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Pain in the Neonate: Acknowledgement to Action

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Abstract

With technological advancement and a better understanding of physiology, today there is irrefutable evidence that neonates do experience pain and even more so than their older counterparts. This pain sensitivity is further accentuated in preterm neonates as their pain modulating mechanism is under-developed. The hospitalized neonate is subjected to several procedures daily which result in pain of differing intensities. In the more premature neonates, even gestationally inappropriate procedures are perceived as noxious stimuli. Acute, prolonged and repetitive pain has been associated with both short and long term morbidities which result in not only delayed recovery but also neurodevelopmental and cognitive deficits in later life. As the sick and premature newborns neither verbalize nor mount vigorous behavioural responses to pain, it is often under recognized by the unpracticed healthcare provider. Several neonatal pain scales are available. However these are mostly validated for acute and not acute, repetitive or chronic pain which is the common problem faced by the sick newborns. Multidimensional pain assessment would include both physiological and behavioral parameters necessitating the use of multiple tools to complement each other. Several therapeutic options are available which include general measures which are neonatal friendly as well as non pharmacological and pharmacological measures. These used as combination therapy have been found to be more beneficial. Training of the healthcare providers so that the pain management protocol is appropriately implemented in the NICU as well as a continuous pain management quality improvement programmes with collaborative participation of all echelons would enable a more pain free and comfortable recovery of the neonates in hospital.

Keywords: Neonate, Pain, Analgesia, Pain Assessment, Pain Management

Introduction

Pain perception is an inherent quality of life that appears early in development.(1) The Committee on Taxonomy of the International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Further, "it is best described in terms of self reports."(2) Verbal communications is the gold standard for interpreting pain. However newborns cannot verbalize effectively. This leads to a problem in recognizing and acknowledging neonatal pain.

Multiple lines of evidence suggest an increased sensitivity to pain in neonates when compared with older age groups. This pain sensitivity is further accentuated in preterm neonates and may not be clinically evident. Critically ill preterm neonates do not mount vigorous behavioural responses to pain and therefore require specialised and detailed assessment.(3) It has been well established that neonates especially pre-terms experience even more pain as their pain modulating adaptive mechanisms are underdeveloped and are more sensitive to noxious stimuli. Neonates though they cannot verbalize, respond to stress and pain through specific pain behaviors as well as changes in physiologic parameters like heart rate, blood pressure and oxygen saturation. Even the most preterm neonates mount increasing responses to the pain caused by mild, moderate or highly invasive procedures and the magnitude of their response increases with their post natal age. Compared with older children, neonates exhibit greater hormonal, metabolic and cardiovascular responses to painful stimuli and may require relatively higher doses of medications for adequate pain control. The metabolism and clearance rates of most pain regulating agents in preterm neonates are slower but increase rapidly with increasing gestational age and maturity.(3) Despite this, the use of effective analgesic measures in NICUs are suboptimal.(4)

Neonates, especially the more premature ones are subjected to painful procedures at a rate of 2-15 /day in NICU.(5) The nature of pain the neonate is exposed to varies from acute pain arising from minor procedures such as heel sticks, venepuncture or lumbar puncture to chronic pain arising from conditions such as necrotizing enterocolitis and prolonged ventilation. In the extremely preterm neonate, even day to day procedures which are 'gestationally inappropriate' such as diaper change, daily weighing and removal of adhesive tapes is perceived as noxious stimuli which make them vulnerable to long term consequences which manifest later as abnormal long term effects.**(Error! Bookmark not defined.)** The consequences of repetitive or prolonged pain in the neonatal period include long-term changes in pain sensitivity and pain processing[6] and may be associated with a variety of neurodevelopmental, behavioral, and cognitive deficits that manifest in later childhood.(7,8) Improved clinical and developmental outcomes highlight the importance of adequate pain control in the human neonate.(9) Despite this evidence,

analgesics are used inconsistently during moderate to severely painful procedures in the newborn period.

Inspite of a plethora of evidence that even the tiniest neonates experience pain, most centers do not have a pain control programme in place and even in those that do, implementation is often suboptimal. Hence, every health care facility caring for newborns should implement an effective pain prevention programme which includes routinely assessing pain, minimizing the number of painful procedures performed, effectively using pharmacologic and non-pharmacologic therapies for the prevention of pain associated with routine minor procedures, and eliminating pain associated with surgery and other major procedures.[10]

Historical Aspects

Before 1980, neonatal pain was hardly recognized, evaluated or treated.[11] In the past neonates were administered paralytic drugs without anesthesia for major surgical procedures because physicians believed that neonates were incapable of interpreting or remembering pain. Further, there was no understanding of the consequences of untreated pain. Subsequent studies and research have shown that the noxious stimuli perceived by neonates affects the neuronal growth by a complex interaction of environmental, medical risk factors and vulnerable brain regions such as hippocampus, basal ganglia and the sub plate neurons.[12,13] [Fig. 1]

These have translated in better understanding of the physiology and means of assessing the effects of pain and stress in neonates. The neonatal pain control group in its summary proceedings in 2006 defined stress as "an actual or perceived threat that leads to a disturbance of the dynamic equilibrium between an organism and its environment" and stress response as "A response based on the individual's perception of as control and predictability of its environment, generally characterized by changes in four primary domains: endocrine, autonomic, immunological, and behavioral."[14]

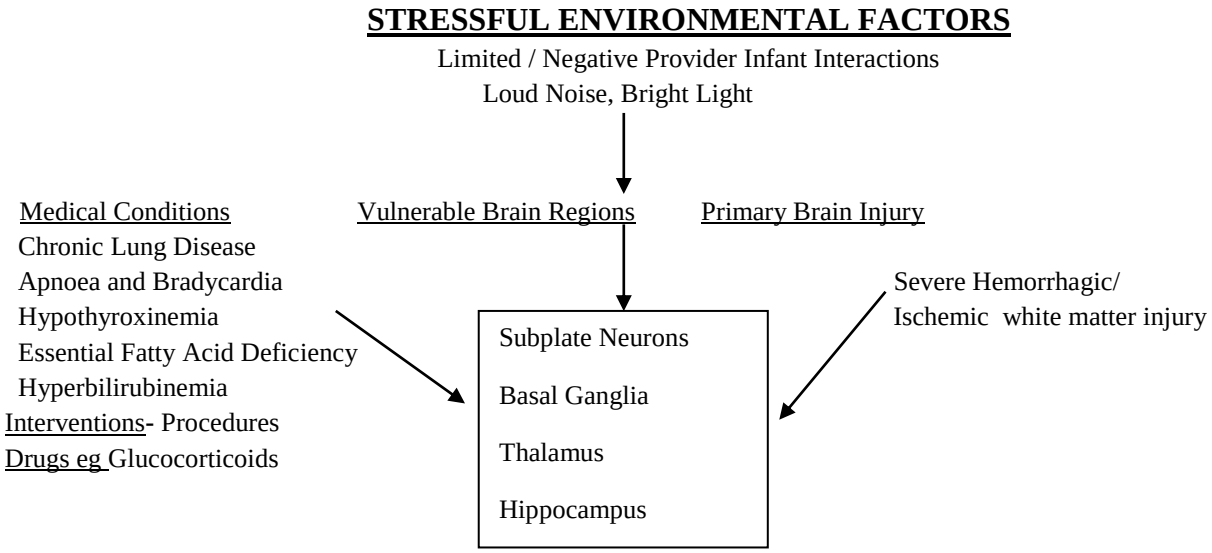

Fig. 1: Interaction of factors potentially affecting the vulnerable regions of Brain[13]

Physiology of Pain in Neonates

The anatomic pathways of the peripheral nervous system appear to be functional by 20 weeks post-conception, although tracts in the spinal cord and brainstem may be variably myelinated, and the areas of pain processing are different from that in the mature central nervous system (CNS). The number and types of peripheral nociceptors is similar to adult numbers by 20 to 24 weeks' gestation in the human fetus, implying a greater density per area of skin. These are connected via peripheral nerve fibers, which consist of the A, delta and C fibers with the developing spinal cord dorsal horn at that time. During development, the thickly myelinated A beta fibers, which transmit light touch and proprioception in the adult, also appear to transmit noxious information to pain processing areas of the spinal cord. Lack of myelination in the A, delta or C fibers or spinal cord tracts was proposed as an argument against pain perception in neonates. But even in adults, most pain impulses are carried, albeit slowly, via unmyelinated C fibers. Thus, incomplete myelination merely implies a slower conduction rate.

Numerous receptor molecules in the membranes of these nociceptors in neonates affect the nerve impulse that is ultimately transmitted to the CNS very early in gestation. These fibers differ from each other in their

response to different types of tissue injury and in their thresholds and other physiologic properties. Thus, the CNS of the developing fetus receives a repertoire of different information, depending on the type and intensity of the noxious stimulation. The biochemical mediators involved include chemicals like bradykinin, calcium, potassium, substance P, and prostaglandins which activate the nociceptors of the A delta and C afferent fibers. This activation leads to the pain impulse and subsequently stimulates local wheal and inflammatory response. More importantly, it also results in local dendritic sprouting of nerves and a state of hyperalgesia, which results in lasting experience of pain till adulthood. By 22 to 24 weeks' gestation, ascending pathways seem to connect with the supraspinal centers in the thalamus, subplate zone, and sensory cortex. However, because of weak linkages between the afferent fibers and dorsal horn of the spinal cord, the effects of pain last longer. In addition, due to over expression of NMDA receptors in the spinal cord, there is hyper-stimulation of dorsal horn interneurons, enroute the transmission to cortical centers, besides the mediation by substance P. This results in increased excitability of uninvolved areas, called 'wind up' phenomenon. Because of this wind up phenomenon, preterms experience a more robust, longer pain response, have a lower threshold and feel painful response from uninvolved tissues. In addition to these physiological peculiarities, the preterm neonate is unable to modulate pain as a term neonate or an adult, due to lack of modulation of pain response and due to paucity of levels of expression of dopamine, serotonin, and norepinephrine in the preterm spinal cord.

By 20 to 22 weeks' gestation, autonomic responses from painful stimuli lead to increases in heart and respiratory rate, implying functionality at that time. By 25 to 26 weeks', the same facial expressions from pain that are seen in adults, such as the brow bulge, eye squeeze, and nasolabial furrow, is evident in preterm infants. These expressions and the autonomic responses provide proof that pain is part of life in the NICU, and although neonates cannot verbalize pain, these expressions and responses allow assessment of pain in term and preterm neonates. These expressions have been used in assessing painful responses in the preterm neonate. (Fig. 2)

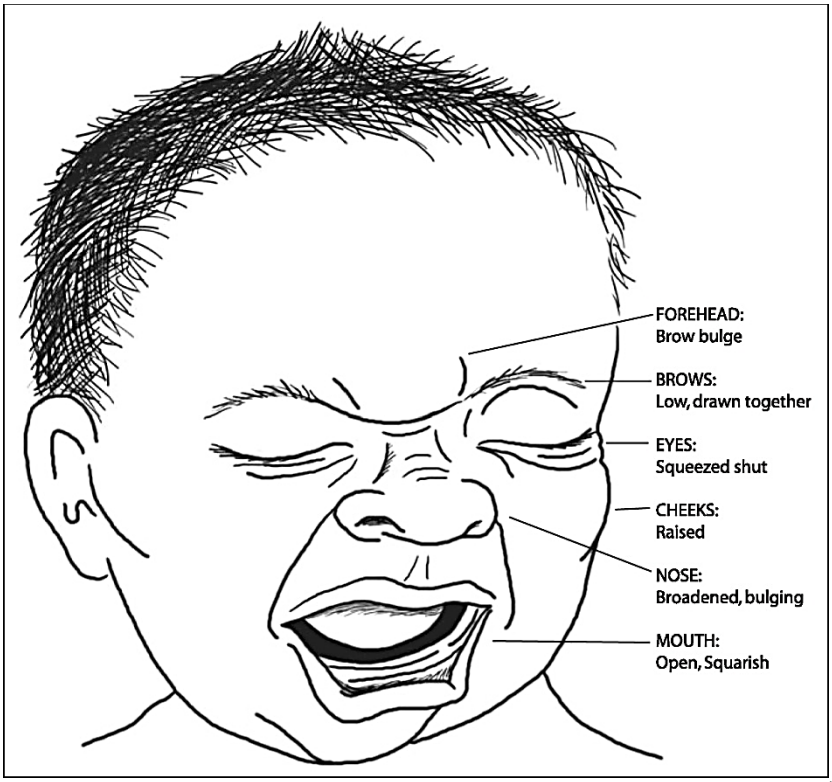

Fig. 2: Facial Expressions of Preterm Neonate in the PIPP Scoring System[(1)]

Assessment of pain and stress in neonates

Accurate pain assessment is the key and central issue that confronts clinicians at the bedside of preterm neonates. Although many validated methods for pain assessment are available, none of them are widely accepted or clearly superior to others.[(15)] The quality of the pain evaluation depends on the knowledge, ability, and willingness of the observer to analyze and judge nonverbal behaviors of a phenomenon as subjective as pain. In this context, validated pain evaluation tools should be used to minimize the different perceptions of neonatal pain among the health professionals, making decisions regarding the need or the intensity of analgesia as objective as possible.

Although several neonatal pain scales are available in the literature, most are validated for acute neonatal pain. Very few are designed to evaluate repetitive acute pain or non-acute pain status, which are the most common and difficult situations when dealing with critically ill newborns. Ideally, the multidimensional pain assessment should include physiologic and behavioral indicators of pain. In the face of the absence of a gold-standard pain measurement tool, the clinical team should use multiple tools that may complete and confirm each other. The Premature Infant Pain Profile (PIPP) is designed to assess pain during and soon after acute invasive procedures and includes incorporation of physiological parameters such as heart rate, oxygen saturation and the behavioural state as per gestational maturation.[16] The PIPP score is the best validated score for neonatal acute pain.

Table 1: The Premature Infant Pain Profile(PIPP)[16]

Process	**Indicator**	**0**	**1**	**2**	**3**
Chart	**GA**	**≥36wks**	**32-35$^{6/7}$**	**28-31$^{6/7}$**	**≤ 28 wks**
Score 15 sec before event	Behavioral state	Active awake Eyes-open Facial move +	Quite awake Eyes- open No facial movements	Active sleep Eyes-closed Facial movements +	Quite/sleep Eyes closed No facial movements
Heart rate Baseline:	Maximum HR	0-4/min increase	5-14/min	15-24/min	≥ 25/min
O2 Saturation Baseline:	Minimum O2 saturation	0-2·4% fall	2·5-4·9% fall	5-7·4% fall	≥ 7·5% fall
Observe for 30 sec after the event	Brow Bulge	None (0-9%)	Min (10-39%)	Moderate (40-69%)	Maximum (≥ 70% of time)
	Eye Squeeze				
	Nasolabial furrow				

- Score the corrected gestational age, Assess base line HR, SPO2 before procedure
- Score behavioral state 15 sec before the event, Observe infant for 30 sec after the event
- The min score=0, max score-21; higher the score greater the pain
- To be done by staff nurse/ resident doctor and record in the file

The Neonatal Infant Pain Scale (NIPS) is relatively simple and has been recommended as the fifth vital sign for newborns who require intensive care. This pain scale can be used by the nursing staff as often as required and includes easily assessable features such as facial expression, type of cry, breathing pattern and states of arousal and posture of arms and legs. The major drawback of the score is that very sick newborns may falsely have low scores.[17] Echelle Douleur Inconfort Nouveau-Ne´ (EDIN) coding system assess chronic pain and to apply this neonatal pain and discomfort scale, nurses observe the infant for several hours during and between caring and feeding and test the efficacy of consoling. EDIN scores greater than 6 indicate pain. The scoring system is based on facial activity, type of body movements, quality of sleep, quality of contact with nursing staff and consolability.[18] The other assessment tools include unidimensional behavioural scales of Neonatal Facial Coding system (NCFS)[19] or behavioural Indicators of Infant pain (BIIP).[20] These scoring systems at most help the care givers in sensitizing to neonatal pain communications. The CRIES Score assesses crying, requirement for increased oxygen administration, increased vital signs, expression, and sleeplessness in both preterm and term infants and, because of its ease of administration, it is used widely by primary care practitioners.[12]

However, no "gold standard" can be recommended for broad adoption in clinical practice because of 2 problems that are common to all assessment methods. This is because:-

1. These methods were developed from studies of neonates who underwent acute painful procedures (heel stick, venipuncture, circumcision). Physiologic or behavioral parameters chosen for inclusion in these methods were specifically those that changed most acutely in response to tissue injury and subsided after painful stimulation was over. Subsequent research, however, noted preterm newborns who were more immature, asleep, or exposed to previous painful procedures were less likely to demonstrate specific responses to pain, whereas previous physical handling accentuated their responses to acute pain.[21-22]
2. Significant inter-observer variability occurs and can be reduced but not eliminated by training or greater experience.[23] The observer variables include many complex characteristics such as age, sex, ethnicity, religion, marital status, personal experience, educational status, professional expertise and socio economic status. The patient variables include gestational age, sex, past experience, physical state of wakefulness, degree of invasiveness of procedure.[24,25]
3. The limitations of assessments are further increased in case of sick neonates such as those on

ventilator. In the setting of NEOPAIN trial, the markers found useful to assess persistent pain in neonates in ventilated babies receiving placebo in contrast to those receiving morphine were: facial expressions of pain, high activity levels, poor response to routine care, and poor ventilator synchrony.[26]

Management and Prevention of Pain

Prevention and management of pain involves a multipronged strategy. It entails creating an environment using general measures conducive to neonatal care, training healthcare workers to recognize pain in the neonate, pharmacological and non-pharmacological measures.

A. **General Measures:** The most obvious strategy would be to reduce the unnecessary painful and stressful conditions in the NICU. Such an approach would include reducing the number of bedside disruptions in care. Other strategies might include bundling interventions, eliminating unnecessary laboratory or radiographic procedures, using transcutaneous measurements when possible, and minimizing the number of repeat procedures performed after failed attempts.[26,27] Table 2 lists suggested general measures that can be adopted in neonatal care units.

Table 2: General measures to reduce pain

S. No.	Measures
1.	Avoid bright light
2.	Limit numbers of painful procedures and unnecessary handling
3.	Clustering nursing interventions
4.	Swaddling and facilitated tucking
5.	Judicious use of Investigations
6.	Bundling investigations

B. **Non Pharmacological Measures:** A variety of non-pharmacologic pain-prevention and relief techniques have been shown to effectively reduce pain from minor procedures in neonates.[Table 3] These include use of oral sucrose/glucose[28-31] breastfeeding,[32] nonnutritive sucking,[33] "kangaroo care" (skin-to-skin contact),[35] alternative female kangaroo care,[36] facilitated tuck (holding the arms and legs in a flexed position), swaddling,[38] and developmental care, which includes limiting environmental stimuli, lateral positioning, the use of supportive bedding, and attention to behavioral clues.[39] These measures have been shown to be useful in preterm and term neonates in reducing pain from a heel stick, venipuncture and subcutaneous injections and are generally more effective when used in combination than when used alone.[38,40]

Oral Sucrose Administration

Sucrose administration is the most widely studied non-pharmacologic intervention for infant pain management. The soothing, calming, and pain-relieving effects of sucrose during painful procedures in neonates are believed to be mediated by the release of endogenous opioid neurotransmitters such as beta-endorphins. Oral sucrose used alone is appropriate only for pain of very short duration (2 to 3 min), such as heel stick puncture and venipuncture. For treatment of moderate-to-severe pain or when pain is expected to last longer than a few minutes, it should be used in combination with other analgesics or local anesthetics.

Table 3: Non-pharmacological Measures

S. No.	Measures
1	Sucrose/ Glucose solution
2	Breast feeding/ breast milk supplementation
3	Skin to skin care
4	Swaddling/ Facilitated tucking
5	Tactile stimulation like stroking, caressing, massaging
6	Distraction measures like talking, music, crooning
7	Non nutritive sucking using pacifiers

- These measures in combination are more effective than when used in isolation.

Oral sucrose can be administered with a syringe or through a pacifier. Sucrose concentrations of 24% to 50% are recommended as lower concentrations have been found to be less effective. Volumes of 0.1 mL of oral sucrose solution are given to preterm infants of 24 weeks' gestational age and up to 2 mL to term infants. The dose must be administered 2 to 3 minutes before

the painful procedure and may be repeated during the procedure. There are no documented adverse effects of oral sucrose in neonates, although hyperglycemia and necrotizing enterocolitis have been postulated as potential effects of repeated dosing. Sucrose has shown to be efficacious and safe in the most mature neonates compared with very preterm neonates. Repeated use of sucrose analgesia in infants younger than 31 weeks' gestation was suggested to increase the risk for poor neurobehavioral development and physiologic outcomes in later weeks of life. The age at which oral sucrose no longer produces analgesic effects is unknown. It is believed to be most effective for neonates and not effective for infants older than 6 months. Combining sucrose, oral tactile stimulation, and parental holding is associated with significantly reduced crying in infants receiving multiple immunization injections. Clinical studies also have shown a pain-reducing effect induced by 30% oral glucose and breastfeeding before venipuncture in newborns.[12]

Cochrane meta-analysis of 57 studies involving 4730 infants has shown that sucrose administration is associated with reduced pain scores (PIPP) at 30 and 60 seconds, decrease physiological (heart rate increase) and behavioral indicators of pain (duration of cry, facial action). However, sucrose did not reduce the duration of first cry after heel lance and was ineffective for analgesia for ROP screening. Due to the various concentrations of sucrose used, the meta-analysis was inconclusive about the optimal concentration of sucrose to be used and also the long term neuro-developmental effects.[41]

Breast Feeding and Other Non Pharmacological Modalities

Breast milk is known to be almost as effective as sucrose analgesia in reducing pain for single painful procedure. However, its effectiveness during repeated painful procedures is not established. A cochrane meta-analysis involving eleven studies shows it to be associated with reduced less duration of cry, less PIPP score and less increase in heart rate in breast fed group. Breastfeeding also involves skin-to-skin contact. One study on breastfeeding documented a decrease in pain scores on the Premature Infant Pain Profile and Douleur Aigue Nouveau-ne (DAN) scale even greater than sucrose or holding alone.[42] Whereas a Cochrane review found that breastfeeding reduced crying time versus swaddling or pacifiers, its analgesic effects were equivalent to those of sucrose.[43] The effects of breastfeeding may be potentiated by multimodal stimulation provided by the touch and smell of the mother and the contained positioning of the infant. Multimodal stimulation or pairing several interventions, viz. massage, voice, smell and eye contact, engages more areas of the brain and saturates the sensory channels, thus decreasing painful stimuli.[44] Another study by Mathai confirmed that the use of rocking paired with a pacifier reduced DAN scores more than sucrose or massage alone during heel lancing.[45] Consensus statements from the International Evidence-based Group for Neonatal Pain and the Canadian Pediatric Society both recommend the use of swaddling, facilitated tucking, and non-nutritive sucking, both with sucrose or with a pacifier, whenever possible.[46] Massage is another comfort measure that can easily be provided to the infant. Although specialized training in massage is useful, neonatal massage done by either a trained mother or professional produced weight gains of 6 to 8 g/day above the weight gain rate/day of the control group.[47] Massage is thought to increase parasympathetic activity, increase vagal activity, and help produce a more calm organized physiological state. Important in the administration of infant massage is the receptiveness of the provider to the state of the infant. Checking if the infant is engaged with the provider or demonstrating aversion signs such as looking away, arching, or crying should be monitored before and during massage. Such no receptive signs must be respected and massage with held until the baby is ready to engage, to avoid overwhelming the infant.

A multipronged approach using several general and non pharmacological measures for day to day procedures in the NICU causing mild pain to the newborn are recommended.[Table 4]

Table 4: Analgesia for Routine Bedside Procedures[10]

Procedure	Analgesia measure recommended			
	General measures	Sucrose Analgesia**	Breast milk**	Facilitated tucking/ stroking/ Caressing
Venipuncture Sampling	+	+	±	+
Heel prick	+	+	+	+
Subcutaneous/ IM injection	+	+	+	+
Adhesive tape removal	+	+	+	+
IV Cannulation	+	+	±	+

****** Either sucrose analgesia or breast feeding can be adopted depending on the availability and feasibility; for slightly longer procedure, sucrose analgesia is preferred over breast milk/ breast feeding·

Changes in the infant's environment can also improve comfort. The neonate in the NICU is exposed many unwarranted visual, auditory, and tactile environmental stimuli that can easily overwhelm the infant's ability to calm and organize his/her physiological and behavioral state.[46,48] The full consequences of multiple, overwhelming stimuli are unknown, but visual stimuli have been shown to trigger new NMDA receptors in the visual cortex.[49] Providing a quieter environment with an organized day–night cycle promotes sleep, normal circadian rhythms and reduces heart rate. Batching treatments to provide quiet periods provides time for the infant to regroup his resources.[50]

C. **Pharmacological measures to reduce pain:** While the non-pharmacological measures and topical anesthetic agents can be used for minor procedures, pharmacologic interventions are usually reserved for neonates experiencing moderate-to-severe pain. Although many analgesic agents are approved and available for infants, due consideration must be given to differences in the pharmacokinetics and pharmacodynamics between preterm and term neonates.

Topical Analgesia: Topical analgesia using local anaesthetics may be used to provide pain relief in bedside procedures such as arterial punctures, PICC line placement or lumbar puncture. Tetracaine 4% can be applied locally to the skin 30-60 minutes before the procedure. It should be applied to the intact skin only and not repeated more than once a day to reduce the risk of methemoglobinemia. Its use in combination with non pharmacological measures provides more effective analgesia.

Systemic Analgesia: Neonates, particularly the sick and very premature ones in the NICU are subjected to several procedures which cause moderate to severe pain. These entail the use of pharmacological agents. However drugs in combination with general and non pharmacological measures would provide more effective relief from pain to these babies. Combination therapy for neonatal analgesia is therefore considered most appropriate.[Table 5]

Analgesia in Ventilated Neonates: While there are definite indications for its use in obviously painful procedures such as chest tube insertion or circumcision, its use in conditions such as mechanical ventilation has been controversial. Besides being difficult to assess pain in such infants, the reasons usually cited to routinely sedate ventilated neonates include improved ventilator synchrony, improved pulmonary function, and decreased neuro-endocrine responses, including cortical, beta-endorphine, and catecholamines. Reasons not to treat include the well-known adverse side effects of pain medication, especially the opiates, including hypotension from morphine, chest wall rigidity from fentanyl, and tolerance, dependence, and withdrawal from both opiates and benzodiazepines. Additionally, adverse effects such as death and IVH are not improved with preemptive treatment.[51]

Two appropriately powered studies enrolled a total of 1048 neonates and demonstrated no differences in the incidence of severe intraventricular hemorrhage, periventricular leukomalacia, or death outcomes between the ventilated infants who received morphine or placebo infusions.[53,54] Pain assessments during tracheal suctioning were unaltered in 1 trial[53] and minimally diminished in the other trial.[54] The largest of these, the Neopain Trial, which randomized 898 babies to receive continuous infusion of morphine or placebo, showed an association between morphine and worsening respiratory outcomes, including a significant increase in the duration of ventilation.[54] Morphine also contributed significantly to hypotension observed during the first 24 hours of life, particularly in infants of 23 to 26 weeks gestation and those with preexisting hypotension. It was associated with the use of additional doses of morphine.[55] Studies have consistently shown that the use of opioids is associated with a significant increase in the time to reach full enteral feeds.[56] Besides these, the NEOPAIN study did not find any added benefit of morphine in terms of either short term outcomes of death or neuro morbidity as assessed by cranial ultrasound or long term neuro developmental outcome. In fact, infants exposed to morphine analgesia may exhibit subtly worse neurobehavioral differences involving motor and popliteal angle on Neurobehavioral Assessment of the Preterm Infant (NAPI) subscales as early as 36 weeks of PCA.[57] Fentanyl has been used as an alternative and has been found superior to morphine in reduction of PIPP scores, reduction in oxygen saturation spells, in addition to improved cardiovascular stability. However, the studies on its use are limited and caution needs to be exercised due to potential side effects of tolerance and chest wall rigidity.[51]

Table 5: Analgesia For Specific Procedures[10, 57,61]

Procedure	Intubated	Non-intubated
Arterial puncture Arterial Cannulation Lumbar puncture	Inj Morphine 0·1-0·2 mg/kg IV EMLA cream locally Sucrose analgesia	EMLA cream locally Sucrose analgesia General measures
PICC line placement	Inj Morphine 0·1- 0·2 mg/kg IV EMLA cream locally Sucrose analgesia	EMLA cream locally Sucrose analgesia General measures
Chest tube placement	Inj Morphine0·1-0·2 mg/kg IV Local infiltration with Lignocaine 2% Sucrose analgesia	Inj Morphine 0·1 mg/kg IV* Local infiltration with Lignocaine 2% Sucrose analgesia
Chest drain removal	Inj Morphine 0·1- 0·2 mg/kg Sucrose analgesia General measures	EMLA cream locally Sucrose analgesia General measures
ROP screening	Inj Morphine 0·1- 0·2 mg/kg IV Local anesthetic eye drops Sucrose analgesia Post screen- Paracetamol may be used	Local anesthetic eye drops Sucrose analgesia Post screen- Paracetamol may be used
ROP Laser surgery	Inj Morphine 0·1- 0·2 mg/kg IV Local anesthetic eye drops Sucrose analgesia Post Op- Syp Crocin 15mg/kg q 6 hourly x 1 day	Inj Morphine 0·1- 0·2 mg/kg IV* Local anesthetic eye drops Sucrose analgesia General measures Post OP- Syp Paracetmol 15 mg/kg q 6 hrly x 1 day
CT/ MRI- for sedation	Inj Morphine 0·1- 0·2 mg/kg IV Inj Midazolam 0·1- 0·3 mg/kg IV	Oral Chloral hydrate 50-100mg/kg Oral Trichlophos 20 mg/kg IV Midazolam 0·1- 0·2 mg/kg IV single dose

*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 needs additional analgesic measures

In contrast to opiates, trials using Midazolam for sedation in ventilated infants has been associated with higher episodes of hypotension, statistically significant higher incidence of adverse neurologic events (death, grade III-IV IVH, PVL) and a longer duration of NICU stay compared to the placebo group.[51,59] Hence, use of Midazolam in ventilated infants has been generally discouraged. However, if the drug needs to be used as infusion for neonates the following is recommended:

1. Doses should be individualized and titrated, and treatment should be limited to a few days;
2. Continuous infusions are preferred over bolus doses; the maximum dose for continuous infusion is 60 mcg/kg per hour in term neonates, and should be decreased for lower gestational ages;
3. The maximum for individual bolus doses is 200 mcg/kg, and should be infused over 1 hour;
4. Doses should be decreased by approximately 30% if treating concurrently with narcotics;
5. Do not use in infants who are hypotensive; and
6. Use with extreme caution in infants being treated with fluconazole or other medications (e.g., erythromycin) that interfere with CYP 3A4 metabolism.[51]

Analgesia During Endotracheal Intubation: The experience of being intubated is unpleasant and painful and seriously disturbs physiologic homeostasis.[60] A consensus statement from the International Evidence-Based Group for Neonatal Pain concluded that "tracheal intubation without the use of analgesia or sedation should be performed only for resuscitation in the delivery room or for life-threatening situations associated with the unavailability of intravenous access."[61] Subsequent to this the AAP has recently provided guidelines for premedication for non emergency intubation. The excerpts from this guideline suggest the use of analgesic, muscle relaxant, hypnotic/ sedative and a vagolytic as an effective strategy. The use of Midazolam is discouraged in preterms due to higher incidences of desaturation, serious cardiovascular and neurological side effects.[62]

Nonopioid Analgesics: Non-opioid analgesics are used to treat pain of lesser intensity and as an adjunct to reduce the total dose of opioids ("opioid-sparing" effect). They are valuable in clinical situations requiring

mild or moderate analgesia, particularly for the pain associated with inflammation (e.g., for meningitis, thrombophlebitis, cellulitis, necrotizing enterocolitis, or septic arthritis). NSAIDs are effective analgesics in the management of mild-to-moderate pain in children, but they have not been studied adequately in neonates. They are most useful for postoperative pain management. They also are more effective in preventing pain rather than relieving it.[62-65] This class of drugs includes acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and ketorolac. The current availability of intravenous preparations, including ketorolac tromethamine, ibuprofen lysine, and paracetamol, holds promise for clinical utility in critically ill neonates. Unfortunately, limited data are available on the pharmacokinetics and pharmacodynamics for most of these drugs in neonates (with the exception of acetaminophen and ibuprofen). Acetaminophen is considered safe and effective in reducing mild-to-moderate pain in the pediatric population, with limited studies on its efficacy and safety in preterm and severely ill infants. It can be administered safely for a shorter duration of time to relieve mild procedural pain in neonates without the risk of hepatotoxicity. The recommended dose is 10 to 15 mg/kg orally or 20 to 30 mg/kg rectally. Higher doses do not lead to greater analgesic effects. Tolerance generally does not occur, but repeated dosing may result in cumulative hepatic and renal toxicity, although this problem has not been addressed formally in neonates. Acetylsalicylic acid is not recommended for use in neonates because it increases the risk of Reye syndrome. Ibuprofen and ketorolac have not become standard analgesics in the newborn period because of the potential adverse effects of renal toxicity and platelet dysfunction. Ibuprofen also displaces bilirubin from its binding sites and is associated with an increased risk of gastritis, which limit its use in the NICU.[12]

Thus several pharmacological agents have been used to provide pain relief to newborns. While utilising them, their pharmacokinetics and adverse effects in the neonates have to be kept in mind particularly when dealing with premature and jeopardised babies.

Ketamine, an NMDA receptor antagonist, also known as a dissociative anesthetic, has come to favor more recently with regards to procedural sedation. The literature of its use in neonates is not as robust as literature supporting use in older pediatric and adult populations. Ketamine is ideal as it provides appropriate sedation, amnesia, and does not have hemodynamic instability as other well-established sedatives. Ketamine maintains respiratory drive, allows for bronchodilation, which improves ventilation and hemodynamic functioning, and has only minimal effects on heart rate and blood pressure. Recommended dosing, as established in a subset of NICU neonates, is 1–2 mg/kg/dose. Doses greater than 2 mg/kg/dose are associated with reduction in heart rate. The dose of 5 mg/kg has been associated with reduced blood pressure without impairing cardiac output.[66]

The most commonly used agents in the NICU are opoids mostly morphine & fentanyl, benzodiazapines-midazolam, acetoaminophen, ketamine, chloral hydrate and triclophos. Their dosages, preparations and dilution along with common adverse effects are shown as in Table 6.

Table 6: Drugs in Neonatal Analgesia

Drug	Dose	Preparation/ Administration	Pharmacokinetics/Adv effect	
Morphine	100 mcg/kg IV bolus 10-30mcg/kg/hour IV infusion	1vial- (1ml=50 mg) Dilute- NS/ 10D/5D Non compatible with	Onset: 5min Peak :15 min T1/2-:6- 8 hrs	Resp depression Bradycardia Hypotension
Fentanyl	5 mcg/kg IV bolus 1-5 mcg/kg/hour IV infusion	1 vial- (1ml=) Dilute in – NS/5D/10D Non compatible-	50-100 times more potent than morphine Rapid onset, better in shock/ hypotension T1/2-:up to 8 hrs in preterm Chest wall rigidity- specific SE	
Midazolam	**0**·1- 0·2mg/kg slow IV 1-8 mcg/kg/min IV infusion	1 vial- 5ml (1ml=1 mg) No dilution required	No analgesic effect/ Only sedation Not recommended in neonates esp. preterm Resp depression/ myoclonic jerk	
Rocuranium	0.6-1.2 mg/kg IV over 1-2 min		Preferred muscle relaxant. Effects reversed with atropine and neostigmine	
Ketamine	1–2 mg/kg/dose	1 vial- 2ml (1ml=50mg)	For procedural analgesia. Maintains respiratory drive with minimum effects on heart rate & blood pressure.	

Paracetamol	10-15 mg/kg/dose PO 30 mg/kg/ dose PR	5ml= 125mg	Rectal route erratic absorption
Chloral hydrate	25-50mg/kg PO		No analgesia/ Only sedation For Procedures like MRI
Triclophos	20 mg/kg PO	5ml=100 mg	No analgesic effect
EMLA cream	0·5- 1g for 1 hr	Lidocaine- prilocaine 2%	Delayed onset – ½ to 1 hr Met hemoglobinemia

D. **Training:** A well established training programme in the hospital which focuses on sensitising healthcare workers involved in neonatal care in recognising and treating pain is mandatory. This process would require constant reinforcement of the pain prevention policy which is an essential requirement of the neonatal wards to ensure its judicious implementation. The medical and nursing staff need to be well versed in providing the appropriate analgesia to the needy newborn while being vigilant in detecting and handling possible adverse effects of the medication provided.

E. **Quality Improvement Protocols:** Every neonatal unit should have a *Quality of Care Improvement Team* which involves all ecchelons in formulating goals and implementing them. They should identify areas which need attention in the pain management programme. Potentially better practices need to be identified, implemented and then studied if they are successful and can be included in the pain control protocol as proven better practices. Such a collaborative effort would also ensure better and more effective implementation of pain management in newborns.

Conclusion

Despite the knowledge that neonates are subjected to several painful procedures in the NICU, evidence suggests that pain is undertreated in these babies. Factors including lack of recognition of pain in the non verbal neonate, limited therapeutic options and concerns about the side effects of medications used often hamper effective implementation of a neonatal pain control programme. Creating an awareness among neonatal health care workers that babies do feel pain even more so than older people and if untreated could have long term deleterious effects is important. Establishing an effective pain control programme and ensuring its implementation is essential in every NICU. Neonatal healthcare workers should be familiar with the adverse effects of medications used .Regular quality checks to identify weak areas in the pain control standard operating procedures and instituting remedial measures ensures that the analgesia services in the NICU are more effective. Utilising a multipronged approach to analgesia services appears to be the key that will not only provide more effective pain relief but would also result in better short and long term outcomes in the hospitalised sick neonates.

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