Published in final edited form as:
Clin Perinatol. 2014 December ; 41(4): 895–924. doi:10.1016/j.clp.2014.08.010.

Pain Management in Newborns

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Abstract

Effective pain management is a desirable standard of care for preterm and term newborns and may potentially improve their clinical and neurodevelopmental outcomes. Neonatal pain should be assessed routinely using context-specific, validated and objective pain methods, despite the limitations of currently available tools. Reducing invasive procedures, and using pharmacological, behavioral or environmental measures can be used to manage neonatal pain. Non-pharmacologic approaches include kangaroo care, facilitated tucking, non-nutritive sucking, sucrose and other sweeteners, massage and acupuncture therapy. They are used for procedures causing acute, transient, or mild pain, or as adjunctive therapy for moderate or severe pain. Local and topical anesthetics can reduce the acute pain caused by skin-breaking or mucosa-injuring procedures. Opioids form the mainstay for treatment of severe pain; morphine and fentanyl are the most commonly used drugs, although other opioids are also available. Non-opioid drugs include various sedatives and anesthetic agents, mostly used as adjunctive therapy in ventilated neonates. Acetaminophen, ibuprofen and other drugs are used for neonates, although their efficacy and safety remains unproven. Approaches for implementing an effective pain management program in the Neonatal ICU are summarized, together with practical protocols for procedural, postoperative, and mechanical ventilation-associated neonatal pain and stress.

Keywords

analgesia; sedation; pain; stress; NICU; infant-newborn

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Disclosure: None

1. Introduction

1.1. Historical Perspective

Routine assessment and management of neonatal pain has evolved to become an important therapeutic goal in the 21st century. During the 20th century, however, most procedures and clinical practices established in neonatal intensive care units (NICUs) uniformly denied or disregarded the occurrence of neonatal pain. One unfortunate consequence was that infant surgery was conducted routinely with minimal or no anesthesia until the late 1980s[1,2]. Robust responses to painful stimuli were often dismissed as physiological or behavioral reflexes, and not related to the conscious experience of pain[3]. A recent historical analysis suggests four related causes contributed to a widely prevalent denial of infant pain[4]: 1) a Darwinian view that held newborns as less evolved human beings, 2) extreme caution and skepticism in interpreting scientific data that suggested infant pain, 3) an extreme reductionism whereby a mechanistic “behaviorism” became the dominant model human psychology in the earlier half 20th century (following J. B. Watson's Behaviorist Manifesto in 1913 [5]), and as the behaviorist movement waned, it was followed by 4) an era placing undue emphasis on the structural development of the brain and its responses[6-8].

This popular precept was challenged by accumulating data on hormonal-metabolic responses to surgical procedures performed under minimal anesthesia[9,10], which were effectively reduced by giving potent anesthesia[11-13], the identification of a “pain system” and initial data on its early development, rich observations on crying activity and other behaviors of newborns subjected to painful stimuli in the NICU – all of which contributed to a scientific rationale for neonatal pain perception and its clinical implications[3]. Once the existence of neonatal pain was acknowledged and methods for clinical assessment had been validated[14,15], the stage was set for advances in neonatal pain management.

1.2. Importance of Neonatal Pain

The American Academy of Pediatrics and the Canadian Pediatric Society (AAP/CPS) updated their guidelines in 2006[16], recommending that each health care facility treating newborns should establish a neonatal pain control program that includes:

- Performing routine assessments to detect neonatal pain
- Reducing the number of painful procedures
- Preventing or treating acute pain from bedside invasive procedures
- Anticipating and treating postoperative pain after surgical procedures
- Avoiding prolonged or repetitive pain/stress during NICU care

Numerous clinical studies have demonstrated that failure to treat pain leads to short-term complications and long-term physiological, behavioral, cognitive sequelae including altered pain processing, attention deficit disorder, impaired visual-perceptual ability or visual-motor integration[17-19], and poor executive functions[20,21]. Conversely, other studies showed needless analgesic therapy prolongs need for mechanical ventilation, delays feeding, or leads to other sequelae including impaired brain growth, poor socialization skills, and impaired

performance in short-term memory tasks[17,18]. About 460,000 neonates in the US require care in Neonatal ICUs (NICUs) each year and are exposed to acute pain from invasive procedures or prolonged pain from surgery or inflammation[22-24]. Assessing neonatal pain is difficult to teach, time- and labor-intensive, often open to subjective interpretation, and a source of conflict in NICU care[25-27].

2. Pain Assessment

Current practice requires the nursing staff to make a global pain assessment of neonates or apply validated pain scoring methods before taking appropriate actions to ameliorate newborn pain or discomfort[24,28,29]. Current nursing workload in the NICU does not allow bedside nurses to assess neonatal pain accurately. Many pain scales lump together behavioral, physiological, and other variables, but these variables may not respond to neonatal pain in similar or specific ways. The inter-rater reliability and subjectivity of human assessments are further limiting factors in their prevalent use[27,30-32].

The use of qualitative or subjective methods[27,32], rather than quantifiable data for neonatal pain assessment, results in inconsistencies and variability in analgesic therapy. Due to a large pharmacokinetic variability of analgesic drugs in neonates, their pain management is often of poor quality and inconsistent from shift to shift[33]. Adopting an objective pain assessment method greatly enhances the quality of pain management in NICUs and elsewhere, by avoiding untreated pain or excessive analgesia. Pain assessment methods should be designed to reduce nursing workload, the side effects of under- or over-dosing analgesics, the clinical practice variability within and across different NICUs, and complications like tolerance, withdrawal or delayed recovery from analgesia/sedation[34-36].

2.1. Pain assessment methods

Currently available methods for neonatal pain assessment may be unidimensional (one parameter) or multidimensional (physiologic, behavioral, or other parameters)[37-39]. Several multidimensional assessment tools with demonstrated validity, reliability, and clinical utility are used in the NICU[15,40,41]. These tools are based on indicators readily assessed at the bedside, such as changes in heart rate, respiratory pattern, blood pressure, or oxygen saturation. Behavioral responses include crying, changes in facial expressions and body movements[42,43]. For example, total facial activity and cluster of specific facial findings (brow bulge, eye squeeze, nasolabial furrow, open mouth) were associated with acute and postoperative pain[44,45].

The tools most commonly used in the NICU for acute pain assessment include the Premature Infant Pain Profile (PIPP)[40], Neonatal Pain Agitation and Sedation Scale (N-PASS)[46,47], Neonatal Infant Pain Scale (NIPS)[48] and the CRIES scale (Crying, Requires Oxygen Saturation, Increased Vital Signs, Expression, Sleeplessness)[15]. Premature infants, the most likely group to undergo painful procedures, are less likely to consistently demonstrate the responses to pain selected by these assessment tools[42,49-51]. These scales have been evaluated for acute pain and some for postoperative pain, but none of these methods assess persistent or chronic pain in neonates[32,52]. Two multicenter studies reported a wide range of pain assessment methods used in NICUs: 12 sites evaluated by the 2002

Neonatal Intensive Care Quality Improvement Collaborative used five different assessment tools[28], whereas 10 sites in the Child Health Accountability Initiative used eight different assessment tools[24]. Limitations of these pain assessment methods include:

- Most methods were developed and validated for neonates undergoing acute pain (e.g., venipuncture, heel stick).
- Many of the signs used in these assessment tools require the subjective evaluation by observers. As a result, there is significant inter-observer variability in the evaluation of behavioral responses[53]
- Some parameters like heart rate variability or palmar skin conductance require specialized equipment not available at the bedside
- Other measures like salivary cortisol or other biomarkers are not available in real-time to be clinically useful.
- Behavioral pain responses may be altered in neurologically impaired neonates and absent in those who receive neuromuscular blockade.

Methods for the assessment of persistent or prolonged pain in neonates (for major surgery, osteomyelitis, necrotizing enterocolitis) have not been developed or validated[32,52,54]. During episodes of persistent pain, newborns exhibit a passive state, with limited or no body movements, expressionless facies, reduced physiological variability, and decreased oxygen consumption. Also, behavioral responses are dependent on the subjective judgments of rotating care providers[32], leading to significant inter-observer variability. Clinicians must also recognize the potentially important relationships between the infant's pain response as well as the sensitivity and receptivity of the infant's care providers[55].

Current efforts to improve the accuracy of pain assessment tools include the use of neuroimaging and neurophysiologic techniques that measure brain activity in order to validate neonatal pain scales[32,56]. Their goal is to provide clinicians at the bedside reliable and accurate methods to detect pain and quantify its intensity.

3. Non-pharmacologic approaches

Non-pharmacologic approaches to pain relief are under-appreciated, under-utilized, and under-studied. [57] These methods of pain relief have demonstrated effectiveness in NICU care in certain situations, and modern NICUs should employ these methods when appropriate. While opinions differ on the use of “complementary and alternative medicine”, up to half the population of the developed countries use this form of therapy[58] and 13.7% of the US population seek advice from alternative therapists and MDs annually. [59] Opinions range from, “Research on alternative medicine is frequently of low quality and methodologically flawed, which might cause these results to be exaggerated”(CAM in the US, IOM, 2005) and “clothe naked quackery and legitimise pseudoscience” [60]” to being “Less dangerous and as effective as pharmacologic therapy”. [61]

3.1. Reduction of Painful Events

Perhaps the most effective method to eliminate neonatal pain is to reduce the number of procedures performed and episodes of patient handling. NICUs and newborn nurseries should develop policies that limit handling and invasive procedures, without compromising the care of the infants. With forethought and planning, “clustered care” can reduce the number of bedside disruptions, but it may increase pain responses[62,63]. Other approaches include:

- **a.** Decrease bedside disruptions by timing routine medical interventions (daily physical examinations) with other care procedures (diaper change or suctioning).
- **b.** Anticipate laboratory testing to minimize the frequency of blood sampling.
- **c.** Use hand-held devices that can perform several analyses (pH, PaO_2, $PaCO_2$, electrolytes, calcium, bilirubin, lactate) from a single small blood sample, thereby reducing the number of heelsticks required for laboratory testing.
- **d.** Place peripheral arterial or central venous catheters in patients who need more than 3-4 heelsticks per day. These procedures should be performed with adequate analgesia.
- **e.** If clinically appropriate, use noninvasive monitoring such as transcutaneous PaO_2, $PaCO_2$, SpO_2, glucose or bilirubin levels, or near infra-red spectroscopy (NIRS) to avoid the need for blood sampling.
- **f.** Consider the use of noninvasive therapeutic approaches for providing analgesia in newborns (e.g. transdermal patches, iontophoresis, compressed air injectors).

3.2. Kangaroo Care and facilitated tucking

Kangaroo care (KC) is defined as skin-to-skin contact, most commonly instituted shortly after birth. KC has been used in developing countries for warmth and bonding, while decreasing morbidity and mortality, especially in preterm neonates.[64] In developed countries, many health care workers are unaware of benefits of KC. During heel sticks, KC decreases crying time, improves pain scores and decreases stress in preterm neonates, similar to facilitated tucking.[65,66] The mechanism of action of KC is unclear. Possibilities include the ability of the newborn to hear the maternal heartbeat, less maternal stress, and enhanced self-regulation.[67,68] KC is safe in preterm neonates who are stable and weigh more than 1000 grams. However, 2 hours of KC daily is not effective in reducing stress levels in preterm neonates as measured by salivary cortisol.[69] Interestingly, during holding, KC decreases adverse cardiorespiratory events.[70]

Facilitated tucking is defined as placing a hand on the baby's hands or feet and positioning the baby to provide support yet allow them to control their own body, and is similar to providing KC. It has been used to alleviate pain during endotracheal suctioning and heel pricks.[71] However, it may not be as effective as oral sucrose for repeated painful procedures[72].

3.3. Non-nutritive sucking, sucrose and other sweeteners

Pain relief has been provided by non-nutritive sucking, with and without sucrose, glucose and breast feeding. Non-nutritive sucking and sweetners appear to work by increasing endogenous endorphins, as naloxone appears to blunt the response; however, the mechanism is not completely understood.[73] Sweetners appear to augment the anti-nociceptive response to pain compared to non-nutritive sucking.[74] Both sucrose and glucose enhance its effectiveness, they both decrease crying time and improve pain scores after acute mild pain such as from heelsticks.[75,76] A recent meta-analysis revealed that glucose is an acceptable alternative to sucrose, decreasing PIPP scores and crying times associated with venipuncture and heel lance.[77] Sucrose is efficacious in reducing the pain from single events such as retinopathy of prematurity screening[78], oral gastric tube insertion[79] and heel lance.[72] However, sucrose is controversial when given repeatedly, possibly leading to adverse long term outcomes.[80] Optimal dosing of sucrose is not known, and a recent Cochrane Review raised concerns about repeated dosing or use in extremely preterm or ill neonates.[81] Breast feeding, especially when accompanied by skin-to-skin contact, is more efficacious than either alone in reducing pain associated with heel prick; however, there are a limited number of studies in the preterm population.[82]

3.4. Massage therapy

Massage therapy involves hands-on and skin-to-skin manipulation of the soft tissue that includes gentle effleurage (rhythmic, gliding strokes confirming to the contours of the body), light petrissage (lifting, rolling, kneading strokes done slowly) and compression (light compression of selected areas) and nerve stroke (very light brushing of the skin). It is thought to work by enhancing vagal activity, modulating insulin, and insulin like growth factor 1 as well as decrease levels of cortisol and epinephrine.[83]. Massage therapy has demonstrated effectiveness in randomized trials. Massage decreased NIPS scores in 13 infants receiving heelsticks preceded by a 2-minute massage in the ipsilateral leg[84], increased weight gain via vagal stimulation[85] and improved neurodevelopmental outcomes in VLBW neonates.[86] It does not induce sleep in stable preterm neonates, limiting its usefulness as a sedative. (Yates CC, 2014, personal communication)

3.5. Acupuncture

Acupuncture is the stimulation of acupuncture points by mechanical or electrical means[87] to elicit pain relief. It works by stimulation of the endorphin system. Despite its use in China for thousands of years and its frequent use by patients in developed countries, it has not gained widespread acceptance in conventional Western medicine.

In conclusion, non-pharmacologic therapies are safe and effective for minor pain and as an adjunct for moderate or severe pain. KC is effective for pain relief during the holding period, it is safe in clinically stable term and preterm neonates weighing more than 1000 grams, and has beneficial effects on growth, mother-infant bonding and long-term neurodevelopmental outcomes. Facilitated tucking can provide some pain relief for endotracheal suctioning but is not as effective as sucrose for repeated skin-breaking procedures. Sucrose, glucose, breast milk and other sweeteners with or without non-nutritive sucking, have specific analgesic effects for most skin-breaking procedures, although the safety of repeated use has not been

established. Massage therapy decreases pain scores and promotes weight gain in preterm neonates, whereas acupuncture has been inadequately studied in neonates. The use of non-pharmacologic therapies is often recommended as the first step in neonatal pain management, particularly because of their favorable side effect profile, their ability to diminish acute pain from invasive or non-invasive procedures, and their beneficial long-term effects as compared to the systemic analgesics.

4. Local anesthetics

4.1. Lidocaine infiltration

Lidocaine inhibits axonal transmission by blocking Na^+ channels. Lidocaine infiltration is commonly used for various penile blocks for circumcision. In this circumstance, its use has demonstrated effectiveness in decreasing pain response to immunizations as long as 4 months after circumcision compared to neonates who received placebo[88]. Compared to a dorsal penile root block or eutectic mixture of local anesthetics (EMLA) cream, the ring block has been shown to be the most effective means of pain relief for circumcision.[89]

4.2. Topical anesthetics

Topical anesthetics are effective for certain types of procedural pain such as venous cannulation[90], lumbar puncture[91], or venipuncture.[92] One study reported combining sucrose with topical analgesia, which resulted in lower Douleur Aigue Nouveau-ne (DAN) scores.[93] Another study demonstrated increased success with venipuncture in young infants and children if the cream were left in place for 2 hours or more.[94] Eutectic Mixture of Local Anesthetic (EMLA) cream was studied in preterm neonates subjected to venipuncture. N-PASS scores were significantly lower in the treated group compared to placebo, leading the authors to recommend this method of analgesia.[95] Tetracaine is also used topically, with varying success. When combined with sucrose, one study found no benefit of this formulation,[96] whereas another review found similar efficacy but with a more rapid onset of action as compared to EMLA cream, making it attractive for clinical use.[97]

Complications of the topical creams include methemoglobinemia and transient skin rashes.[98] Concerns for methemoglobinemia are exaggerated In preterm neonates, because of a thinner epidermis, high dermal permeability, and limited circulating anti-oxidants. However, when used properly (as recommended by the FDA), very few neonates develop toxic methemoglobinemia even after repeated EMLA use[99-102]. Newer topical anesthetics include 4% tetracaine and 4% liposomal lidocaine, with a shorter onset of action, but they are not more effective.

Unfortunately, topical anesthetics have not been effective in providing pain relief for the heel prick, one of the most common skin breaking procedures[103], although they may reduce hyperalgesia following the tissue injury associated with heelsticks[104].

5. Opioid therapy

Opioids provide the most effective therapy for moderate to severe pain in patients of all ages. They produce both analgesia and sedation, have a wide therapeutic window, and also

attenuate the physiologic stress responses of neonates. Morphine and fentanyl are the most commonly used opioids, although some NICUs report the use of more potent (e.g., sufentanil)[105], shorter acting (e.g., alfentanil[106,107], remifentanil[108,109]), or mixed opioids (e.g., tramadol[110]).

5.1. Morphine

Morphine is the most commonly used opioid for neonatal analgesia, often used as a continuous infusion in ventilated or postoperative infants, or intermittently to reduce the acute pain associated with invasive procedures. Its effectiveness and safety for these indications has not been established, but remains under active investigation.

Morphine improves ventilator synchrony in ventilated neonates[111,112], although recent multicenter trials have questioned the benefit of routine morphine infusions in ventilated preterm infants. The NEOPAIN multicenter trial evaluated 898 ventilated preterm infants (23-32 weeks gestation) randomly assigned to morphine or placebo infusions[113]. Open-label morphine was given for additional analgesia based upon the clinical judgment of clinicians in each of the NICUs. There were no differences in the rates of mortality, severe intraventricular hemorrhage (IVH), or periventricular leukomalacia (PVL) between the two groups, even though neonates in the morphine group appeared to have lower Premature Infant Pain Profile (PIPP) scores and smaller increases in heart rate and respiratory rate[113]. These differences were small, but reached statistical significance because of the large sample size. Infants treated with morphine were more likely to develop hypotension[114], required a longer duration of mechanical ventilation, and took longer to tolerate enteral feeds[113,115].

Another trial that randomized 150 ventilated term and preterm neonates in two Dutch centers found no differences in the analgesic effects of morphine vs. placebo using multiple measures of pain assessment. A lower incidence of IVH occurred in the morphine group, but no differences in poor neurologic outcome occurred between the two groups[116]. A systematic review selected 13 RCTs on the use of opioids in ventilated infants. Pooled data from 4 studies using PIPP scores showed reduced pain in the patients who received morphine vs. placebo (weighted mean difference -1.71, 95% CI -3.18 to -0.24)[117]. Additional analyses demonstrated no differences in mortality rates (5 RCTs), duration of mechanical ventilation (10 RCTs), or neurodevelopment outcomes evaluated at 5-6 years of age (two RCTs) and no differences in secondary outcomes (rates of NEC, BPD, IVH, PVL, and hypotension), except that preterm infants in the morphine groups took longer to tolerate full enteral feeds[117].

Morphine analgesia is associated with significant side effects in preterm infants, but it may or may not alter their long-term cognitive or behavioral outcomes[17,117-121]. A retrospective study of 52 term neonates with hypoxic-ischemic insults following birth asphyxia showed less brain injury on magnetic resonance imaging (MRI) and improved neurodevelopmental outcomes in infants who received morphine in the first week after birth compared to those who did not receive opioid therapy[122]. The routine use of morphine infusions is not recommended for ventilated preterm neonates, but may be beneficial for term neonates following birth asphyxia.

Morphine analgesia may not be associated with the same risk profile in ventilated term infants, but may still cause increased duration of ventilation. A retrospective study of 62 ventilated term newborns found that postoperative morphine infusions prolonged the need for mechanical ventilation, but was not associated with apnea, hypotension, or other complications[123]. A series of RCTs comparing intermittent vs. continuous morphine infusions found that morphine is safe and effective for postoperative pain in term neonates and older infants[124-130]. Currently, however, there are no RCTs that have investigated the safety and efficacy of postoperative morphine analgesia in preterm neonates.

The analgesic effects of morphine in reducing acute procedural pain are controversial[116,131,132]. During CVL placement, one RCT found that ventilated neonates receiving morphine alone and morphine plus tetracaine had lower pain scores than the no treatment or tetracaine alone groups. However, patients who received morphine required greater ventilatory support in the 12 hours following the procedure[132]. In contrast, the NEOPAIN and Dutch morphine trials evaluated the responses to heelstick or tracheal suctioning respectively in preterm infants randomized to continuous morphine or placebo infusions and found no difference in pain scores between the two groups[116,131,133]. Morphine pharmacodynamics studies in ventilated preterm neonates also found no relationship between plasma morphine levels and responses to tracheal suctioning[133,134]. Of note, the preparation of morphine infusions in the NICU from regular morphine vials involves the manual dilution of small volumes, leading to significant inaccuracies in the concentrations delivered to neonates[135].

5.2. Fentanyl

As a highly lipophilic drug, fentanyl provides rapid analgesia with minimal hemodynamic effects in term and preterm newborns, although its popular use is not supported with evidence from large multicenter RCTs. Smaller trials reported that fentanyl reduces stress hormone levels, episodes of hypoxia, and behavioral stress scores in ventilated infants as compared with placebo controls[136-138]. Although infants who received fentanyl required greater ventilatory support, no differences occurred in clinical outcomes between the fentanyl- and placebo-treated groups[137,138]. Another RCT reported that behavioral pain scores and cytokine release following heelsticks were reduced to a greater extent with fentanyl (1-2 mcg/kg) as compared facilitated tucking[139].

Fentanyl[140-143] or its shorter-acting derivatives (e.g., alfentanil[106], remifentanil[144,145]) are often used for analgesia prior to procedures in preterm and term newborns. A randomized trial in 20 preterm newborns found that overall intubating conditions were significantly improved in those receiving remifentanil vs. morphine. However, no complications occurred following either IV morphine or remifentanil[145].

Although the AAP/CPS guidelines do not recommend the routine use of continuous fentanyl infusions in ventilated preterm neonates, this occurs frequently in many NICUs[146,147]. A multicenter RCT in 131 mechanically ventilated preterm infants (23-32 weeks gestation), fentanyl infusions reduced acute pain (PIPP) scores; no differences occurred in the prolonged pain (EDIN) scores for between the two groups although fewer neonates showed EDIN scores >6 in the fentanyl (6.8%) vs. placebo groups (10.6%)[148]. Those receiving

fentanyl infusions had longer duration of mechanical ventilation and delayed passage of meconium[148].

Fentanyl analgesia is associated with less sedative or hypotensive effects, reduced effects on gastrointestinal motility or urinary retention, but greater opioid tolerance and withdrawal as compared with morphine[148-151]. A single-center RCT compared infusions of fentanyl (1.5 mcg/kg/hr) vs. morphine (20 mcg/kg/hr) in 163 ventilated neonates and reported similar pain scores, catecholamine responses, and vital signs in both groups. There were no adverse respiratory effects or difficulties in weaning from ventilation in either group, but decreased beta-endorphin levels and gastrointestinal dysmotility occurred in the fentanyl group[151]. In another double-blind RCT, single doses of fentanyl (3 mcg/kg) reduced physiological and behavioral indicators of pain, improved postoperative comfort scores, and increased growth hormone levels in ventilated preterm neonates[136]. Among postoperative preterm infants, fentanyl and tramadol provided equally effective analgesia, with no differences between the two groups for the duration of mechanical ventilation or the time to reach enteral feeds[110].

Fentanyl should be used when a rapidly acting opioid is required for analgesia in a controlled setting, where any associated side effects (bradycardia, hypotension, laryngospasm and chest wall rigidity[152]) can be addressed rapidly and adequately. Other indications include fentanyl analgesia for postoperative pain (following cardiac surgery)[153,154], or for patients with pulmonary hypertension (primary or secondary)[155,156]. A single-center RCT using continuous fentanyl infusions following cardiac surgery found significant differences in postoperative complications and mortality compared to intermittent doses of morphine and diazepam[13], although it is unclear whether these clinical outcomes were related to anesthetic management or postoperative analgesia. Further studies of fentanyl analgesia for ventilated preterm neonates, and for term and preterm neonates exposed to postoperative pain, are required to evaluate its safety and efficacy in these patients.

Based on current evidence and clinical experience, the routine use of fentanyl infusions in ventilated preterm infants cannot be recommended at this time[117], except for neonates undergoing tracheal intubation, central line placement, or surgery. Morphine analgesia may be used in ventilated term neonates following surgery or birth asphyxia, or in those requiring moderately invasive procedures such as central venous catheterization, tracheal intubation, or chest tube placement. Exercise extreme caution if using opioid analgesia for preterm neonates at 22-26 weeks gestation or in those with preexisting hypotension because of the increased risk for adverse events including hypotension, bradycardia, severe IVH, impaired gut motility, and worse neurodevelopmental outcomes[114]

5.3. Remifentanil, Alfentanil, Sufentanil

Remifentanil has a chemical structure similar to that of fentanyl, but has twice its analgesic potency with an ultra-short duration of action (3–15 minutes). It is metabolized by plasma esterases in erythrocytes and tissue fluids, thus its excretion is independent of liver and renal function[157]. Remifentanil is used for pain relief during brief procedures such as central line placement[144] or tracheal intubation[145]. Alfentanil is more potent than morphine but has approximately one-third the potency of fentanyl and has a short duration of action (20–30

min)[106,158]. These drugs have been used successfully for tracheal intubation and other brief invasive procedures in neonates, but detailed safety and efficacy data are lacking[159]. For a summary of the opiates see Table 1.

6. Non-opioid therapies

6.1. Benzodiazepines

Benzodiazepines inhibit Gamma Aminobutyric Acid A ($GABA_A$) receptors[160] and are commonly used in NICU's, but they have no analgesic effects. These drugs provide sedation and muscle relaxation, making them useful for non-invasicve procedures such as imaging studies and as an adjunct for motion control in invasive procedures. Their adverse effects include myoclonic jerking, excessive sedation, respiratory depression and occasional hypotension.

6.1.1. Midazolam—Miidazolam is the most commonly used benzodiazepine in the NICU, although concerns regarding its usage have been raised. While there are relatively few studies to support the use of midazolam in neonates, it is common practice to use this drug for mechanical ventilation or procedural pain.[161] One recent review found no apparent clinical benefit of midazolam compared to opiates in mechanically ventilated neonates.[162] There are some concerns regarding the use of midazolam in neonates. One study reported an increased incidence of adverse short-term effects (intraventricular hemorrhage, periventricular leukomalacia or death) and a longer hospital stay associated with midazolam compared to morphine.[163] Midazolam has also been associated with benzyl alcohol exposure.[164] A recent Cochrane Review found insufficient data to promote the use of intravenous midazolam as a sedative in the NICU, in addition to “concerns about the safety of midazolam in neonates”.[165] It is also used for non-invasive procedures such as CT scans[166] and less invasive procedural sedation.[167] One recent study found a significant effect of midazolam on pain scores after surgery.[168] There have been no long-term studies describing benefit or harm with midazolam. In summary, midazolam appears to provide sedative effects in mechanically ventilated neonates, but it should be used with caution because of reported adverse effects, particularly when used alone. The decreased number of GABAa receptors in neonates compared to adults may contribute to the neonate's risk of neuroexcitability and myoclonic activity that resembles, and in some cases, may progress to seizure activity.[169]

A starting dose of 100 mcg/kg with a maintenance dose of 50-100 mcg/kg/hour can be used in neonaes to provide sedation.[170] Oral midazolam is also effective, with 50% bioavailability compared to the IV preparation.[171,172] Finally, intranasal midazolam was effective for fundoscopic exams in older children, but this mode of delivery has not been tested in neonates.[173] Metabolism of these drugs occurs through glucuronidation in the liver, and there is potential for decreased bilirubin metabolism, especially in asphyxiated or preterm newborns. Its half-life is only 30-60 minutes, which is prolonged in preterm and sick neonates. Recent pharmacokinetic data reveal a significant effect of maturation and body weight on the clearance of midazolam, which has elucidated the ability to predict levels in this age group.[174] However, it adheres to the tubing in patients on extra corporeal membrane oxygenation (ECMO), increasing their dosing requirements by 50%.[175]

6.1.2. Lorazepam—Lorazepam has also been used in the NICU, albeit not as routinely as midazolam. It has a longer acting drug than midazolam, with a duration of action 6-12 hours, so it does not have to be given as an infusion. It has been used successfully for seizure control in neonates who are refractory to phenobarbital and phenytoin despite its potential for neuronal toxicity.[176] Its use has also been associated with propylene glycol exposure.[164] For a summary of the benzodiazepines see Table 2.

6.2. Other Sedatives

6.2.1. Phenobarbital—Phenobarbital is usually considered as the drug of choice for seizure control. There is sparse evidence for antinociceptive effcts of phenobarbitol in animals,[177] but it has no significant analgesic effects in humans. It was used in conjunction with opioids for sedation[178], although there is little recent evidence that it is effective. Classically, it has been used for neonatal abstinence syndrome, but recent work by Ebner and others has demonstrated that opiates shorten the time required for treatment.[179] However, because of its anticonvulsant effects, phenobarbital is an attractive agent for patients with seizures.

6.2.2. Propofol—Propofol has become popular as an anesthetic agent for young children, but it has not been studied extensively in neonates.[180] One study compared propofol to morphine, atropine and suxamethonium for intubation and found that propofol led to shorter intubation times, higher oxygen saturations, and less trauma than the combination regimen in neonates, but these effects were not significantly different[181,182] However, propofol should be used with caution in young infants because its clearance and potential for neurotoxicity are inversely related to neonatal and postmenstrual age. There is significant inter-individual variability in the pharmacokinetics of propofol in preterm neonates[183] and its use can lead to severe hypotension, with transient decreases in heart rate and oxygen saturations.[184]

6.2.3. Ketamine—Ketamine is a dissociative anesthetic that provides analgesia, amnesia, and sedation. Although ketamine has been used extensively in older children, there have been limited studies in neonates. Ketamine increases blood pressure and heart rate, increases the respiratory drive and leads to bronchodilation.[185] Since ketamine does not affect cerebral blood flow significantly, it is a good choice for unstable, hypotensive neonates requiring procedures such as intubation or ECMO cannulation.[186] In our lab, ketamine decreased neuronal cell death in the presence of repetitive pain in immature rodents, which would also make it attractive for preterm neonates,[187] although no significant differences occurred in human studies. Doses for effective management of the pain caused by endotracheal suctioning in ventilated neonates were 2 mg/kg in one Finnish study.[188] In spite of these theoretical advantages, ketamine is a potent anesthetic with minimal study in neonates. As such, it should only be used for invasive procedures.

6.2.4. Dexmedetomidine—Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that provides potent sedative and analgesic effects, while causing minimal respiratory depression. Although dexmedetomidine is approved for sedation of patients undergoing surgical or other procedures, the clinical experience using this drug in neonates

is limited. Ongoing research on its safety, dosing, and efficacy is being conducted in preterm and term infants, particularly following cardiac surgery[189-195]. Therefore, the routine use of this drug in ventilated neonates is not recommended until sufficient data demonstrating its safety and efficacy, and its pharmacokinetics and pharmacodynamics have been published. Clinicians using this drug should note that the plasma levels producing sedation (0.4–0.8 mcg/L) are lower than those producing analgesia (0.6-1.25 μg/L), at least in older children,[196-199] and that it may cause seizures[200], bradycardia[201,202] and hypothermia[201] in neonates. However, it appears to be useful for radiological procedures[203-205] and supraventricular tachyarrhythmias[195,206] in infants and children.

6.2.5. Chloral Hydrate—Chloral hydrate is not available in the US, but is commonly used in European NICUs when sedation is required without analgesia. It is commonly used for radiological procedures, electroencephalography, echocardiography, and dental procedures in older patients. It is converted to trichloroethanol, which is also metabolically active.[207] A recent retrospective review found an increased incidence of apnea and desaturation in term neonates less than one month and in preterm neonates less than 60 weeks post conceptual age who were undergoing magnetic resonance imaging.[208] One study evaluated the combination of chloral hydrate and acetaminophen in ophthalmologic surgery for retinopathy of prematurity, comparing it to intravenous opioid analgesia. While there was a general reduction in pain scores, some of the infants in this study had very high pain scores with the chloral hydrate preparation, making this combination questionable at best.[209] In summary, this drug should be used for sedation without analgesia and with caution in preterm and young term neonates.

6.3. Acetaminophen (Paracetamol)

Acetaminophen inhibits the COX-2 enzymes in the brain; it has been well studied in newborns.[210] It is frequently used in conjunction with other pain relief to decrease opioid use, especially for postsurgical pain.[211] Intravenous acetaminophen decreased the amount of opioids needed after surgery and is particularly useful for routine postsurgical care with opioid-sparing effects.[212] The main toxicity of this drug is liver damage, but when given in appropriate doses, it is safe and effective. One of the main concerns surounding acetaminophen is drug overdosage, which can lead to significant liver toxicity.[213] Acetaminophen has also been used for procedural pain such as immunizations or circumcision.[214]

In infants, oral, rectal and intravenous formulations of acetaminophen have minimal adverse effects in infants. In contrast to its use in older children or adults, acetaminophen rarely causes hepatic or renal toxicity in newborns[214-218]. In addition, IV acetaminophen does not induce hypothermia in neonates[219]. The pro-drug is available as another IV formulation, marketed in European and other countries as Propacetamol, although it causes more frequent side effects[220-222].

In both preterm and term infants, the clearance of acetaminophen is slower than older children, so oral/rectal dosing is required less frequently[221,223-229]. Single **oral** doses of 10 to 15 mg/kg may be given every 6-8 hours, 20 to 25 mg/kg can be given **rectally** at the same

time intervals. These doses were primarily based upon antipyretic dose-response studies and may not apply for pain control. Although limited data are available for **IV** acetaminophen in neonates, a pharmacokinetic analysis in 158 infants suggests a loading dose of 20 mg/kg and maintenance doses of 10 mg/kg every 6 hours for infants at 32-44 weeks postmenstrual age[229]. However, maintenace dosing for ELGANs is controversial and may be less, or about 7.5 mg/kg every 6-8 hours for neonates between 23 and 32 weeks postmenstrual age.[212,230] Recommended total daily doses based on postmenstrual age are:

- 24 to 30 weeks gestation – 20 to 30 mg/kg/day
- 31 to 36 weeks gestation – 35 to 50 mg/kg/day
- 37 to 42 weeks gestation – 50 to 60 mg/kg/day
- 1 to 3 months postnatal – 60 to 75 mg/kg/day

Wider use of aecatminophen as an analgesic will allow clearer definition of the adverse effects and safety profile of this useful drug in the neonatal population[34].

6.4. Non-steroidal Anti-inflammatory Drugs (NSAIDS)

NSAIDS are used extensively for pain relief in children and adults but drugs like indomethacin[231,232] and ibuprofen[233-235] are mainly used for patent ductus arteriosus closure in neonates. They act by inhibiting the cyclogenase enzymes (COX-1 and COX-2) responsible for converting arachidonic acid into prostaglandins, thus producing their analgesic, anti-pyretic, and anti-inflammatory effects.[236] There are little data on the analgesic effects of NSAIDS in neonates, although both ibuprofen and indomethacin have been used for ductal closure. Concern over side effects of renal dysfunction, platelet adhesiveness and pulmonary hypertension, have limited their study to this indication.[237] However, ibuprofen has demonstrated beneficial effects on cerebral circulation in human studies as well as beneficial effects on the development of chronic lung disease in baboon experiments[238], making it potentially useful as an analgesic in preterm neonates.

7. Implementing pain management in the NICU: A Quality Improvement Approach

Pain in modern day NICUs is inadequately treated, despite the overwhelming evidence depicting the adverse consequences of unreleived pain/stress. Carbajal et al found that preterm neonates experienced 10-14 painful procedures daily, the majority of which (80%) were not preceded by specific analgesia.[22] Numerous other NICUs have noted similar findings.[239-241] Even more concerning is the potential that chronic pain may be ignored, especially in mechanically ventilated neonates.[242] Barriers include inadequte ability to assess prolonged neonatal pain, lack of knowledge of theraputic effectiveness, and exaggerated concerns over analgesic side effects. Further, the inherent difficulties in conducting human pain research in neonates require an ethical approach that will leave most studies seriously flawed.

7.1. Developing NICU specific guidelines

A suggested approach to evidence based recommendations for the treatment of neonatal pain includes the following[243]:

1. Recognition of neonatal pain as a valid concern
2. Recognition of acute procedural and chronic neonatal pain in need of treatment
3. Validated assessment tool for neonatal pain
4. Educational resources for care givers and parents in the NICU
5. Protocolized stepwise treatment plan for the procedures and conditions encountered in the NICU utilizing non-pharmacologic and pharmacologic approaches to teatment
6. Continued auditing to ascertain approprite treatment for neonatal pain
7. A well planned program of coordination, facilitation and using local champions and project teams will elicit a beneficial change in practice

Stevens et al identified 3 overarching themes which captured influences on optimal pain practices in the NICU[244]:

1. A culture of collaboration and support among all health care providers **and patients' families**
2. Threats to autonomous decision making, such as autocratic leadership and hierarchical relationships
3. Complexities in care delivery, related to the complexities of the patients as well as the system of care

The authors recommend a quality improvement approach, involving all members of the health care team and families to discuss the causes, prevention and evidence based treatment of pain. Education must be provided with continual assessment, which should be documented consistently according to Joint Commission requirements. By utilizing this approach, the authors were able to decrease the number of painful procedures to less than 2 per day in neonates between 27 and 32 weeks post conceptual age.[69]

7.2. Analgesia for invasive procedures

Analgesia and dosing for specific procedures are listed in Table 3 below.

7.3. Post operative analgesia

Opiates remain the mainstay of post operative pain relief. However, because of the concerns surrounding prolonged opiate therapy, many centers are using intravenous acetaminophen to augment opiate therapy. Its use has decreased the amount of opiates received by post operative patients.[212] See acetaminophen section and Table below for dosing information.

7.4. Analgesia for mechanical ventilation

Mechanical ventilation is one of the most common sources of chronic pain in modern NICUs. Newer, more effective surfactants, the use of prenatal steroids and improved nutrition has brought about a new generation of survivors, many of whom require several months of assisted ventilation. Despite several well-conducted studies in ventilated preterm neonates, the ideal method of analgesia for assisted ventilation in preterm neonates is still unknown.[178,245,246] Thus, analgesia for mechanical ventilation is controversial for a variety of reasons.[247]

Mechanical ventilation leads to changes in neuroendocrine parameters, pain scores, and physiologic responses.[248,249] Assisted ventilation in neonates is presumed to be associated with chronic repetitive pain, which in turn is associated with adverse long-term sequelae.[250] Ventilated neonates treated with opiates have demonstrated improved ventilator synchrony[251], improved pulmonary function, and decreased neuroendocrine responses, including cortisol, beta-endorphin, and catecholamines.[247] Reasons not to treat include the well-known adverse side effects of analgesics, especially the opiates, including hypotension from morphine[252], chest wall rigidity from fentanyl and alfentanil[106], and tolerance, dependence, and withdrawal from both opiates and benzodiazepines. Additionally, adverse effects such as death and IVH are not improved with preemptive treatment, and may lead to adverse short-term effects.[253]

Chronic pain assessment is poorly validated and difficult to assess in this patient population, and most studies have evaluated only acute pain scores.[242] If patients are treated, opiates are the most common class of drugs, with morphine being the most well studied. Fentanyl may be advantageous in hypotensive, younger neonates because it has fewer cardiovascular effects. One recent study demonstrated improved acute pain scores with fentanyl but time on the ventilator was prolonged compared to placebo.[254] Remifentanil, especially when short-term intubation is needed[255], and dexmedetomidine are promising agents but neonatal data are limited.[256,257] The benzodiazepines, midazolam and lorazepam, have been used in ventilated neonates, but midazolam has been associated with adverse effects in one small study.[178] Significant gaps in our knowledge exist, especially in regard to long-term effects of treatment, or lack thereof, and in chronic pain assessment associated with assisted ventilation. Recent data from the NEOPAIN trial suggest improved long term outcomes at school age from the morphine treated group, with fewer children requiring special education. (Hall RW, personal communication) In conclusion:

- If neonatal patients exhibit irritability on assisted ventilation, first assess optimization of ventilation
- Treat acute pain and stress episodically as needed
- Do not treat ventilated patients pre-emptively
- There is no clear cut advantage for any opioid in the management of ventilated preterm neonates
- Key questions remain regarding chronic pain assessment, long term outcomes and safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to acknowledge NIGMS IDeA Program award P30 GM110702 (RWH), the European Economic Commission – FP7 Programme and Oxnard Foundation (KJSA) for research funding during the preparation of this article.

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Synopsis

Pain management in neonates has made great strides over the last several years. Because of the serious short and long term adverse effects of pain and because of humanitarian reasons, all NICU patients deserve a focus on pain prevention, routine pain assessments and evidence-based strategies for pain management, using both non-pharmacologic and pharmacologic apporaches. Since pain strategies continue to fall short, future research should address systems-based practice and knowledge transfer approaches on how to improve pain management in NICUs, how best to assess pain, especially prolonged or chronic pain, and how to incorporate the many variables affecting pain found in modern day neonatology, such as light, sound, touch, parental separation, thermal stress and extrauterine malnutrition. Continued emphasis on neonatal pain management research may help to decrease some of the adverse neurodevelopmental outcomes commonly found in our NICU graduates.

Table 1

Opioids

Drug	Advantages	Disadvantages
Morphine	Potent pain relief Better ventilator synchrony Sedation Hypnosis Muscle relaxation Inexpensive	Respiratory depression Arterial hypotension Constipation, nausea Urinary retention CNS depression Tolerance, dependence Long term outcomes not studied Prolonged ventilator use
Fentanyl	Fast acting Less hypotension	Respiratory depression Short half life Quick tolerance and dependence Chest wall rigidity Inadequately studied
Remifentanil	Fast acting Degraded in the plasma Unaffected by liver metabolism	

Table 2

Benzodiazepines

Drug	Advantages	Disadvantages
Benzodiazepines	Better ventilator synchrony Antianxiety Sedation Hypnosis Muscle relaxation Amnesia Anticonvulsant	No pain relief Arterial hypotension Respiratory depression Constipation, nausea Urinary retention Myoclonus Seizures CNS depression Tolerance, dependence Alters bilirubin metabolism Propylene glycol and benzyl alcohol exposure
Midazolam	Most studied benzodiazepine Quickly metabolized	Short acting Benzyl alcohol exposure
Lorazepam	Longer acting Better anticonvulsant	More myoclonus reported Propylene glycol exposure
Diazepam		Not recommended in the neonate

Table 3
Summary of procedures and recommendedations for pain relief

Skin-breaking Procedures	Proposed interventions	Comments
Heelstick	Use non-pharmacologic measures + mechanical lance, squeezing the heel is the most painful phase	Venipuncture is more efficient, less painful; Local anesthetics, acetaminophen, heel warming do not reduce heelstick pain
Venipuncture	Non-pharmacologic measures, use topical local anesthetics	Requires less time & less resampling than heelstick
Arterial puncture	Non-pharmacologic measures, use topical and sub-cutaneous local anesthetics	More painful than venipuncture
Intravenous cannulation	Non-pharmacologic measures, use topical local anesthetics	
Central line placement	Non-pharmacologic measures, use topical local anesthetics, consider low-dose opioids or deep sedation based on clinical factors	Some centers prefer using general anesthesia
Finger stick	Non-pharmacologic measures and use mechanical device	Venipuncture is more efficient, less painful; Local anesthetics, acetaminophen, or warming may not reduce finger stick pain
Subcutaneous injection	Avoid if possible, use non-pharmacologic measures and topical local anesthetics if procedure cannot be avoided	
Intramuscular injection	Avoid if possible, use non-pharmacologic measures and topical local anesthetics if procedure cannot be avoided	
Lumbar puncture	Non-pharmacologic measures and topical local anesthetic, Lidocaine infiltration, careful positioning	Use IV analgesia/sedation, if patient is intubated and ventilated
Peripheral arterial line	Non-pharmacologic measures and topical local anesthetic, Lidocaine infiltration, consider IV opioids	
Circumcision	Non-pharmacologic measures and topical local anesthetic, Lidocaine infiltration, IV/PO acetaminophen pre- and post-procedure	Lidocaine infiltration for distal, ring, or dorsal penile nerve blocks (DPNB); liposomal lidocaine is more effective than DPNB
Suprapubic bladder aspiration	Non-pharmacologic measures and topical local anesthetic, Lidocaine infiltration, consider IV fentanyl (0.5-1 mcg/kg)	
Arterial or venous cutdown	Non-pharmacologic measures and topical local anesthetic, Lidocaine infiltration, IV fentanyl (1-2 mcg/kg), consider deep sedation	Most arterial or venous cutdowns can be avoided, consider referral to Interventional Radiology
Peripherally inserted central catheter (PICC)	Non-pharmacologic measures and topical local anesthetic, Lidocaine infiltration, consider IV fentanyl (1 mcg/kg) or IV ketamine (1 mg/kg)	Some centers prefer using deep sedation or general anesthesia
ECMO Cannulation	Propofol 2-4 mg/kg, Ketamine 1-2 mg/kg, fentanyl 1-3 mcg/kg, muscle relaxant as needed	
Skin-breaking Procedures	**Proposed interventions**	**Comments**
Tracheal intubation (e.g., for mechanical ventilation)	Give fentanyl (1 mcg/kg) or morphine (10-30 mcg/kg), with midazolam (50-100 mcg/kg), ketamine (1 mg/kg), use muscle relaxant only if experienced clinician, consider atropine	Superiority of one drug regimen over another has not been investigated
Gastric tube insertion	Non-pharmacologic measures, consider local anesthetic gel	Perform rapidly, use lubricant, avoid injury
Chest physiotherapy	Gentle positioning, Fentanyl (1 mcg/kg) if a chest tube is present	Avoid areas of injured or inflamed skin, areas with indwelling drains or catheters
Removal of intravenous catheter	Solvent swab, consider non-pharmacologic measures	
Wound treatment	Non-pharmacologic measures, use topical local anesthetics, consider low-dose opioids, or deep sedation based on extent of injury	See also “dressing change”

Skin-breaking Procedures	Proposed interventions	Comments
Umbilical catheterization	Non-pharmacologic measures, IV acetaminophen (10 mg/kg), avoid sutures to the skin	Cord tissue is not innervated, but avoid injury to skin
Bladder compression	Consider non-pharmacologic measures or IV acetaminophen (10 mg/kg) if severe or prolonged	
Tracheal extubation	Use solvent swab for tape, consider non-pharmacologic measures	
Dressing change	Non-pharmacologic measures and topical local anesthetic, consider deep sedation if extensive	

* Nonpharmacologic measures include: pacifier, oral sucrose, swaddling, skin-to-skin contact with mother

* The frequency of procedures can be reduced without sacrificing the quality of neonatal intensive care.