Review: PAIN RELIEF IN NEONATES - ABOUT TIME!

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PAIN RELIEF IN NEONATES—ABOUT TIME!

...It seems unbelievable how long it took the medical community to realize that newborns also feel pain.

It is the basic right of every individual, irrespective of age or size, to have alleviation of pain. Pain in newborn infants is a ubiquitous phenomenon. Newborns in the hospital setting are routinely subjected to painful procedures from very early in their lives. All newborns will experience iatrogenic pain in the first days of life, commencing with vitamin K injection and blood collection for sugars, bilirubin or lately metabolic screening before discharge from the hospital. Neonates admitted to present day neonatal intensive care units (NICU) are constantly exposed to pain, discomfort or noxious stimuli of variable intensity for a variety of reasons. These include major surgical procedures, needle pricks for blood drawing and cannulations.

All newborns will experience iatrogenic pain in the first days of life, commencing with vitamin K injection and blood collection for sugars, bilirubin or lately metabolic screening before discharge from the hospital.

The painful situation may be short lived or chronic as in the case of necrotising enterocolitis and prolonged ventilation. Even apparently innocuous care giving procedures like diaper changes, daily weighing and removal of adhesive tape results in noxious stimuli. All these events, especially in preterm infants individually or cumulatively, result in adverse sequelae in the form of death, poor neurologic outcomes, abnormal somatization and response to pain later in life. Both humanitarian considerations and scientific principles favor improved management strategies to prevent pain and stress whenever possible and, when discomfort is unavoidable, to provide prompt and appropriate treatment.

Neonatal pain myths (1)

Evaluation of pain is considered difficult in neonates and young infants as pain has been considered a subjective phenomenon. Early studies of neurologic development concluded that neonatal responses to painful stimuli were decorticate in nature and that perception or localization of pain was not present. Furthermore, because neonates may not have memories of painful experiences, they were not thought capable of interpreting pain in a manner similar to that of adults. On a theoretical basis, it was also argued that a high threshold of painful stimuli may be
adaptive in protecting infants from pain during birth. These traditional views have led to a widespread belief in the medical community that the human neonate or fetus may not be capable of perceiving pain.

**Definitions of Pain**

The International Association of the Study of Pain (IASP) defines that pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. According to the IASP “Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life”. However, this definition of pain by the IASP does not apply to humans incapable of self-reporting pain e.g. newborn and older infants. Anand and coworkers state that the “relationships between feeling pain and reporting pain are highly context-dependent”. This new perspective in pain definition has dramatically changed the way pain is quantified in newborns and infants (Table 1).

**Table 1. Pain definitions as applied to neonates**

<table>
<thead>
<tr>
<th>Pain</th>
<th>An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (note that the inability to communicate verbally or nonverbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>An actual or perceived threat that leads to a disturbance of the dynamic equilibrium between an organism and its environment</td>
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<tr>
<td>Stress Response</td>
<td>A response based on the individual’s perception of control and predictability of its environment, generally characterized by changes in four primary domains: endocrine, autonomic, immunological, and behavioral</td>
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<tr>
<td>Analgesia</td>
<td>Absence of pain in response to stimulation that would normally be painful.</td>
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<tr>
<td>Anesthesia</td>
<td>Achieving unconsciousness (lack of implicit recall and lack of awareness of surgery), analgesia, suppression of autonomic responses to noxious stimuli, and immobility</td>
</tr>
<tr>
<td>Pain control Sedation</td>
<td>Diminution in the intensity or duration of pain or both. A medically controlled state of depressed consciousness or unconsciousness from which a patient may be aroused, with or without the loss of protective airway reflexes, and a decreased ability to respond appropriately to verbal or painful stimuli</td>
</tr>
</tbody>
</table>

Since the 1980’s it has become increasingly evident that the fetus and newborn perceives and responds to pain. Pain can be acute, established, or chronic. It can also be classified as physiologic, inflammatory, neuropathic, or visceral, with each of these categories further divided according to the degree of severity. Once pain occurs, a series of sequential neurobiological changes take place involving activation and modulation of the pain system. If pain is prolonged or repetitive, the
developing pain system may be modified permanently, resulting in altered processing at the spinal and supraspinal levels\(^5\). Over the last several years, evidence from both clinical and preclinical research has shown that newborns are more sensitive to pain than older infants, children, and adult.

All infants experience pain, but for normal newborns the painful experience is limited to a heel lance or venepuncture for metabolic screening or intramuscular injection of vitamin K or vaccines. For preterm or ill term neonates, the experience is very different. They are exposed to repeated procedural pain\(^3\) extensive tissue damage resulting from surgery, or the invasiveness of endotracheal tubes placed for mechanical ventilation. Thus, at a time when most healthy term infants are learning about their environment and preterm infants are growing in the protective uterine environment, \(8\%\) of neonates are coping with pain that, if left untreated, will interfere with normal growth and development\(^6\). Multiple sources of clinical and experimental evidence support the need for providing adequate analgesia / anesthesia for newborns who undergo invasive procedures (medical, surgical, diagnostic, and therapeutic) or develop conditions associated with a significant component of pain (eg, skin burns, necrotizing enterocolitis)\(^7\).

**Nociception**

This is defined as the ability to feel pain caused by the stimulation of a nociceptor. Nociceptors are pain receptors in the somatic and visceral organs that can detect mechanical, thermal or chemical changes above a set threshold. Once stimulated, a nociceptor transmits a signal along the spinal cord to the brain. Nociception triggers a variety of autonomic responses and may also result in a subjective experience of pain in conscious beings. It comprises of four stages: transduction, transmission, modulation and perception as shown in figure 1.
Thus it appears that nociceptive activity, rather than pain, should be discussed with regard to the neonate, because pain is a sensation with strong emotional associations. The focus on pain perception in neonates and confusion over its differentiation from nociceptive activity and the accompanying physiologic responses have obscured the mounting evidence that nociception is important in the biology of the neonate. This is true regardless of any philosophical view on consciousness and "pain perception" in newborns. In the literature, terms relating to pain and nociception are used interchangeably and in this review the two will be considered the same.

**Development of nociception in the fetus and newborn:**

The neural pathways for nociception as shown above are traceable in the newborn and the density of pain fibres in the skin are similar to that of adults. Electron microscopy and immunocytochemical studies show that the development of various types of cells in the dorsal horn (along with their laminar arrangement, synaptic interconnections, and specific neurotransmitter vesicles) begins before 13 to 14 weeks of gestation and is completed by 30 weeks. Lack of myelination has been used as an index of immaturity and often cited as reason for neonates to be incapable of feeling pain. But even in the peripheral nerves of adults, nociceptive impulses are carried through unmyelinated (C-polymodal) and thinly myelinated (A-delta) fibers. Moreover, pain pathways to the spinal cord, brain stem and thalamus are completely myelinated by 30 weeks; whereas the thalamocortical pain fibers in the posterior limb of the internal capsule and corona radiata are myelinated by 37 weeks. Infants as young as 25 weeks post menstrual age (PMA) have been shown to have cortical responses to noxious stimuli. Painful and tactile stimuli elicit specific haemodynamic responses in the somatosensory cortex, implying
conscious sensory perception in preterm neonates. Somatosensory cortical activation occurs bilaterally following unilateral stimulation and these changes are more pronounced in male neonates or preterm neonates at lower gestational ages. Near infrared spectroscopy studies in preterm infants from 28-36 weeks gestation undergoing tactile, non-noxious and painful stimuli (venepuncture) found that somatosensory cortical activation occurs bilaterally following unilateral stimulation. These suggest that neonates do have the required neuronal connections to experience the affective components of pain.

**Pain neurotransmitters**

Various substances have been identified for transmission and control of pain but substance P is the one best investigated in babies in whom significant levels were demonstrated. Endogenous opioids are released in the human fetus at birth and in response to fetal and neonatal distress.

### Changes during Pain

**Physiological**

Changes in heart rate, oxygenation and palmar sweating have been observed in neonates undergoing painful clinical procedures. The magnitude of changes in the heart rate was related to the intensity and duration of the stimulus and to the individual temperaments of the babies. Large fluctuations in oxygenation above and below an arbitrary "safe" range of 50 to 100 mm Hg have been observed during various surgical procedures in neonates. Tracheal intubation in awake preterm and full-term neonates caused significant hypoxemia together with increases in arterial blood pressure and intracranial pressure. The increases in intracranial pressure with intubation were abolished in preterm neonates who were anesthetized. In addition, infants' cardiovascular responses to tracheal suctioning were abolished by opiate-induced analgesia.

**Hormonal and Metabolic**

Plasma renin activity increased after venepuncture in full-term neonates. In preterm neonates receiving ventilation therapy, chest physiotherapy and endotracheal suctioning there were large increases in plasma epinephrine and norepinephrine; this response was decreased in sedated infants. In neonates undergoing circumcision without anesthesia, plasma cortisol levels increased markedly during and after the procedure. Preterm and full-term neonates who underwent surgery under minimal anesthesia documented a marked release of catecholamines, growth hormone, glucagon, cortisol, aldosterone, and other corticosteroids, as well
as suppression of insulin secretion. These results indicated that the nociceptive stimuli during surgery performed with minimal anesthesia were responsible for the massive stress responses of neonates.

**Consequences of pain**

**Medical**

Pain may worsen already compromised physiological states like hypoxia, hypercarbia, acidosis, hyperglycemia or respiratory distress. Babies who received good peri-operative analgesia showed stable course and faster recovery.

**Neurodevelopmental**

Preterm infants <1000g who have been exposed to repeated noxious stimuli are less responsive to painful stimuli at 18 months of age but at 10 years of age rate medical pain higher than their normal weight counterparts.

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**General Principles for Prevention of Pain in Newborns**

1. Neuroanatomical components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate.

2. Pain in newborns is often unrecognised and under treated. Neonates do feel pain, and analgesia should be prescribed when indicated during medical care.

3. If a procedure is painful in adults it should be considered painful in newborns, even if they are preterm.

4. Compared with older age groups, newborns may experience a great sensitivity to pain and are more susceptible to the long-term effects of painful stimulation.

5. Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality.

6. Sedation does not provide pain relief and may mask the neonate’s response to pain.

7. A lack of behavioural responses (including crying and movement) does not necessarily indicate a lack of pain.

8. Severity of pain and the effects of analgesia can be assessed in the neonate. Health care professionals have the
9. Treatment should include the appropriate use of environmental, behavioural and pharmacological interventions.

10. Environment should be as conducive as possible to the well being of the neonate and family.

11. Education and validation of competency in pain assessment and management for all neonatal doctors and nurses, is a professional responsibility of clinical units.

**Guidelines for newborn pain:**

All neonatal units are required to have a neonatal pain control program which emphasizes the following\(^{(20)}\). See Figure 2

1. Providing routine assessments to detect neonatal pain
2. Reducing the number of painful procedures
3. Preventing or treating acute pain from bedside invasive procedures
4. Anticipating and treating postoperative pain following surgery
5. Avoiding prolonged or repetitive pain and stress during neonatal intensive care

**Pain Assessment Scales: The Fifth Vital Sign\(^{(21)}\)**

Selecting the most appropriate tool for evaluating neonatal pain is essential to its management. Documentation of pain is also crucial as there can be variation in pain perception in babies between various caregivers. Many pain scoring tools exist and a few that are used commonly are given in Table 2.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Variables Included</th>
<th>Type of Pain</th>
<th>Psychometric Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPP (Premature Infant Pain Profile)</td>
<td>Heart rate, oxygen saturation, facial actions; takes state and gestational age into account</td>
<td>Procedural, postoperative (minor)</td>
<td>Reliability, validity, clinical utility well established</td>
</tr>
<tr>
<td>NIPS (Neonatal Infant Pain Score)</td>
<td>Facial expression, crying, breathing patterns, arm and leg movements, arousal</td>
<td>Procedural</td>
<td>Reliability, validity</td>
</tr>
<tr>
<td>NFCS (Neonatal Facial Coding System)</td>
<td>Facial actions</td>
<td>Procedural</td>
<td>Reliability, validity, high degree of sensitivity to analgesia</td>
</tr>
<tr>
<td>N-PASS (Neonatal Pain, Agitation, and Sedation Scale)</td>
<td>Crying, irritability, behavioral state, facial expression, extremity tone, vital signs</td>
<td>Postoperative, procedural, ventilated</td>
<td>Reliability, validity, includes sedation end of scale, does not distinguish pain from agitation</td>
</tr>
<tr>
<td>CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness)</td>
<td>Crying, facial expression, sleeplessness, requires oxygen to stay at &gt;95% saturation, increased vital signs</td>
<td>Postoperative</td>
<td>Reliability, validity</td>
</tr>
<tr>
<td>COMFORT Scale</td>
<td>Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure</td>
<td>Postoperative, critical care, developed for sedation, recently validated for postoperative pain in 0- to 3-year-old infants</td>
<td>Reliability, validity, clinical utility</td>
</tr>
</tbody>
</table>

**Managing Pain in Neonates**

Multiple classes of drugs have been evaluated for the prevention and management of neonatal pain and stress, including opioid analgesics, local anesthetics, general anesthetics, sedatives, hypnotics, non-steroidal anti-inflammatory drugs (NSAIDs),
and sucrose. Although much research has been performed with these agents, many questions remain unanswered thus preventing the optimal use of these drugs in clinical practice. Pain in neonates can be managed by pharmacological and non-pharmacological interventions. Using analgesics to relieve short-term procedural pain in newborns is questionable because of these agents’ poor effectiveness and potential side effects. Non-pharmacological pain relief strategies are convenient, inexpensive, can be used without prescriptions, and are also well tolerated by infants. Procedural pain in newborns has been relieved by non-pharmacological interventions, such as nonnutritive sucking (NNS), swaddling, facilitated tucking, oral sucrose, breast feeding and skin-to-skin contact.

Behavioral approach

Good planning will result in avoiding redundant and unnecessary blood sampling. Care should be taken to avoid other routine care before a prick. Baby should be well swaddled and preferably held by the mother. If situation allows, procedure should be done during or after a feed. Eyes should be shielded from the glare of procedure lamps. After the procedure baby should be held and comforted till all cues of pain have disappeared.

Procedural pain relief

1. Non-nutritive sucking: Using a pacifier would not be a feasible option in India because of the obvious disadvantages. Pacifiers are dipped into sucrose solutions and given to babies to combine the synergism of non-nutritive sucking with sucrose analgesia.

2. Breast feeding: Babies in a comfortable position in the mother’s arms and breast feeding showed a statistically significant difference in the duration of crying during and after immunization. This has potential for use in well babies especially in immunization clinics.

3. Swaddling: or facilitative tucking of the infant ensures smooth execution of procedure but this is feasible only in certain infants and also depends on the procedure. Blood drawing from extremities would benefit by tucking.

4. Kangaroo care: Gray et al found that 10–15 minutes of kangaroo care between mothers and their term newborns reduced crying, grimacing, and heart rate during heel-stick procedures. Johnston et al showed that kangaroo care significantly reduced the acute pain responses of preterm neonates at 32–36 weeks’ and 28–32 weeks gestation.

Oral Sucrose for Neonatal Pain

Oral sucrose and other sweet tasting solutions have been used to promote calm and to reduce pain in infants over the past century, and even before this time. Prophet Mohammed, circa 632AD, recommended giving infants a well chewed date. Sugar solutions combined with alcohol, cocaine or opium, were given to infants from the
1840s to early 1900s. It was only in 1991 that Blass\textsuperscript{(42)} reported that 2mL 12% sucrose compared with 2mL water significantly reduced crying time during heel prick and circumcision.

The underlying mechanism of the analgesic effects of sweet tasting solutions is considered to be due to an orally mediated release of endogenous opioids. Calming effects were shown to be sweet taste, and not volume dependent, as small volumes of 0.2 mL sucrose were equally as effective as larger volumes of 0.6 mL and 1.0 mL. The effects of sweet taste peak at two minutes following administration, and persist for around five to eight minutes\textsuperscript{(41)} and are dependent on contact with the tongue, and not sweet ingestion directly via a nasogastric tube\textsuperscript{(42)}. Despite a large number of studies the mechanism of sweet taste and pain protection is unclear.

Guidelines for using oral sucrose in neonates:

**Indications for use:**

Any short-term procedural pain

1. Intravenous access
2. IM injection
3. Tape removal
4. Lumbar Puncture
5. Suturing
6. Arterial or venous blood sampling
7. Suctioning (i.e. nasal)
8. Urinary catheterization
9. Suprapubic tap
10. NG/OG insertion
11. Dressing change
12. Immunization
13. Retinopathy of Prematurity screening (ROP exam)
14. Chest tube insertion/removal

**Principles:**

1. 24% sucrose water when placed in the mouth, induces endogenous opioid production providing analgesia for minor procedures
2. Do not use more than 3 doses during a single procedure
3. Do not use for infants requiring ongoing pain relief (e.g. postoperative), since these infants will require acetaminophen or an opioid such as fentanyl or morphine.

4. It is important to realize that although an infant may still cry and show signs of pain when 24% sucrose water is used, studies have consistently shown that the sensation of pain and its negative effects will be diminished.

5. Analgesic effect of 24% sucrose water appears to be less effective after 46 weeks post conceptual age.

**Dosages:**

**ONLY oral administration/dose**

1. Intubated infants: 0.1ml
2. Infants < 1000 grams: 0.1ml
3. Infants <= 28 week gestation: 0.1ml
4. Infants that are NPO without NEC evidence: 0.1ml
5. Infants >= 1000 to 2000 grams: 0.1-0.2ml
6. Infants >= 2000 grams: 0.1-0.5ml

**Procedure:**

1. Using a 1ml sterile syringe or a dropper, draw up desired dose, place tip of syringe/dropper into the side of infant’s mouth onto anterior portion of the tongue and dispense solution slowly, allow the baby to savour the sweetness.

2. Wait 2 minutes and then perform intervention

3. For infants requiring occasional sucrose doses, nurse may draw dose directly from container (discarding when procedure is completed).

4. If giving more than 0.1ml, it may be best to give a portion of the dose 2 minutes prior to the procedure, and then the remainder of the dose intermittently, throughout the procedure.

**Contraindications:**

Use of 24% sucrose water is contraindicated in the following infants:

1. Infants at high risk for NEC
   a. Asphyxiated infants
   b. Infants with congenital heart disease that are not on established feeds
   c. Infants with feeding intolerance
   d. Infants without bowel sounds
2. Infants with esophageal atresia or tracheo esophageal fistula
3. Infants who are sedated or on other pain medications that are at risk for aspiration
4. Post-op infants who need to avoid excessive saliva production

**Documentation:**
1. Document on nursing flowsheet-medication area the amount and number of doses used.
2. Assess pain score using a suitable scale before, during, and after the procedure documenting on the nursing flowsheet.
3. Repeat doses may be administered during single procedure if indicated by pain score, not exceed 3 doses.

Concomitant use of various non-pharmacological techniques achieves greater clinical effectiveness than any one of these techniques used alone.

Some of the studies wherein oral sucrose was used in various painful proceedings in infants are summarized in Table 3.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Procedure</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Metrics used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abad 1996</td>
<td>28 preterm (29 - 36 weeks gestational age) infants, postnatal age 1-26 days</td>
<td>Venipuncture</td>
<td>2 ml of 12% sucrose via syringe (n = 8) 2 ml of 24% sucrose via syringe (n = 8) 2 ml of spring water via syringe (n = 12) 2 minutes prior to venipuncture</td>
<td>Time crying for 3 minutes after venipuncture Heart rate: pre solution, post solution, 5 minutes after venipuncture Mean 2% saturation and respiratory rate pre solution, post solution, 5 minutes after venipuncture</td>
<td>Median, IQR Mean, SEM Mean, SD</td>
<td>Significant group effect noted, (F (2, 25) = 4.26; p = 0.0256) for cry duration 3 minutes after venipuncture. Cry duration was significantly reduced in 2 ml of 24% (0.48 g) sucrose group (19.1 sec) compared to 2 ml of 12% (0.24 g) sucrose (63.1 sec) and water (72.9 sec) groups (p &lt; 0.05). Significant group effect for HR, F (2, 25) = 6.37, p = 0.006. Overall time effect, F (2, 50) = 14.15, p &lt; 0.001. No significant interaction between treatment group and time. Post hoc Tukey test showed that group receiving 2 ml of 12% sucrose (0.24 g) had lower HR compared to the 2 ml of 24% sucrose group (0.48 g) or water group at all three time points (pre solution, p = 0.048; post solution, p = 0.010; 5 minutes after, p = 0.007). No significant differences noted between groups over time for oxygen saturation and respiratory rates (no p-values reported).</td>
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<tr>
<td>Hameerghi 1996a</td>
<td>15 preterm (32-34 weeks gestation) infants greater than 24 hours of age</td>
<td>Heel Lance</td>
<td>1 ml of 25% sucrose via syringe into mouth 2 minutes prior to heel lance 1 ml of sterile water via syringe into mouth 2 minutes before heel lance (n=15, cross-over design)</td>
<td>Duration of first cry and % time crying 5 minutes after lance Heart rate (at -2, 0, 1, 3.5 minutes from heel lance) Behavioral scores (four facial expressions and the presence of cry) -2, 0, 1, 2, 3, 5 minutes Quality/intensity of sucking</td>
<td>Median, IQR Not reported Not reported</td>
<td>Significant decreases in total percentage of time crying over 5 minutes (median 6%, interquartile range 3.3 - 15.3) in the 1 ml of 25% (0.25 g) sucrose group compared with water group. [median 16.0%, range 5 - 27.3, p = 0.016]. Duration of first cry was significantly decreased in the 1 ml of 25% (0.25 g) sucrose group (median 12 sec, interquartile range 8 - 22 sec) compared to control group (median quartile 23 sec, range 15 - 45, p = 0.004). No significant differences in HR between groups, p-value not reported. Mean pain scores were significantly lower in the group receiving 1 ml of 25% sucrose (0.25 g) of sucrose at both 1 minute and 3 minutes after heel lance (p = 0.01, p = 0.03, respectively). The clinical interpretation of the quality of sucking was significantly more intense in the 1 ml of 25% (0.25 g) sucrose group than in the water group (p = 0.04).</td>
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<tr>
<td>Study</td>
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<tr>
<td>C</td>
<td>Rame-rghri 1968b: 60 term (37-42 weeks gestational age) 2-5 days old infants</td>
<td>Heel Lance</td>
<td>2 ml of 25% sucrose via syringe into mouth 2 minutes prior to heel lance (n = 15) 2 ml of 50% sucrose via syringe into mouth 2 minutes prior to heel lance (n = 15) 2 ml of commercial sweet tasting solution (Calpol) via syringe into mouth 2 minutes prior to heel lance (n = 15) 2 ml of sterile water via syringe into mouth 2 minutes prior to heel lance (n = 15)</td>
<td>Duration of first cry after lance % time crying over 3 minutes after heel lance Percent change in heart rate over 5 minutes (at -2.0, 1.3, 5 minutes from heel lance) Behavioral scores (four facial expressions and the presence of cry) -2, -1, 0, 1, 2, 3, 5 minutes</td>
<td>Median, IQR Not Reported Median, IQR</td>
<td>Significant decrease in duration of first cry and percent crying during 3 minutes after heel lance in the 2 ml of 25% (0.5 g) sucrose, 2 ml of 50% (1.0 g) sucrose and Calpol groups (p = 0.02) (data in graph form only) Significant increase in heart rate for 3 minutes after heel lance in water group compared with 2 ml of 50% (1.0 g) sucrose group and Calpol group, p = 0.000 Pain score (0-5) was significantly higher in water group (score = 2, range 1-5) than in other three groups. 2 ml of 50% (1 g) sucrose group (score = 0, range 0-3); 2 ml of 25% (0.5 g) sucrose group (score = 0, range 0-2); Calpol group (score = 0, range 0-1), p = 0.05</td>
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<tr>
<td>D</td>
<td>Blass 1997: 72 infants, 22-40 hours old</td>
<td>Heel Lance</td>
<td>2 ml of either of the following solutions: water 12% sucrose protein mixture 7% lactose dilute fat (coconut and soy oil) concentrated fat, fat and lactose mixture Ross Special Formula (RSF) (water, protein, lactose, fat) milk n=8 for all groups</td>
<td>Crying time (%) during blood collection and 1, 2 and 3 minutes after heel lance Mean % of crying time per minute at 1, 2 and 3 minutes after heel lance (recovery period)</td>
<td>Mean Proportions Graphically reported</td>
<td>Significantly less crying time during blood collection in the sucrose group (47%) compared to the water group (92%, p = 0.015)</td>
</tr>
<tr>
<td>E</td>
<td>Johnson 1997a: 85 preterm infants (25-34 weeks gestational age) 2 - 10 days of age</td>
<td>Heel Lance</td>
<td>0.05 ml of 24% sucrose via syringe into the mouth just prior to heel lance (n = 27) 0.05 ml of 24% sucrose via syringe into the mouth just prior to heel lance and simulated rocking 15 minutes prior to heel lance (n = 14) 0.05 ml of sterile water via syringe into the mouth just prior to heel lance and simulated rocking 15 minutes prior to heel lance (n = 24) 0.05 ml of sterile water via syringe into the mouth just prior to heel lance</td>
<td>HR at baseline and 3 x 30 second blocks Behavioral facial actions (Neonatal Facial Coding System-NFCS) at baseline and 3 x 30 second blocks</td>
<td>Not reported</td>
<td>Although heart rate increased across all phases of procedure F(3,59) = 2.94, p = 0.04, there was no significant differences noted between groups F: (3,59) = 0.666, p = 0.566 Decrease in percent facial action in 0.05 ml of 24% (0.012 g) sucrose alone group and combined 0.05 ml of 24% (0.012 g) sucrose and rocking group compared to water group, F (3, 150) = 2.765, p &lt; 0.02</td>
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<tr>
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<tr>
<td><strong>F</strong></td>
<td>102 healthy term infants, gestational age 37-42 weeks, median postnatal age 1.8 days (range 1-15 days)</td>
<td>Heel Lance</td>
<td>2 ml of 25% sucrose (n=35) 2 ml of human milk (n=33) 2 ml of sterile water (n=34) All solutions syringed onto anterior part of tongue for one minute Heel prick performed 2 minutes after intervention</td>
<td>Median cry time during 3 minutes after lance Percent change HR 1.2, 3 minutes after heel lance</td>
<td>Median, IQR</td>
<td>Significant decrease in crying times for 2 ml of 25% (0.5 g) sucrose group (median 36, interquartile Range 18-43) compared to human milk (median 62, interquartile range 29-107) and sterile water [(median 52, interquartile range 32-151), p = 0.0009]. Recovery time for crying was significantly reduced in 2 ml of 25% (0.5 g) sucrose group (median 72, interquartile range 48-110) compared to human milk (median 112, interquartile range 72-180) and sterile water [(median 124, interquartile range 82-180), p = 0.004]. Percent change in heart rate after heel lance was significantly lower in the group receiving 2 ml of 25% (0.5g) sucrose compared to groups receiving human milk and sterile water at 1, 2 and 3 minutes (p = 0.008, p = 0.01, p = 0.032, respectively).</td>
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<tr>
<td><strong>G</strong></td>
<td>30 preterm infants (GA 32-36 weeks, postnatal age &lt; 24 hours)</td>
<td>Heel Lance</td>
<td>25% sucrose solution (volume not reported) was given via syringe into the mouth or via NG tube 2 minutes prior to first heel lance (n = 15), and via the alternate route for the second heel lance within 48 hours Sterile water via syringe into the mouth or via NG-tube 2 minutes prior to first heel lance and for the second heel lance the alternate route within 48 hours (cross over design, n = 30)</td>
<td>%cry over 5 minutes after sampling Behavioral scores (four facial expressions and the presence of cry) at 1, 3, and 5 minutes after the lance for a total behavioral score</td>
<td>Median, IQR</td>
<td>Median percentage cry in intracutaneous water group was 22% (interquartile range 10.6-40) &amp; 27% (interquartile range 11.6-47) for infants in NG tube water group. Median percentage cry in intracutaneous 25% sucrose group was 8% (interquartile range 0.5-15) and 18.3% (interquartile range 11.6-41.6) for NG-tube 25% sucrose group. Significant reduction in crying time (p = 0.006) noted in the 25% sucrose group compared with water group when infants received 25% sucrose intracutaneously, not via NG-tube route. For infants in 25% sucrose group, significant reduction in crying time noted (p = 0.008) when solution given intraorally compared to NG-tube route Behavioral scores for the intracutaneous water group was 9 (interquartile range 6-12) and 10 (interquartile range 6-14) for N-G tube water group. Behavioural scores for intracutaneous 25% sucrose group was 5 (interquartile Range 3-6) and 9 (interquartile range 8-10) for NG-tube sucrose group. Significant reduction in behavioral scores noted in 25% sucrose group (p = 0.032) compared with water group when infants received 25% sucrose intracutaneously but not via NC route. For infants in 25% sucrose group, there was significant reduction in behavioral score, p = 0.001 when solution was given intraorally compared to via NG tube.</td>
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<td>Study</td>
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<td>Johnston</td>
<td>48 preterm neonates mean gestational age of 31 weeks (range 25-34 weeks) within 10 days of birth</td>
<td>Heel Lance</td>
<td>0.05 ml of 24% sucrose as a single dose, followed by 2 doses of sterile water (n=15) 3 doses of 0.05 ml of 24% sucrose (n=17) 3 doses of 0.05 ml of sterile water (n=16) given by syringe to anterior surface of the tongue at: 2 minutes prior to heel lance just prior to lancing 2 minutes after lancing</td>
<td>PIPP scores in five 30 second blocks</td>
<td>Reported Means, SD</td>
<td>Statistically significant difference between groups (F = 0.143, p &lt; 0.0001) for mean PIPP scores. Post-hoc analysis found significantly lower PIPP scores with repeated doses of 0.05 ml of 24% (0.012 g) sucrose compared to placebo groups across all blocks of time, p &lt; 0.05. PIPP scores for repeated doses of 0.05 ml of 24% (0.012 g) sucrose were significantly lower compared to single doses of 0.05 ml of 24% (0.012 g) sucrose (8.25 vs. 6.25) only at last block of time, p &lt; 0.05. PIPP scores for single doses of 0.05 ml of 24% (0.012 g) sucrose compared to placebo showed trend towards statistical significance in favour of 0.05 ml of 24% (0.012 g) sucrose (F = 3.485, p = 0.07)</td>
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<td>Isik</td>
<td>113 healthy term newborns gestational ages between 37 and 42 weeks, median postnatal age= 20 days (range 2-5 days)</td>
<td>Heel Lance</td>
<td>2 ml of 30% sucrose (n=28) 2 ml of 10% glucose (n=29) 2 ml of 30% glucose (n=28) 2 ml of distilled water (n=28) syringed into the anterior third of the tongue for 1 minute 2 minutes prior to heel lance</td>
<td>Mean cry time during 3 minutes after lancing Mean maximum heart rate 3 minutes from heel lance Mean recovery time for heart rate % change in heart rate at 1, 2, 3 minutes after heel lance</td>
<td>Reported means, SD Reported Means and SEM</td>
<td>Infants who received 2 ml of 30% (0.6 g) sucrose (mean crying time of 51 seconds) cried significantly less than those who received 30% glucose (mean crying time of 35 seconds). 10% glucose (mean crying time of 103 seconds) or sterile water (mean crying time of 105 seconds), p = 0.02. No significant difference between groups with respect to maximum heart rate after heel lance, (p = 0.71), or mean recovery time, (p = 0.09). No significant difference found in percent change in heart rate at 1 or 3 minutes after heel lance, (p = 0.14, p = 0.53), respectively. At 2 minutes after heel lance, percent change in heart rate favoured group receiving sucrose (p = 0.05) compared to other groups</td>
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<tr>
<td>Storm</td>
<td>48 preterm, median gestational age of 32 wk, median postnatal age of 14 days</td>
<td>Heel Lance</td>
<td>2 ml of 15% sucrose, n = 12 1 ml of 25% sucrose, n = 12 milk via NG tube n = 12 milk via NG tube, + 25% sucrose, n = 12 All infants were given water prior to a second heel lance</td>
<td>Differences in crying time for pre heel lance to heel lance procedure Changes in heart rate from pre-heel lance to heal lance procedure Difference in skin conductance from pre heel lance to heel lance procedure</td>
<td>Not reported</td>
<td>Significantly less crying in infants receiving 1 ml of 25% sucrose (p &lt; 0.05) and milk (1 ml of 25% sucrose (p &lt; 0.05). No significant differences between groups in changes in heart rate from pre-heel lance to heel lance procedure (no p-value reported). No statistically significant smaller increase in skin conductance variables compared to their water control session (p-value not reported).</td>
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<td>Study Source</td>
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<tr>
<td>Gomnally 2001</td>
<td>94 term newborns, mean gestational age 39.4 weeks on 2nd or 3rd day of life</td>
<td>Heel Lence</td>
<td>No holding and sterile water given by pipette (n=21) No holding and 0.250 ml of 24% sucrose solution given by pipette (n=22) Holding and 0.250 ml of 24% sucrose solution by pipette (n=22) All solutions given 3 times at 30 second intervals.</td>
<td>% time crying 1, 2, 3 minutes after heel lence Mean HR pre-intervention, 1, 2, 3 minutes after heel lence, Mean vagal tone index pre-intervention, 1, 2, 3 minutes after heel lence Pain concentration scores for facial activity pre-intervention, 1, 2, 3 minutes after heel lence</td>
<td>Not reported</td>
<td>Crying decreased over time [F(2,60) = 10.0, p &lt; 0.001] but no significant interaction noted for time with holding, taste, or holding and taste. Effect of taste on crying was significant [F(1,81) = 4.1, p &lt; 0.05] in favour of 0.25 ml of 24% (0.18 g) sucrose. Effect of holding not statistically significant [F(1,81) = 3.0, p = 0.09]. No statistically significant interaction between taste and holding to reduce crying [F(1,81) = 0.80, p = 0.37]. Effect of combined interventions was additive. Although no significant differences in mean heart rate due to holding or sucrose as main effects, there was significant interaction between holding and taste [F(1,81) = 8.99, p &lt; 0.004], indicating synergistic effect that was also dependent on pre-intervention heart rate [F(1,81) = 9.23, p &lt; 0.004]. No significant main effects noted for vagal tone, as with heart rate, effect of vagal tone was dependent on pre-intervention vagal tone for both holding and taste interventions [F(1,81) = 4.82, p &lt; 0.03]. Pre-intervention levels interacted to decrease heart rate and vagal tone in infants who had higher rates before interventions. Pain concentration scores measuring facial expressions of pain decreased over time [F(1,65) = 28.5, p &lt; 0.001]. Only the effect of holding reduced pain scores [F(1,65) = 5.6, p &lt; 0.02]. No difference as to whether infant received sucrose (taste main effect [F(1,65) = 0.17, p = 0.66].</td>
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<td>Mitchell 2004</td>
<td>30 preterm infants Water group: mean gestational age 27.3 weeks, mean postnatal age 8.2 weeks Sucrose group: mean gestational age 26.5 weeks, mean postnatal age=8.5 weeks</td>
<td>Eye Exam for retinopathy</td>
<td>Pacifier and 3 doses of 0.1 ml sterile water via syringe into the mouth (n=15). Pacifier and 3 doses of 0.1 ml 24% sucrose via syringe into the mouth (n=15) 1st dose given 1.5 minutes before local anesthetic eye drops. 2nd dose right at placement of the eye speculum. 3rd dose 120s after 2nd drop. All infants received proparacaine hydrochloride 0.5% eye drops and were swaddled before the eye examination</td>
<td>PIPP at baseline, at eye drop instillation, at examination of left eye and at 30s, 60s, 90s and 120s after the exam</td>
<td>Mean, SEM</td>
<td>Statistically significant differences in mean PIPP scores were found between sucrose group (mean 8.8, Mean SE 0.7) and the water group (mean 11.4, Mean SE 0.5) during the eye examination p = 0.0077. However this was not sustained after the eye examination.</td>
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<td>M</td>
<td>190 preterm and term infants, mean gestational age of 33.7 weeks, under 7 days post natal age</td>
<td>Heel Lance</td>
<td>0.5 ml of 24% sucrose via syringe to the anterior surface of the tongue followed by pacifier (n=64) 0.5 ml 24% sucrose without pacifier (n=62) 0.5 ml sterile water with pacifier (n=64) 2 minutes prior to heel lance</td>
<td>PIPP scores at 30 and 60 seconds after heel lance</td>
<td>Reported Means, SD</td>
<td>Statistically significant difference in mean PIPP scores at both 30 seconds (F = 8.23, p &lt; 0.001) and 60 seconds (F = 6.49, p &lt; 0.001) in favour of 0.5 ml of 24% (0.12 g) sucrose group and 0.5 ml of 24% (0.12 g) sucrose with pacifier group. Posthoc Tukey tests showed infants who received sucrose and pacifier had significantly lower PIPP scores after heel lance at 30 seconds (mean 8.16, SD 3.24) compared to infants receiving sucrose alone (mean 9.77, SD 3.04, p = 0.007) and water with pacifier (mean 10.19, SD 2.67, p &lt; 0.001). At 60 seconds after heel lance, PIPP scores were significantly lower for 0.5 ml of 24% (0.12 g) sucrose with pacifier group (mean 8.78, SD 4.03) compared to the 0.5 ml of 24% (0.12 g) sucrose alone group (mean 11.20, SD 3.25, p = 0.005) and water with pacifier group (mean 11.20, SD 3.47, p = 0.007). No significant differences in PIPP scores found between 0.5 ml of 24% (0.12 g) sucrose alone group or water with pacifier group at both follow-up times</td>
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<td>N</td>
<td>57 term infants, mean age at time of procedure 30-43 hours</td>
<td>Circumcision</td>
<td>Gomco method and pacifier dipped in water (n=14) Gomco method and pacifier dipped in 24% sucrose (n=14) Mogen method and pacifier dipped in 24% sucrose (n=15) Mogen method and pacifier dipped in 24% sucrose (n=14) All infants had EMLA cream applied 1-3 hours before procedure</td>
<td>Time spent crying during procedure Time spent grooming Procedure stages: 1) Table - Restraint, 2) Restraint - Forceps, 3) Forceps - Excision, 4) Excision - Unrestraint 5) Unrestraint - End</td>
<td>Median and Means, Graphically Not reported</td>
<td>Cumulative mean time crying for forceps to unrestraint interval in the Gomco-sucrose group was 56 seconds (median = 76 sec) in the Gomco-water group (p = 0.0001). Crying time in Mogen-sucrose and Mogen-water groups were not significantly different. Overall, mean crying time significantly decreased in infants treated with sucrose compared to infants treated with water (p = 0.0001). Significantly less time spent grooming in the Gomco-sucrose group compared to the Gomco-water group (p = 0.0001). No significant differences between Mogen-sucrose and the Mogen-water groups. Overall, mean time grooming was significantly reduced in infants treated with sucrose compared to infants treated with water (p = 0.0001).</td>
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<td>Study</td>
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<td>Acharya 2004</td>
<td>39 preterm neonates (mean 30.5 weeks gestational age), mean postnatal age 27.2 days</td>
<td>Venipuncture</td>
<td>2 ml of 25% (0.5g) sucrose administered by syringe into front of infant’s mouth over 2 minutes. 4 minutes prior to venipuncture</td>
<td>Duration of first cry (beginning to end of first cry); total duration of crying (onset of first cry to cessation of all crying) Mean change in heart rate from Pre-procedure, procedure and post-procedure phase of venipuncture Mean SaO2 (%) at pre-procedure, procedure and post-procedure Neonatal Facial Coding System (NFCS) changes across 3 phases of venipuncture</td>
<td>Mean SD</td>
<td>Mean duration of first cry lower in infants who received sucrose [18.5 (24.4) seconds] compared to infants who received water [52.3 (56) seconds] (estimated Treatment effect =33.7, ( p &lt; 0.001 )). Mean total duration of crying was significantly lower in infants who received sucrose [31.9 (41.9) seconds] compared to infants who received water [7.2 (66.7) seconds] (estimated treatment effect = 40.6, ( p &lt; 0.001 )). Mean change in heart rate from pre-procedure to procedure was lower in the infants receiving sucrose compared to water (estimated treatment effect = 4.16, ( p = 0.038 )). No significant differences between groups with respect to changes in oxygen saturation from pre-procedure to procedure phase (( p = 0.17 )). Changes in mean NFCS scores were significantly lower in the sucrose group compared to water group from pre-procedure to procedure phase (estimated treatment effect = 1.08, ( p = 0.013 )) and between the pre-procedure and post-procedure phase (estimated Treatment effect = 2.39, ( p &lt; 0.001 )).</td>
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<tr>
<td>Stevens 2005</td>
<td>66 preterm infants (26-30 weeks), postnatal age 72 hours</td>
<td>Heel lance</td>
<td>Standard care-positioning and swaddling (n=21) Standard care-positioning and swaddling and 0.1 ml sterile water via syringe into the mouth immediately followed by a pacifier 2 min prior to painful procedure (n=20) Standard care-positioning and swaddling and 0.1 ml 24% sucrose via syringe into the mouth immediately followed by a pacifier 2 min prior to painful procedure (n=22) These interventions were given every time there was a painful procedure during the first 28 days of life.</td>
<td>PIPP at day 7, 14, 21, 28 at routine heel lance</td>
<td>Not reported</td>
<td>Significant main effect of group (( p = 0.03 )) with differences occurring between the sucrose+ pacifier group and standard care group: t(50) = -2.54, ( p = 0.01 ). Mean PIPP scores were generally higher in the standard care group. No significant main effect of time. Adverse Effects: No group differences for adverse events, clinical outcomes or neurobiological risk status.</td>
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<td>Ogawa 2005</td>
<td>100 healthy full term infants Heel lance group gestational age (GA) 40 weeks range 38-42 weeks Heel lance + sucrose group GA 39 weeks range 37-41 weeks Venipuncture group GA 39 weeks range 37-41 weeks Venipuncture + sucrose group GA 39 weeks range 37-41 weeks</td>
<td>Heel lance (HL) Or Venipuncture (VP)</td>
<td>Heel lance + 0.1 ml of sterile water on infant’s tongue vs syringe 2 min before procedure (n=25) Heel lance + 0.1 ml of 50% sucrose on infant’s tongue vs syringe 2 min before procedure (n=25) Venipuncture + 0.1 ml of sterile water on infant’s tongue vs syringe 2 min before procedure (n=25) Venipuncture + 0.1 ml of 50% sucrose on infant’s tongue vs syringe 2 min before procedure (n=25)</td>
<td>Duration of first cry (sec), First crying time/total procedure time (%) and the ration of crying: no crying NFCS score 1 min after oral administration of water/sucrose (m), disinfection of skin before HL or VP (m), during skin puncture (m), during blood sampling (m), during compression to stop bleeding (m), during application of plaster (m) and 1 min after application of plaster (m)</td>
<td>Reported Medians, range and Mean, SD Reported in graph form, median and interquartile range</td>
<td>Significant reduction in duration of first cry in heel lance group given sucrose compared to heel lance alone, p &lt;0.05. Significantly reduced NFCS scores in sucrose group during heel lance (median 47, interquartile range 31-60) and during compression to stop bleeding (median 32, interquartile range 8-54) compared to the water group (median 58 interquartile range 54-65, median 52, interquartile range 41-61 respectively) (p &lt; 0.01). Sucrose did not significantly reduce NFCS scores during or after venipuncture.</td>
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<td>Gal 2005</td>
<td>23 neonates, gestational age 24-29 weeks, postnatal age 28-53 days</td>
<td>Eye examination for Retinopathy of Prematurity (ROP)</td>
<td>2ml of sterile water 2 ml of 24% sucrose (n=23, crossover design) Mydriatic eye drops (Phenylephrine HCl 1%, cyclopentolate HCl 0.2%) and local anaesthetic eye drops (proparacaine HCl 0.5%), 2 drops given to both groups prior to exam</td>
<td>Decreased oxygen saturation by &gt;10% pre-examination, at eye speculum insertion &amp; post-exam. PIPP scores at 5 min &amp; 1 min pre-exam, eye speculum insertion, &amp; 1 min &amp; 5 min post-exam.</td>
<td>Percentage of population Means, SD reported</td>
<td>No significant difference in oxygen saturation between water group and sucrose group. PIPP score at the eye exam significantly lower in the group given sucrose (mean 6.3, SD 4.5) compared to the placebo group (mean 10.5, SD 4.0, p = 0.31); however, this effect was not sustained at 1 and 5 min post-exam.</td>
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<td>Rogers 2006</td>
<td>80 infants less than or equal to 90 days of age requiring bladder catheterization Subgroup analysis performed: infants 1-30, 31-60, and 61-90 days of age</td>
<td>Bladder Catheterization</td>
<td>2ml of sterile water via syringe 2 min before procedure (n=40) 2 ml of 24% sucrose via syringe 2 min before procedure (n=40)</td>
<td>Percentage of subjects crying at maximal insertion (%)</td>
<td>Percentage</td>
<td>Subgroup analysis of infants (1-30 days) receiving sucrose were significantly less likely to cry during maximal catheter insertion compared to water group (28.6%, vs. 78.6%, p = 0.006).</td>
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<td>Grabeksi 2005</td>
<td>32 preterm infants, mean gestational age 28 weeks, mean postnatal age 50.8 days</td>
<td>Eye exam for retinopathy of prematurity</td>
<td>Sterile water delivered either directly into the mouth or via a nipple 2 min prior to eye exam (n=16) Doses were adjusted by weight &lt;1kg = 0.5 cm³ (0.12g); 1.1-1.5kg = 0.6 cm³ (0.24g); 1.5-2kg = 1.5 cm³ (0.36g); &gt;2kg = 2.0 cm³ (0.48g). All infants were swaddled and offered a pacifier. All infants received tropicamid 0.6% and phenylephrine 2.5% eye drops approx. 30 min before exam. Topical tetracaine was instilled into the eyes just prior to the exam.</td>
<td>% of the eye exam the infant spent crying Mean HR at baseline, posteye drop instillation, post-study drug, during eye exam and post eye exam* RR and oxygen saturation at baseline, post eye drop instillation, post-study drug, during eye exam and post eye exam* PIPP at baseline, during eye exam, post eye exam* *measures are taken at 1 minute intervals and are averaged for each study period – study period times (in min) is not defined</td>
<td>Mean, SD</td>
<td>No significant difference in crying time between the sucrose and water groups. Significant increases in HR, in both groups from baseline, p &lt; 0.01. No differences between the sucrose and placebo groups in HR at any time point. Significant reduction in oxygen saturation in infants receiving sucrose after the study drug (mean 95%, SD 4%) compared to the water group (mean 97%, SD 3%). Significant reduction in oxygen saturation in infants receiving sucrose during the eye exam (mean 93%, SD 5%); p &lt; 0.05 compared to the water group (mean 96%, SD 3%); p &lt; 0.05. No significant difference in RR and oxygen saturation at two minutes post-exam. No significant differences in PIPP scores between the sucrose and placebo groups before, during and after eye exam.</td>
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<td>McCullough 2005</td>
<td>20 infants, Mean (SD) gestational age 30.7 weeks (2.3)</td>
<td>NG tube (NGT) insertion</td>
<td>0.5 - 2ml of Sterile water 2 min prior to procedure. 0.5 - 2ml 24% sucrose 2 min prior to procedure Volume of solution was adjusted for current body weight &gt; 2 kg = 2 ml 1.3 kg to 2 kg = 1.5 ml &lt;1.5 kg = 0.5 ml</td>
<td>Incidence of cry Baseline heart rate and change in HR from base-line during NGT insertion Baseline oxygen saturation and change in oxygen saturation from baseline during NGT insertion Neonatal Facial Coding Score (NFCS) during NGT insertion and after insertion</td>
<td>Percentage Mean, SD Median</td>
<td>There was a non significant trend (p = 0.069) for fewer sucrose-treated infants to cry during NGT insertion (8/25), compared with the placebo group (14/25). Infants in the sucrose group had higher mean pre-treatment baseline heart rate than placebo group but showed no change in heart rate during NGT insertion (mean change -0.7 bpm). The placebo groups heart rate increased during NFT insertion (mean change +11). This difference approached statistical significance (p = 0.055). No significant changes in mean oxygen saturation occurred in either groups. Sucrose group had a significant lower mean NFCS score during NGT insertion compared with the water group [range 0-4 vs. 3 (range 0-4)], median difference 1 (95% CI 0 to 2) p = 0.004. After NGT insertion, the NFCS scores fell to a median of 0 in both groups. To see if NFCS is specific for pain, authors analyzed the 4 components on their own. Nasolabial folds showed a significant inhibition in the sucrose group [present in 4/26 or (15%) compared with 12/25 (48%) in the placebo group; p = 0.012].</td>
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</table>
References for Clinical Trials with Oral Sucrose

D. Blass 1997 - Blass EM Pediatrics 1997;99:825-9;
H. Johnston 1999a - Johnston CC et al Biology of the Neonate 1999;75:100-6;
M. Gibbins 2002 - Gibbins S et al Nursing Research 2002;51:375-82;
Other Modalities for Neonatal Pain

Local anesthetics

Cutaneous infiltration of lidocaine or other local anesthetics treats pain from skin-breaking procedures like lumbar puncture, ICD insertion, for about 60-90 minutes (43). EMLA cream (eutectic mixture of local anesthetic) has been used for circumcision but studies have shown that it is effective but inferior to dorsal penile nerve block (44). Disadvantage includes the prolonged time for onset of action. For elective planned procedures e.g. lumbar puncture, circumcision, intravenous lines, arterial lines, where more than 60 minutes time is available, EMLA cream is helpful. Interestingly, EMLA cream is not useful in heel prick pain (45). Anesthetic eye drops in combination with oral sucrose have been tried for reducing pain during ROP screening.

Regional anesthesia

This may be used appropriately e.g. dorsal penile block for circumcision if there is sufficient knowledge of techniques and dosages of various agents (46).

Peri-operative pain relief

Millions of newborns undergo surgery for various conditions around the world every year. Pain interventions must plan for intra-operative and post-operative periods. Potential drug therapeutic groups include opioids and opioid antagonists, sedatives/hypnotics, vapor anesthetics, local anesthetics, or NSAIDs, and there is opportunity to combine multiple types of analgesic intervention.

Opioid analgesics

Morphine: This is useful for moderate to severe acute pain, for pre-operative sedation, and during anesthesia. Morphine and its metabolites are cleared by the kidneys and partly by biliary excretion. It is administered usually by a continuous infusion of 10-30 µg/kg/hour in ventilated neonates for perioperative pain relief (47). Neonates, especially pretermers are more sensitive to opioids and are at risk for apnea, hypotension and urinary retention. Fentanyl: This is a synthetic opioid that is 50-100 times more potent than morphine. The main side effects are apnea, bradycardia and chest wall rigidity. In ventilated neonates both morphine and fentanyl infusions produce evidence of physiological pain relief but may prolong ventilation (48).

Others: Remifentanil and alfentanil have been used for short procedures like tracheal intubation or placement of central lines but safety data are lacking in neonates (49).

Non-opioid analgesics

Acetaminophen: (paracetamol) is often prescribed to manage mild to moderate procedural or post-operative pain. Data on newborn pain relief has been generally
negative but it is effective in ages 3-6 months and older. Plasma clearance of acetaminophen is slower in neonates and hence should be administered in a dose of 10-15mg/kg orally or 20-25mg/kg rectally every 6-8 hours.

**NSAIDS**

Generally not used for analgesia in neonates since safer and better alternatives are available.

**Figure 2. A stepwise approach for management of pain in neonates**

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<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
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<th>Step 6</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Avoid painful procedure, physical handling</td>
<td>Topical anesthetic cream or gel</td>
<td>Acetaminophen or NSIDs</td>
<td>Slow intravenous infusion of opioids</td>
<td>Local anesthetics: subcutaneous infiltration or nerve blocks</td>
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<td>Deep sedation/analgesia or general anesthesia</td>
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<td>Agents used (example)</td>
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<td>Fentanyl, morphine, ketamine, alfentanil, anesthetics or sedatives</td>
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<td></td>
<td></td>
<td></td>
<td>Lidocaine, bupivacaine, ropivacaine</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Fentanyl, morphine, alfentanil, remifentanil</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Acetaminophine, propacetamol, ibuprofen</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Lidocaine-prilocaine, liposomal lidocaine, amethocaine, tetracaine</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Sucrose 24%, glucose 36%; breastmilk</td>
</tr>
<tr>
<td></td>
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<td>None</td>
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</table>

**What should be done?**

Despite published data on the complex behavioral, physiologic, and biochemical responses of neonates and the detrimental short- and long-term clinical outcomes of exposure to repetitive pain, clinical use of pain-control measures in neonates undergoing remains sporadic and suboptimal.

Prevention of pain should be the goal of all caregivers involved with newborns. Every healthcare facility dealing with neonates should have a written pain prevention policy which includes regular pain assessment, reduction of painful procedures, use
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Supportive (where applicable)</th>
<th>Oral sucrose</th>
<th>Morphine</th>
<th>Paracetemol</th>
<th>Local anesthesia</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT/OGT insertion</td>
<td>Sw</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veneupuncture/IV cannulation</td>
<td>Sw, NNS, BF</td>
<td>✔</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IM/SC injections/vaccinations</td>
<td>Sw, NNS, BF, SSC</td>
<td>✔</td>
<td></td>
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</tr>
<tr>
<td>Heel prick</td>
<td>Sw, NNS, BF, SSC</td>
<td>✔</td>
<td></td>
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</tr>
<tr>
<td>Plaster removal</td>
<td>Sw, NNS, BF, SSC</td>
<td></td>
<td></td>
<td></td>
<td>Use adhesive remover</td>
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</tr>
<tr>
<td>Dressing change</td>
<td>Sw, NNS, BF, SSC</td>
<td>✔</td>
<td></td>
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<tr>
<td>UVC/UAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Do not clamp or stitch skin</td>
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</tr>
<tr>
<td>Arterial puncture/line</td>
<td>Sw, NNS, BF</td>
<td>✔</td>
<td></td>
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<tr>
<td>PCVC</td>
<td>Sw, NNS</td>
<td>✔</td>
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<tr>
<td>Lumbar puncture</td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td>EMLA</td>
<td>Use max 1g per procedure</td>
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<tr>
<td>ET suction</td>
<td></td>
<td>✔ bolus</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Procedure</td>
<td>Supportive (where applicable)</td>
<td>Oral sucrose</td>
<td>Morphine</td>
<td>Paracetamol</td>
<td>Local anesthesia</td>
<td>Remarks</td>
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<tr>
<td>Elective ET intubation</td>
<td>Sw, NNS, BF</td>
<td>✓ bolus</td>
<td></td>
<td></td>
<td></td>
<td>0.1mg/kg only in presence of doctor</td>
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<tr>
<td>ROP screen/eye exam</td>
<td></td>
<td>✓ bolus</td>
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<tr>
<td>Post-op laser/caput pain</td>
<td></td>
<td></td>
<td></td>
<td>✓ Q4-6H</td>
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<td></td>
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<tr>
<td>Post hernia repair</td>
<td></td>
<td></td>
<td></td>
<td>✓ Q4-6H</td>
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</tr>
<tr>
<td>Post-op Major surgery</td>
<td></td>
<td>✓ infusion</td>
<td></td>
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<td>At least 72 hours post-op</td>
</tr>
<tr>
<td>Suprapubic tap</td>
<td>NNS</td>
<td>✓</td>
<td></td>
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<tr>
<td>Mechanical ventilation</td>
<td></td>
<td></td>
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<td></td>
<td>Consider phenobarb. Morphine on case by case basis</td>
</tr>
<tr>
<td>Bladder catheterization</td>
<td>NNS</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suture removal</td>
<td>NNS</td>
<td>✓</td>
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</tr>
</tbody>
</table>

**Sw:** swaddling; **NNS:** non-nutritive sucking; **SSC:** skin to skin contact; **H&R:** holding and rocking; **BF:** breast feeding

**Oral sucrose:** Preterm: 1-2 pacifier dip (one dip=0.2ml) 2 minutes before procedure. Term: 0.5 ml/kg by syringe on tip of tongue. Maximum: 8 times in 24 hours. Do not use on babies who are sedated or have poor suck. Do not use for pacifying or settling baby.

**Local anesthetic:** EMLA cream to be used cautiously in G6PD deficiency.


**Clinical indicator:** to keep pain score in babies below 6.
of sucrose with other non-pharmacological methods of pain reduction and the use of topical anesthesia when time permits. Facilities providing surgery to neonates should have clear post-operative pain relief protocols, which at the present time is opioids. For all major procedures like chest drain insertion, abdominal paracentesis, endotracheal intubation etc should be given short acting opiates with other non-pharmacological methods.

The study of the development of pain mechanisms is, quite literally, in its infancy. Recent work has emphasized the importance of studying pain pathways in terms of developmental neurobiology. The infant pain response is not simply an immature adult one but stems from a quite different underlying structural and functional connectivity within the CNS. Currently, too few pediatric patients receive adequate pain relief, and there is little rationale for the choice of treatment. The challenge now is to unravel developing pain mechanisms for the benefit of these patients and to encourage pharmaceutical companies to support the effective evaluation of existing and new drugs for pediatric pain, thereby fulfilling the basic right of the child to safe and effective treatments.

References:


