administer as oral morphine (in mg/kg/dose) q 4 hours

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