ASSESSMENT AND MANAGEMENT OF PROCEDURAL PAIN IN NEONATES

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The AIMS of the presentation are to:

1. **Understand the importance of the management of the pain in neonates**
    - neuroanatomical pathway of pain conduction in neonate (term and preterm)
    - pathophysiological changes while painful procedures are performed
2. **Assess the level of pain experienced by the neonatal patient**
    - tools for pain assessment in neonates containing both observational and pathophysiological signs in neonates
3. **Get the evidence based recommendations for the treatment of pain in neonates**
    - the commonly used Clinical Guidelines for procedural pain and pain management
    - advantages and disadvantages for each of them

According to the standard **Definition** given by the International Association for the Study of Pain (IASP), the pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (www.lasp.org). It means that the pain is always subjective. Therefore, pain can only be assessed by self-reporting of the person experiencing it. Lacking that, it may be inferred indirectly, from activation of nociceptor nerve pathways, by biochemical changes, by changes seen during functional neuroimaging, or by physiological and behavioural assessments.

Before the work by Anand and Hickey, it was thought that newborns could not feel pain, and, as a consequence, no adequate analgesic treatment was given. Two other reasons for this policy were the *fear of the adverse events of analgesics* and the *lack of good pain assessment tools for infants*. Unless more powerful tools of functional neuroimaging to use while studying neonates are designed, the only mode of detecting neonatal pain are before mentioned indirect measures.

Common **misconceptions** concerning newborn pain still exist and include:

1. Newborns do not feel pain because their nervous system is too immature. This false premise lies in the misbelief that newborns do not have the neurological substrate for the perception of pain because of lack of myelination, incomplete pain pathways from the periphery to the cortex, or immaturity of the cerebral cortex;
2. Even if newborns do feel pain, they cannot remember it;
3. Even if they feel or remember pain, it doesn't cause them harm;
4. Even if newborns feel or remember pain, and, even if it is harmful to them, we cannot safely give them local or systemic analgesia or anesthesia, because it is too dangerous to administer it.

But, the **evidence** about the neonatal pain experience which refute these misconceptions, constitute the consensus statements by Anand and the AAP:

- Peripheral receptors, nerve pathways, and the cerebral cortex can function properly to process pain by mid-gestation (Anand, 1993). At birth, a neonate has developed the neural pathways for nociception and for experiencing pain, but the pain responses of a newborn baby is not simply a copy or immature version of that of an adult;
- It is true that fetus and newborns have unmyelinated nerve fibers, but they can conduct the stimuli, although slower than the adults. Neuroanatomical components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate;

- Compared with older age groups, newborns may experience a greater sensitivity to pain and are more susceptible to the long-term effects of painful stimulation;
- The nerves of young babies respond more readily to noxious stimuli, because the neonatal threshold for sensitisation is decreased. Sensitisation refers to the phenomenon that a noxious event increases the sensitivity of the nociceptor system to another such event – or to a much milder or even entirely non-noxious event. The experience of severe pain to a mildly painful stimulus is called hyperalgesia, and pain in response to a stimulus which would normally not be painful is called allodynia. This happens in adults and babies, but in babies this occurs more quickly and the sensitised area is larger than in adults, for the same initial stimuli;
- The pathways that descend from the brain to the spinal cord are not well developed in the newborn, so the ability to reduce or inhibit nociception via central brain mechanisms is limited;
- A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain;
- Analgesia, sedation, and anesthesia can be safely provided to newborns in most circumstances.

And at the end, considering many other reasons which probably still need to be discovered, a noxious event which appears minor to adults, can have unexpectedly widespread effects in the baby's nervous system; it is sensed more intensely and potentially more diffusely than it would be in the adult, thus causing more deleterious effects on the neonatal health and wellbeing.

In addition to being more sensitive to start with, the neonate's nervous system seems much more active than that of an adult in transforming its connections and central nerve pathways in response to stimuli. This reshaping - also called plasticity - involves both structural and chemical changes of the nervous system. It has been shown to occur in response to noxious events in the short term, and there are indications that such changes, once established, can persist until adult life. What precisely this implies for later childhood and adult life is as yet unclear, but the present feeling is that this potential for long term harm is a valid reason for working towards more effective management of neonatal pain. **Newborns are as sensitive to pain as adults, AND preterm infants are even more sensitive to pain.** Neurotransmitters in the dorsal horn of the spinal cord are associated with nociception and increased somatosensory excitability in the preterm spinal cord. On the other hand, neurotransmitters in descending inhibitory nerve fibers are only present at term. Thus, there is diminished inhibition of pain in premature infants.

Difference in response

Repeated tissue damage in newborn infants will naturally activate primary sensory neurons in the skin and underlying tissues. In many ways, these afferents respond in a similar way to those of adults. Neurotrophic factors will have more far-reaching effects if administered or up regulated in the neonatal period. The physiological properties of primary sensory neurons are highly influenced by the levels of neurotrophic factors in the skin during a critical period of development. The up-regulation of neurotrophic factors provides a likely explanation for the observation that early skin wounds lead to long-term hyper-innervation and hypersensitivity of the injured area.

Difference on central level

The region of secondary hyperalgesia and allodynia that surrounds an area of tissue damage results from central synaptic rather than peripheral receptor alterations. The hyper-excitability of sensory neurons in the dorsal horn of the spinal cord and brainstem that follow inflammation is termed central sensitization in the newborn, the synaptic linkage between afferents and dorsal horn cells is still weak and electrical stimulation often evokes only a few spikes at long and variable latencies. Expression in the neonatal spinal cord show sawider distribution than in the adult and decreases over the first postnatal 3 weeks. Different combinations of subunits will affect desensitization, ionic permeability, and current/voltage relationships. There are also changes in the

distribution of the flip-flop variants with postnatal age; the flip variants are generally more sensitive to agonists than the flop, resulting in higher levels of depolarization from glutamate release (Watanabe and others1994).

The implications of these findings on immature sensory processing in the spinal cord are not clear. Another important feature of infant dorsal horn cells is that their receptive fields are larger, that is, occupy a relatively larger area of the body surface, than in adults. The fields gradually diminish over the first 2 postnatal weeks

The persistent pain response of the infant in intensive care will depend on the ability of the developing sensory nervous system to activate mechanisms of peripheral and central sensitization. C-fiber-evoked activity matures after the first postnatal week in rats, and from P10, repetitive C-fiber stimulation produces a classical “wind-up” as reported in the adult dorsal horn in 18% of cells.

Descendent pathways

Another contributory factor will be the immaturity of descending inhibition. It is well established in adults that descending pathways originating in higher centers can modulate the output of spinal nociceptive neurons and are activated in the presence of persistent pain

The risk of neonatal intensive care unit (NUICU)

The survival of preterm infants is dependent on highly sophisticated intensive care, associated with an exceedingly high number of painful procedures. This is particularly true for infants with extremely low gestational ages (GAs) who also receive less analgesia. Repeated pain exposures during critical windows of central nervous system development are associated with permanent changes in peripheral, spinal, and supraspinal pain processing, neuroendocrine function, and neurologic development. These changes can be manifested by alterations in pain thresholds, stress responses, cognitive function, behavioral disorders, and long-term disabilities.

The painful procedures commonly performed in the Neonatal Intensive Care Unit can be diagnostic or therapeutic. **Diagnostic** procedures include:

- Heel lancing
- Arterial puncture
- Endoscopy
- Lumbar puncture
- Suprapubic bladder tap
- Venipuncture
- Eye examination (Retinopathy of prematurity)

Therapeutic procedures include:

- Bladder catheterization
- Central line and chest tube insertion/removal
- Dressing change
- Gavage tube insertion
- Intramuscular injection
- Laser therapy for retinopathy
- Peripheral venous catheterization
- Mechanical ventilation
- Removal of adhesive tape
- Suture removal
- Tracheal intubation/extubation
- Ventricular tap
- Surgical interventions

The reason why neonatal pain relief is so important for the newborn child is that the repeated episodes of pain in NICU do occur, they are very stressful for parents, it is humane to help the

patients, the immature nervous system cannot modulate effectively, long term effects are documented, and pain habituation may alter the preterm brain and prolonged pain may leave permanent consequences in neonates. Newborn pain, which itself is generally a consequence of intervention, has immediate, short term and long term consequences.

Immediate: newborn infants subjected to a variety of noxious stimuli have immediate hormonal, physiological and behavioral responses.

Term and preterm infants behave differently in their **short term** response to pain. Prior pain experience in healthy, term babies appears to increase subsequent behavioral response to pain. By contrast, in preterm infants prior pain experience appears to diminish subsequent behavioral response to pain.

The **long term** consequences constitute an emerging field of research and importance as the possible impact of multiple, neonatal pain exposure in NICU on neurodevelopment, potentially contributes to later problems with attention, learning and behavior. Painful neonatal experiences DO have long-term consequences, and even if not expressed as conscious memory, memories of pain maybe recorded biologically and alter brain development and subsequent behavior.

Physiological changes are presented as increase in heart rate and blood pressure, respiratory rate, oxygen consumption, mean airway pressure, muscle tone and intracranial pressure.

Behavioural changes are noted as facial expression and body movements.

Change in facial expression:

- Grimacing
- Screwing up of eyes
- Nasal flaring
- Deep nasolabial groove
- Curving of the tongue
- Quivering of the chin

Body Movements

- Finger clenching
- Thrashing of limbs
- Writhing
- Arching of back
- Head hanging

Hormonal changes could be seen as increased release of Cortisol, Catecholamines, Glucagon, Growth hormone, Renin, Aldosterone and Antidiuretic hormone, and on the other hand, there is reduced secretion of Insulin.

Autonomic changes are expressed as mydriasis, sweating, flushing, pallor, etc

Pain assessment: Could the pain be measured?

The kind of structural and functional changes of the developing pain pathways depends on the moment, location, and kind of pain stimulus. While self-report, usually by using a linear analog scale, is regarded as the most reliable indicator of pain and considered the gold standard, neonates cannot verbalize their pain and thus depend on others to recognize, assess and manage their pain. Pain assessment tools were developed to measure pain in newborns as objectively as possible. There are pain assessment tools for procedural pain, postoperative pain, and prolonged pain. All pain assessment tools are based on the degree to which changes are expressed, alone or in combination.

Commonly used methods for assessment of pain in newborns depend on the type of the patients, type and duration of pain, etc. The most explored scales for pain assessment are:

Premature Infant Pain Profile (PIPP) is aimed for assessment of pain in premature neonates. This scale includes the following indicators : gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow. Scores vary between 0 (no pain) and 21 (maximum pain), and this scale has very high interrater and intrarater reliability (> 0.93). It is more

appropriate for premature newborns, but is acceptable also in term newborns. The scale has feasibility and utility established at bedside.

Neonatal Facial Coding Scale (NFCS) includes brow bulge, eye squeeze, nasolabial furrow, open lips, stretch mouth, lip purse, taut tongue, chin quiver and tongue protrusion. This scale has lower interrater and intrarater reliability (> 0.85). The feasibility is established at bedside.

Neonatal Infant Pain Scale (NIPS) is based on the following signs: facial expression, cry, breathing patterns, arms, legs, state of arousal. The interrater reliability is >0.92, and no data about the intrarater reliability. And, the fisibility is not established.

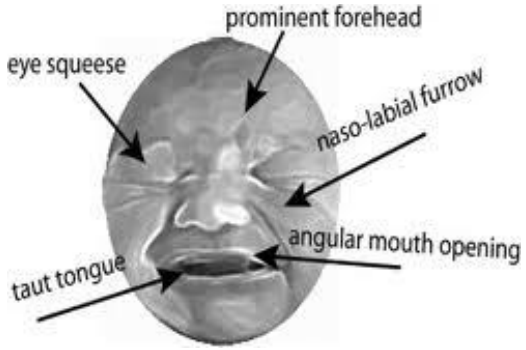
CRIES score is preferred by the nurses because of its ease of conducting. The scoring system includes crying, oxygen requirements, increased vital signs, expression, sleeplessness. The score has low interrater reliability (> 0.72), no data about the intrarater reliability. And, the feasibility is not established.

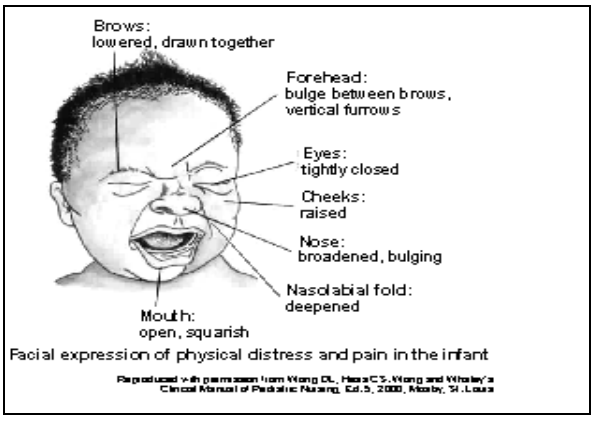
BPSN —Bernese Pain Scale for Neonates contains 9 items, each scored 0-3 points:

- 3 physiologic: heart rate, respiratory rate, and oxygen saturation
- 6 behavioral: grimacing, body movements, crying, skin color, sleeping patterns, consolation items.

Higher scores for the behavioral items and greater changes in the physiologic items indicate deeper pain, whereas a total score of <11 is considered non-painful (sensitivity 100.0% and specificity 89.4%). The initial psychometric testing of the BPSN demonstrates good construct validity with differentiation between painful and non-painful procedures, This scale has the highest intrarater reliability (0.98-0.99), and pretty high interrater reliability coefficients (0.86-0.97)

The COMFORTneo scale is a pain assessment tool modified from the COMFORT behavioral scale, and was validated for prolonged pain in 2009, but not for procedural pain. The COMFORTneo scale measures alertness, calmness, respiratory response or crying, body movement, facial tension, and muscle tone. Scores vary between 6 (no pain) and 30 (maximum pain).





General principles for the prevention and management of pain in newborns

- Pain in newborns is often unrecognized and undertreated. Neonates do feel pain, and analgesia should be prescribed when indicated during medical care;
- If a procedure is painful in adults, it should be considered painful in newborns, even if they are preterm. Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality;
- The appropriate use of environmental, behavioral and pharmacological interventions can prevent, reduce or eliminate neonatal pain in many clinical situations;
- Sedation does not provide pain relief, but may mask the neonate's response to pain;
- Clinical units providing health care to newborns should develop written guidelines for the management of neonatal pain;

- When pain is prolonged, striking changes occur in the infant's physiologic and behavioral indicators. During episodes of prolonged pain, neonates enter a state of passivity with few, if any, body movements; an expressionless face; decreased heart rate and respiratory variability; and decreased oxygen consumption, all suggestive of a marked conservation of energy.

Prolonged or repeated pain also increases the response elicited by future painful stimuli (hyperalgesia) and even by usually nonpainful stimuli (allodynia). Therefore, pain scales that are used in postoperative neonates should be sensitive to the changes in response that can occur when pain is prolonged

Systematic approach to pain management

- Prevention, limiting, avoiding noxious stimuli
- Assessment of neonatal pain by standardized methods with demonstrable validity, reliability and clinical utility
- Treatment including non-pharmacological (behavioural) and pharmacological

Reduction of painful procedures

Clearly, the most effective way of reducing minor procedural pain in the neonate is to reduce the number of procedures performed. There currently is a paucity of research regarding effective ways to accomplish this, but strategies for reducing the number of procedures that neonates experience should be developed and their effectiveness should be tested. Such an approach might include reducing the number of bedside disruptions in care, bundling interventions, eliminating unnecessary laboratory or radiographic procedures, using transcutaneous measurements when possible, and minimizing the number of repeat procedures performed after failed attempts.

Environment should be as conducive as possible to the well being of the neonate and family. Avoiding unnecessary noxious stimuli (acoustic, visual, tactile, vestibular) is crucial, and minimizing painful or stressful procedures (use of central lines-umbilical, rather than peripheral; central or peripheral long lines rather than repeated IV lines for longer term use; arterial line rather than repeated arterial stabs) are very successful. Non-invasive measurement where possible (oximeter in small babies, bilirubinometer prior to blood sampling). The prevention of pain in neonates should be the goal of all caregivers, because repeated painful exposures have the potential for deleterious consequences. Neonates at greatest risk of neurodevelopmental impairment as a result of preterm birth (ie, the smallest and sickest) are also those most likely to be exposed to the greatest number of painful stimuli in the NICU and prone to bad outcome. Although there are major gaps in the knowledge regarding the most effective way to prevent and relieve pain in neonates, proven and safe therapies are currently underused for routine minor, yet painful, procedures. Every health care facility caring for neonates should implement an effective pain-prevention program, which includes strategies for minimizing the number of painful procedures performed.

Reducing pain from bedside care procedures

- Neonates in the NICU often experience painful procedures during routine care, such as needle insertions, suctioning, gavage-tube placement, and tape removal, as well as stressful disruptions, including diaper changes, chest physical therapy, physical examinations, nursing evaluations, and exposure to environmental stimuli.
- Despite increased awareness by caregivers that neonates in the NICU frequently experience pain, effective pain relief for these routine procedures is often underused.

Assessment and reassessment can be performed by the abovementioned scales:

- Premature Infant Pain Profile (PIPP)
- Neonatal Facial Coding Scale (NFCS)
- Neonatal Infant Pain Scale (NIPS)
- CRIES Score
- BPSN —Bernese Pain Scale for Neonates

- COMFORTneo for prolonged pain

The **management** of the procedural, prolonged and postoperative pain is the objective of several evidence based Clinical Guidelines regularly updated and synchronized. Those are:

- Up to date recommendations: AMERICAN ACADEMY OF PEDIATRICS; 2006 and revision 2012,
- Committee on Fetus and Newborn, Section on Surgery, and Section on Anesthesiology and Pain Medicine. Position statement. CANADIAN PAEDIATRIC SOCIETY. 2007
- Guideline summary NGC 8271: NP management of procedural pain in breastfeeding infant (ABM Clinical protocol 23); 2010
- Royal Prince Alfred Hospital policy (Clinical Guidelines) Neonatal Pain Policy, 2009
- Murki S and Subramanian S. Sucrose for analgesia in newborn infants undergoing painful procedures: RHL commentary (last revised: 1 June 2011). *The WHO Reproductive Health Library*; Geneva: World Health Organization.
- Cochrane reviews: Two reviews, Revision 2009 and 2012
- Italian society of neonatology, Management of Procedural pain; 2009

Objectives

These updated statements are intended for health care professionals who care for neonates (preterm to 1 month of age). Strategy of pain management contains:

1. Emphasize that despite increased awareness of the importance of pain prevention, neonates in the NICU continue to be exposed to numerous painful minor procedures daily as part of their routine care;
2. Importance of precise assessing neonatal pain by health care professionals;
3. Implementation of effective strategies to prevent and treat pain associated with routine minor procedures; and
4. Review appropriate methods to prevent and treat pain associated with surgery and other major procedures.

Grades of recommendations and level of evidence are as agreed by the professionals:

A: At least one good-quality meta-analysis of randomized controlled trials (RCTs), or a sufficiently powered good-quality RCT with a very low risk of bias, directly applicable to the target population

B: A body of evidence including good-quality systematic reviews of case–control or cohort studies directly applicable to the target population, or good-quality case–control or cohort studies with a very low risk of confounders or bias and a high probability of the relationship being causal. Evidence extrapolated from good-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low or low risk of bias

C: A body of evidence including well-conducted case–control or cohort studies with a low risk of confounders or bias and a moderate probability of the relationship not being causal, directly applicable to the target population and demonstrating overall consistency of results, or evidence extrapolated from good-quality systematic reviews of case–control or cohort studies, or good-quality case–control or cohort studies

D: Non-analytical studies, e.g. case reports, case series or evidence extrapolated from well-conducted case–control or cohort studies with a very low risk of bias

GPP: Good practice points; Recommended practice, based on the clinical experience of the group that developed the guidelines

(Modified from the SIGN Guidelines Developer's Handbook 2008)

General principles

Environmental, behavioral and non-pharmacological comfort measures are recommended for each procedure, e.g. the use of a pacifier with sucrose combined with distraction techniques. The

pharmacological options used in combination with these measures can have additive or synergic effects in controlling procedural pain and stress. For planned procedures, such as blood sampling or creating a vascular access, the optimal baseline state of quiet wakefulness should be obtained before starting the procedure. If possible, do not interrupt sleep; plan the procedure far from mealtimes and from any other painful invasive procedures to allow for recovery. Conduct the procedure in a calm and relaxing environment, reducing noxious stimuli (light and noise) as much as possible. During the procedure, the neonate should preferably be contained in warm sheets and accompanied during and after the procedure. Monitoring pain and stress as the fifth vital sign during ongoing analgesia or invasive procedures with scales validated for infants may facilitate the fine tuning of analgesic measures and improve awareness of how the newborn feels. At the end of the procedure, continue to monitor the physiological parameters until they return to the baseline state. Plan no other invasive procedures for at least 2 h after the procedure

Heel lancing: Venipuncture is the preferred method for blood sampling in term newborns as it is less painful, more efficient and requires less resampling. This approach may not apply to the care of extremely preterm infants [A].

Environmental measures

- Warming the heel is ineffective for heel lancing [C]
- Do not squeeze the heel, which must be well perfused and squeezing is itself a cause of pointless pain [D]. It is the most painful part of the procedure
- Use techniques to distract the neonate and provide stimuli to stop pain transmission to the cerebral cortex, such as sensorial saturation (a technique consisting in the mother or nurse massaging and talking to the baby while administering oral glucose before the puncture) [B]
- Consider involving the mother in procedures whenever possible, using skin-to-skin contact or breastfeeding during non-routine sampling [B]. The efficacy of breastfeeding during multiple painful procedures has not been documented. Ensure the parent or carer holds the infant, *OR* use swaddling, containment by flexing and holding the infant and employ multisensory stimulation;
- Use an automatic lancet rather than a manual lancet [B]

Non-pharmacological measures

- Use sucrose and non-nutritive sucking (NNS) or human milk [A]
- The use of oral sucrose alone has recently proved ineffective in the case of repeated heel lances in term infants in the first 2 days of life [B]
- Alternatively, use a glucose solution [C]
- The use of less-concentrated solutions is recommended in premature infants because solutions with higher concentrations of sucrose/glucose (24–33%) have a high osmolarity, up to 1000 mOsm [D]
- The use of NNS seems to have a synergic effect with the sweet taste and is recommended, whenever possible [B]
- The use of multiple doses for a given procedure (2 min before, immediately before and 2 min after heel lancing) seems more effective than a single dose [B]
- The long-term safety of multiple doses of oral sucrose has not been demonstrated [A]

Pharmacological measures

- The use of EMLA cream is not recommended, as it is ineffective for heel lancing pain [B]
- Pre-emptive analgesia with paracetamol before the procedure is not recommended, as it is ineffective [A]

Intramuscular or subcutaneous injections

Environmental measures

- It is preferable to administer drugs intravenously wherever possible [GPP].

- Adopt all the environmental measures mentioned in the heel lancing section. Choose a smaller gauge needle wherever possible [GPP].

Local pharmacological measures

- Apply EMLA cream (0.5–1 g) 60 min before the procedure [B]

NOTE: Application of EMLA cream (0.5-1g) 60-90 minutes prior to injection (for single injection) was not considered practical for Vit K injection as to ensure maximum compliance this is given shortly after birth at most hospitals

Nasogastric or orogastric tube insertion

- Use a pacifier with sucrose [GPP]
- Use holding, swaddling or containment by flexing and holding the infant. Use sucrose and non-nutritive sucking (NNS) or human milk [A]
- Use a gentle technique with appropriate lubrication ensuring the head is in the neutral or "sniffing" position, and inserting the tube in a vertical direction at right angles to the face

Central venous catheter insertion by surgical cut-down

Non-pharmacological measures

- Use sucrose and NNS or human milk during the preparatory phase whenever possible [GPP]

Local pharmacological measures

- Apply EMLA cream 60 min before the procedure [C] or proceed directly with the subcutaneous infiltration of lidocaine 1% at a dosage of 2–4 mg/kg buffered with sodium bicarbonate 8,4% in 1:10 dilution [D] The buffered solution can reduce the pain of the local infiltration

Systemic pharmacological measures

- Sedation: administer a slow i.v. bolus of fentanyl [D] and midazolam, as necessary [GPP], or an i.v. bolus of ketamine[GPP].
- Closely monitor the patient and anticipate any need for ventilatory and circulatory support in the event of respiratory depression [GPP].
- General anaesthesia: administer an i.v. bolus of fentanyl and a muscle relaxant [GPP]

Lumbar puncture

Environmental measures

- Whichever position is chosen (on the side, sitting in the crib or on the nurse's or mother's arm), avoid any extreme flexion of the neck and knees towards the chest because this can cause significant hypoxemia, especially in critical patients, as well as carrying a risk of vertebral fractures [D].
- It is advisable to perform LP with an atraumatic needle, as it separates the fibers of the yellow ligament without severing them, and early stylet removal improves the success rates [C].
- This avoids post-LP fluid exudation and the risk of secondary headache and the, albeit rare, onset of epidermoid tumours in the spinal canal [D]

Non-pharmacological measures

- Use sucrose and NNS or human milk [GPP]

Local pharmacological measures

- Apply EMLA cream to the puncture site 60 min before the procedure [A]
- The use of other local anaesthetics, such as subcutaneous lidocaine infiltration, is not recommended as a front-line anaesthetic measure [C], and there are no reports on its use for deeper anaesthesia after EMLA.

Systemic pharmacological measures

- The use of systemic analgesia and sedation with a slow i.v. opiate bolus can be recommended in some cases if the neonate is intubated. If term infants are not intubated, a

bolus of midazolam can be suggested if the infant is particularly restless, monitoring the vital signs (especially blood pressure). After the procedure, keep the neonate supine, continue with pain control measures and monitor the physical parameters until they return to the baseline state [GPP].

- Consider using paracetamol for the treatment of headache following subarachnoid puncture [D]

Endotracheal intubation

Many different approaches are reported and a great variety of drugs are used, alone or in combination, as premedication for elective intubation in neonates.

- Combinations of opiate and muscle relaxant [B] and remifentanil and midazolam [B], or propofol [B], thiopental [B] and ketamine [D] have been proposed.
- Using appropriate analgesia and sedation during tracheal intubation facilitates the procedure (fewer attempts and shorter times), reducing potentially harmful physiological fluctuations and pain [A]
- In nasal intubation, small doses (0.3 mL/kg) of lidocaine gel 2% may be useful [D]

Endotracheal suction

This is considered a stressful procedure and may be associated with the same physiological responses that accompany other painful procedures

- Use a pacifier; may consider giving sucrose
- Use swaddling or containment, by holding the infant
- Consider continuous intravenous infusion of opioids (morphine) or slow injection of intermittent opioid doses (morphine), although this may not be indicated in preterm infants

Chest tube insertion

Anticipate the need for intubation and ventilation in neonates breathing spontaneously

Non-pharmacological measures

- Apply appropriate behavioral pain control measures [GPP]

Local pharmacological measures

- If the procedure is not urgent, apply EMLA cream to the puncture site[GPP]. If it is urgent, proceed directly with subcutaneous lidocaine 1% infiltration [D]

Systemic pharmacological measures

- In intubated and ventilated neonates, administer a slow i.v. opiate bolus [D] In non-intubated neonates, consider a bolus of ketamine, except for VLBWI, but anticipate the need for intubation and ventilation in neonates breathing spontaneously [D]
- After the procedure, consider the use of bolus or continuous venous infusions of opiates, monitoring the pain scale [D]

Chest tube removal

Non-pharmacological measures

- Apply appropriate behavioural pain control measures [GPP]

Local pharmacological measures

- Apply EMLA cream to the site of insertion [D].

Systemic pharmacological measures

- Consider a slow i.v. opiate bolus [GPP].

Screening for ROP

Non-pharmacological and environmental measures

- Perform the screening procedure away from meals [GPP].

- Use appropriate behavioural pain control measures and sucrose and NNS [A], or human milk [GPP].
- Conduct the ophthalmoscopy without using the blepharostate, the positioning of which causes pain [C]

Pharmacological measures

- In the case of RetCam screening, apply local anaesthesia with oxybuprocaine 0.4% or tetracaine 1% eye drops and consider a slow i.v. opiate bolus or ketamine [D]

Laser therapy for retinopathy of prematurity

Non-pharmacological measures

- During preparations for the procedure, adopt appropriate behavioral pain control measures [GPP]
- Use a pacifier with sucrose
- Consider slow intravenous opioid infusion (morphine)
- Other approaches may include the use of short acting anesthetic agents
- Consider oral paracetamol after extubation and use of a pain score.

Pharmacological measures

- In general, combine a local anaesthetic with a general anaesthesia, administering a slow i.v. opiate bolus in association with a muscle relaxant before intubation, or combine local naesthesia with sedation using low doses of opiates combined with midazolam or ketamine, supporting the airways with a positive pressure [D]
- Nasopharyngeal prongs or a laryngeal mask are a valid alternative to ventilatory support during brief measures if the neonate has not already been intubated [D]
- At the end of the procedure, arrange for postoperative analgesia for the first 24–48 h [D]

Ongoing analgesia for routine NICU care and procedures

- Reduce acoustic, thermal, and other environmental stresses
- Use swaddling or containment, by holding the infant ± multisensory stimulation
- Use a pacifier and if possible and safe to do so, give with sucrose (do not use routine, repeated doses of sucrose in infants < 31 weeks gestation)
- Consider low-dose continuous infusion of morphine if patient is ventilated, although this may not be indicated in preterm infants
- The use of midazolam is not recommended

Interventions with evidence of benefit

- Venipuncture is less painful than heel lancing for blood sampling in newborns
- Sucrose is safe and effective in reducing pain from heel lancing
- Sucrose is safe and effective in reducing pain from venepuncture and heel lancing in preterm infants
- Pacifiers (dummies), non nutritive sucking, rocking, are effective in reducing pain responses
- Sucrose with pacifiers are effective in reducing pain responses in newborn infants
- Sucrose and holding are effective in reducing pain responses
- Multisensory stimulation (massage, voice, eye contact and perfume smelling) with oral glucose and sucking is most effective in reducing pain responses to heel lancing in term and preterm infants
- Breast feeding is effective in reducing pain responses during heel lancing in healthy newborns
- Skin to skin contact is effective in reducing pain responses during heel lancing in newborns
- Automated lancets are superior to conventional lancets (less need for repeat punctures, shorter procedure time, increased volume of blood collected, reduction in haemolysed blood samples)

- A fully retractable automatic lancet is superior to a partially retractable automatic lancet (less pain, less time to perform, fewer punctures but more expensive)

Interventions with no evidence of benefit or with evidence of harm

- EMLA cream, topical amethocaine, lignocaine ointment, oral paracetamol are not effective for heel lancing pain
- Warming the heel does not reduce pain or aid blood collection during heel lancing
- Midazolam maybe associated with a higher incidence of adverse neurological events and longer NICU stay
- Routine repeated use of sucrose analgesia in preterm neonates <31 weeks post-conceptional age in the first week of life may result in poorer neurobehavioural development and physical outcomes
- Routine morphine infusion in preterm ventilated newborns has no measurable analgesic effect and no effect on poor neurological outcome

Recommendations

Assessment of pain and stress in the neonate

1. Caregivers should be trained to assess neonates for pain using multidimensional tools.
2. Neonates should be assessed for pain routinely and before and after procedures.
3. The chosen pain scales should help guide caregivers in the provision of effective pain relief.

Reducing pain from surgery

1. Any health care facility providing surgery for neonates should have an established protocol for pain management. Such a protocol requires a coordinated, multidimensional strategy and should be a priority in perioperative management.
2. Sufficient anesthesia should be provided to prevent intraoperative pain and stress responses to decrease postoperative analgesic requirements.
3. Pain should be routinely assessed by using a scale designed for postoperative or prolonged pain in neonates.
4. Opioids should be the basis for postoperative analgesia after major surgery in the absence of regional anesthesia.
5. Postoperative analgesia should be used as long as pain-assessment scales document that it is required.
6. Acetaminophen can be used after surgery as an adjunct to regional anesthetics or opioids, but there are inadequate data on pharmacokinetics at gestational ages less than 28 weeks to permit calculation of appropriate dosages.

Reducing pain from other major procedures

1. Analgesia for chest-drain insertion comprises all of the following:
   - general nonpharmacologic measures;
   - slow infiltration of the skin site with a local anesthetic before incision unless there is life-threatening instability; and
   - systemic analgesia with a rapidly acting opiate, such as fentanyl.
2. Analgesia for chest-drain removal comprises the following:
   - general nonpharmacologic measures and
   - short-acting, rapid-onset systemic analgesic.
3. Although there are insufficient data to make a specific recommendation, retinal examinations are painful, and pain-relief measures should be used. A reasonable approach would be to administer local anesthetic eye drops and oral sucrose.
4. Retinal surgery should be considered major surgery, and effective opiate-based pain relief should be provided.

Challenges and major dilemma regarding pain management in neonates

Sucrose for procedural pain in infants (2012)

The use of oral sucrose has been the most extensively studied pain intervention in newborn care to date. More than 150 published studies relating to sweet-taste-induced calming and analgesia in human infants have been identified, of which 100 (65%) include sucrose.

With only a few exceptions, sucrose, glucose, or other sweet solutions reduced pain responses during commonly performed painful procedures in diverse populations of infants up to 12 months of age. Sucrose has been widely recommended for routine use during painful procedures in newborn and young infants, yet these recommendations have not been translated into consistent use in clinical practice. One reason may be related to important knowledge and research gaps concerning analgesic effects of sucrose. Notably, the mechanism of sweet-taste-induced analgesia is still not precisely understood, which has implications for using research evidence in practice.

More research is needed about the understanding of the mechanisms of sucrose-induced analgesia; highlight existing evidence, knowledge gaps, and current controversies; and provide directions for future research and practice.

This use of the term analgesia, defined by the International Association for the Study of Pain, is particularly open to criticism when describing effects of most analgesic agents. “Absence of pain,” based on observational measures (behavioral indicators including facial expressions, crying, body movements) and composite measures (behavioral and physiologic indicators plus other indicators such as behavioral state, nurses perception of pain) is rarely achieved, yet the term is widely used in neonatal pain studies.

This highlights the subjective nature and selection of terms and the lack of clarity surrounding the term “pain” in infants among clinicians and researchers. In addition, the emotional component of pain in infants is not able to be interpreted. Despite many years of debate, this lack of clarity of the definition and meaning of these terms still has an impact on the interpretation of infants’ responses to sucrose, especially because the mechanisms of sucrose are not fully understood in either animals or humans.

- Despite the strong evidential base of analgesic effects of sucrose in newborn and young infants for single painful procedures, there remain knowledge gaps concerning the following:
- Opioid pathways involved in mechanism of effect, especially in the developing infant;
- Effectiveness when administered with concomitant opioid analgesics;
- Effectiveness when administered concurrently with other pain management strategies such as skin-to-skin care;
- Use, safety, and effectiveness when used repeatedly for extended periods in extremely low birth weight infants and sick infants requiring prolonged hospitalization.
- Despite the extensive work, the mechanisms of analgesic effects of sweet solutions in human infants remain poorly understood. On the basis of animal studies, the key mechanism is believed to be sweet-taste-induced b-endorphin release. However, elevated serum levels of b-endorphin in response to oral sucrose has not been identified in human neonates.
- Prolonged use of sucrose raises important questions related to effectiveness and safety, although there is a paucity of data relating to long-term outcomes. Johnston et al reported that preterm infants ,31 weeks’ gestational age who received 10 doses of sucrose per 24 hours in the first week of life, had poorer neurologic outcomes compared with infants who received fewer sucrose doses.
- No differences in any safety outcomes after consistent use of sucrose for preterm infants over the first month of life were reported in another study.
- These are the only studies that have reported on longer-term outcomes in infants after repeated sucrose use the same argument applies to glucose, because many studies have shown that glucose, if sufficiently concentrated, also reduces pain in infants.

However, although basic science and clinical researchers and clinicians continue to address the knowledge and research gaps relating to analgesic effects and mechanisms of sucrose, we need to remain cognizant that untreated or poorly treated pain in fragile infants has well documented short-term adverse consequences and potential longer-term negative effects. Clinicians therefore have an ethical responsibility to minimize pain exposure; use sucrose appropriately for single painful procedures, along with other evidence-based strategies including NNS, kangaroo care, and breastfeeding when feasible, and monitor use and effectiveness of these strategies over short- and long-term periods. Importantly, clinicians' decisions must be based on the best evidence available and not swayed by single studies or pervasive myths.

Remaining knowledge and research gaps concern the mechanism of the effects of sucrose, determination of the best indicator or combination of indicators for assessing pain in infants, effectiveness and safety for repeated use in extremely preterm infants and critically ill infants, effectiveness for infants exposed to antenatal methadone or receiving postnatal opioid analgesics, and best dosing regimes.

Conclusions

Profound research concerning pain-reducing properties of sucrose has been conducted over the past 25 years, with indisputable evidence that small volumes significantly reduce behavioral responses and composite pain scores to painful procedures in new-born and young infants.
Recommendations for practice include using small volumes of sucrose for painful procedures only; avoiding use for calming irritable infants who are not undergoing procedures; giving solutions in aliquots over the duration of the procedure for prolonged procedures; avoiding use of.10 doses per 24 hours, especially during the first week of life; and using other effective strategies during painful procedures when feasible. Future research needs to address remaining areas of uncertainty with the ultimate aim of ensuring that no infant suffers unnecessary pain during painful procedures.

Breastfeeding or breast milk for procedural pain in neonates. Shah PS, Aliwalas LL, Shah VS. Cochrane Database of Systematic Reviews, 2006, Issue 3. Revision 2012

It is recommended to limit the sucrose administration to newborns younger than 32 weeks postmenstrual age, because there is a negative association between the frequent use of sucrose in this group of patients and neurologic development at a postmenstrual age of 38 weeks. Another effective and safe non-pharmacologic intervention for treating procedural pain is breast-feeding or giving supplemental breast milk. A randomized controlled trial with 101 term infants demonstrated even lower PIPP scores during a heel lance puncture when the infants were given breastfeeding during the procedure than when they were given sucrose.

Authors' conclusions

If available, breastfeeding or breast milk should be used to alleviate procedural pain in neonates undergoing a single painful procedure compared to placebo, positioning or no intervention.

- Administration of glucose/sucrose had similar effectiveness as breastfeeding for reducing pain.
- The effectiveness of breast milk for repeated painful procedures is not established and further research is needed.
- These studies should include various control interventions including glucose/ sucrose and should target preterm neonates
- The effectiveness of several forms of non-pharmacologic interventions to treat procedural pain in infants has been proven with a high level of evidence.
- The use of sucrose with or without nonnutritive sucking is the most frequently studied intervention.
- Animal research suggests that sweet solutions like sucrose modulate pain through opioid mechanisms.
- Little research has been done in human newborns, and the findings reported thus far have been ambiguous.

- The greatest analgesic effect occurs when sucrose is administered ~2 minutes before the painful stimulus. The analgesic effect lasts~4 minutes
- The combination of sucrose with nonnutritive sucking provides better pain relief than both methods separately
- Sucrose is recommended extensively for pain relief in preterm infants and has shown to be highly effective and safe for single procedures. Sweet taste solutions seem to trigger endogenous opioid and non-opioid pathways.
- Facilitated Tucking (FT) is described as holding the infant by placing a hand on his or her hands and feet and by positioning the infant in a flexed midline position while in either a side-lying, supine, or prone position. This technique provides the infant with support and the chance to control his or her own body. Several studies reported that FT stabilizes behavioral and physiologic states during single heel sticks and endotracheal suctioning, reducing the infant's stress in coping with pain.
- Although current evidence supports the effectiveness of NPIs for a single painful procedure, there is little research examining their effectiveness across repeated painful procedures.

Management of pain in late preterm (2012)

It was concluded that giving breast milk during a painful procedure is a non-invasive, safe and natural method for pain relief in late preterm infants. It can not be concluded that breast milk has a superior analgesic effect compared with sucrose in late preterm infants during a heel lance procedure, as was suggested for term newborns in preceding trials. It is recommended the use of expressed breast milk or sucrose if late premature neonates receiving a heel lance experience difficulties with breastfeeding.

Sucrose for analgesia in newborn infants undergoing painful procedures
Stevens B, Yamada J, Lee GY, Ohlsson A. Cochrane database of reviews, 2013

Sucrose is safe and effective for reducing procedural pain from single events. An optimal dose could not be identified due to inconsistency in effective sucrose dosage among studies. Further investigation on repeated administration of sucrose in neonates and the use of sucrose in combination with other non-pharmacological and pharmacological interventions is needed. Sucrose use in extremely preterm, unstable, ventilated (or a combination of these) neonates needs to be addressed. Additional research is needed to determine the minimally effective dose of sucrose during a single painful procedure and the effect of repeated sucrose administration on immediate (pain intensity) and long-term (neurodevelopmental) outcomes.

Plain language summary

Sucrose for analgesia in newborn infants undergoing painful procedures:

- Healthcare professionals need strategies to reduce newborn babies' pain. Sucrose (sugar) provides pain relief for newborn babies having painful events such as needles or heel pricks.
- Pain medicine is usually given for major painful events (such as surgery), but may not be given for more minor events (such as taking blood or needles). Pain medicine can be used to reduce pain, but there are several other methods including sucking on a pacifier (dummy) with or without sucrose.
- Researchers have found that giving sucrose to babies decreases their crying time and behaviors such as grimacing.
- More research is needed to determine if giving repeated doses of sucrose is safe and effective, especially for very low birth weight infants or infants on respirators.
- Although the authors of the Cochrane systematic review of sucrose analgesia in newborn infants could not establish an optimal sucrose dose, only small volumes are required, such as 0.1 to 1 mL or~0.2 to 0.5 mL/kg.

- Researchers and clinicians should take into account tailoring doses based on context in which sucrose is to be used, including gestational and postnatal age of the infant, severity of illness, and the painful procedure being performed.
- Finally, a consensus on the definition of "pain" in infants may greatly assist pain researchers to use consistent terms and to use consistent outcome measurements in future studies.

Conceptual model of use of analgesia in Neonatal intensive care unit

Patient related factors
- Ability to feel and express pain;
- Biological profile (age, gender, birth weight)
- painful situations occurrence

Professional related factors
- Individual factors (sensibility, empathy, motivation)
- Technical factors (knowledge of assessment methods, drug availability and their adverse effects

Services related factors
- Established clinical protocols, compliance with them
- Availability of resources, material and human

Sucrose and non nutritive sucking in the light of Baby Friendly Hospital Initiative
- Do some pain relief methods interfere with the successful breastfeeding? (sucrose, dummy, non-nutritive sucking)
- What is the cost-benefit ratio in such cases?
- Do these procedures comply with BFH standards?
- How will the external assessors react in such situations?
- What is the method of choice for neonatal pain assessment?
- Does it need special training?

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