REVIEW ARTICLE

The influence of pain, agitation, and their management on the immature brain

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Preterm infants are exposed to frequent painful procedures and agitating stimuli over the many weeks of their hospitalization in the neonatal intensive care unit (NICU). The adverse neurobiological impact of pain and stress in the preterm infant has been well documented, including neuroimaging and neurobehavioral outcomes. Although many tools have been validated to assess acute pain, few methods are available to assess chronic pain or agitation (a clinical manifestation of neonatal stress). Both nonpharmacologic and pharmacologic approaches are used to reduce the negative impact of pain and agitation in the preterm infant, with concerns emerging over the adverse effects of analgesia and sedatives. Considering benefits and risks of available treatments, units must develop a stepwise algorithm to prevent, assess, and treat pain. Nonpharmacologic interventions should be consistently utilized prior to mild to moderately painful procedures. Sucrose may be utilized judiciously as an adjunctive therapy for minor painful procedures. Rapidly acting opioids (fentanyl or remifentanil) form the backbone of analgesia for moderately painful procedures. Chronic sedation during invasive mechanical ventilation represents an ongoing challenge; appropriate containment and an optimal environment should be standard; when indicated, low-dose morphine infusion may be utilized cautiously and dexmedetomidine infusion may be considered as an emerging adjunct.

INTRODUCTION

The rate of preterm birth is rising around the world. Improved neonatal intensive care has reduced the mortality and increased the survival of preterm infants. Despite advances in neonatal intensive care, preterm birth remains a leading cause of neurodevelopmental disability.[1] Neurodevelopmental challenges in infants born preterm often follow severe intraventricular hemorrhage (IVH) and white matter injury (WMI).[2–4] More recent studies are shifting the paradigm of brain injury in the preterm infant from a "one-hit brain injury" to overall alteration in trajectory of brain maturation.[5] An important modifiable factor that has been gaining interest in the clinical and research setting is pain in the neonatal intensive care unit (NICU).

In April 2019, an expert panel met at the annual Neonatal Neurocritical Care Special Interest Group (www.NNCC-SIG.org) meeting to review approaches to measuring and managing pain in the NICU. In this article, the panel will review the topic in detail, addressing factors related to (a) the link between pain and aberrant maturation in the developing brain; (b) methods to assess pain in the NICU; (c) nonpharmacologic and pharmacologic management of pain and agitation in preterm infants; and (d) knowledge gaps and future research directions.

HISTORICAL PERSPECTIVE ON PRETERM PAIN

As recently as 30 years ago, preterm infants underwent major surgical procedures without perioperative or postoperative analgesia.[6] The traditional definition of pain relying on self-reported perception and emotional experience presents challenges in non-verbal populations, including but not limited to preterm infants.[7] Careful investigation, including basic science and clinical research, documented the unique susceptibility of preterm infants to adverse metabolic, behavioral, and clinical responses to acute pain, sparking a revolution in pain science in the neonatal intensive care.[8,9] Ascending pathways mediating nociception connect peripheral sensory neurons to the thalamus between 20 and 24 weeks of gestation, while descending inhibitory pathways mature beyond term gestation.[8] In fact, preterm infants have lower flexor reflex thresholds and poor localization and discrimination of sensory input, leading to increased hormonal and physiologic responses to painful stimuli compared to older patients.[10,11] After tissue damage, preterm infants experience prolonged hyperalgesia and allodynia, leading to chronic periods of nociception and stress.[12]

In the modern era, provision of analgesia prior to major procedures ranging from endotracheal intubation to invasive surgery represents standard neonatal care.[13] However, investigation of the relative short- and long-term safety of newer analgesic and anesthetic agents challenges investigators and clinicians.[14,15] Nonpharmacologic comfort measures have also been widely implemented for minor procedural pain; however, the optimal bundle of interventions remains undefined due to gaps in available evidence.[16] At the confluence of nonpharmacologic and pharmacologic therapy, sucrose continues to require careful investigation despite decades of widespread utilization.[17] Finally,

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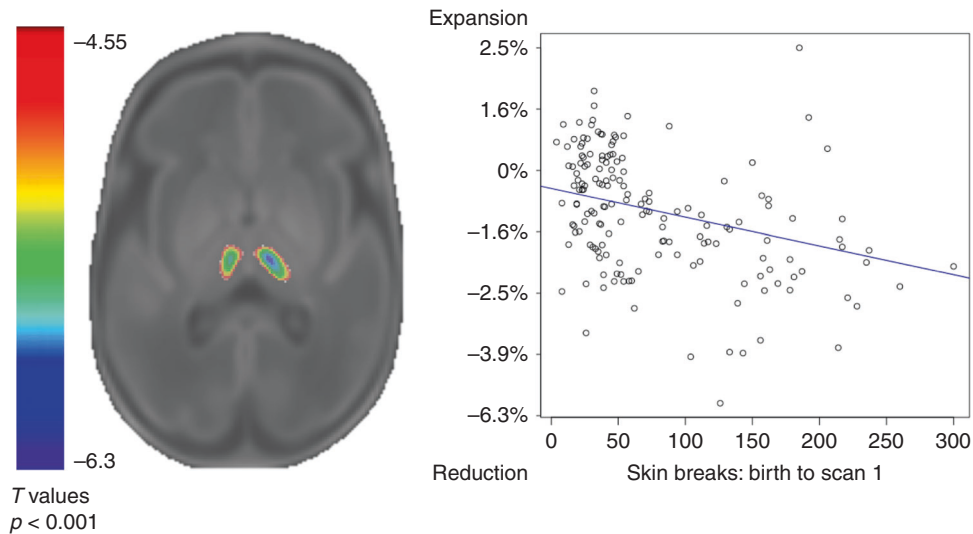C McPherson et al.

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Fig. 1 Growth of the thalamus associated with neonatal pain: The left image illustrates a deformation-based morphometry t-statistic map reflecting reductions in thalamus volume associated with early skin-breaking procedures overlaid on a magnetic resonance image developed as a T1-weighted image template from a median postmenstrual age of 32 weeks. The right scatterplot illustrates the association between volume loss in the lateral thalamus and an increasing exposure to skin-breaking procedures between birth and magnetic resonance imaging. Reproduced with permission from Duerden et al.[25].

the optimal approach to preterm infants experiencing chronic agitation, most commonly from invasive mechanical ventilation, perplexes both clinicians and investigators.[18]

IMPACT OF PAIN ON NEURODEVELOPMENT IN THE PRETERM INFANT

Patterns of injury in the immature brain, such as WMI, result from vulnerability of specific cell populations during certain times in development.[5,19] WMI is seen in ~1/3 of very preterm infants as a specific pattern of injury on clinical magnetic resonance imaging (MRI), reflecting these selective cell vulnerabilities.[4,20] In the preterm brain, early lineage oligodendroglia are vulnerable to insults that do not impact mature myelin-forming oligodendrocytes. Buser et al.[21] identified how the primary mechanism of myelination failure in the preterm infant involves dysmaturation, a disrupted cellular response whereby pre-oligodendrocytes fail to differentiate in diffuse astrogliotic lesions (i.e., pre-oligodendrocyte maturation arrest). Dysmaturation of *neuronal* structures was then identified in experimental and clinical imaging studies.[5,22–27] Brain dysmaturation, including that measured in the white matter and in the gray matter, is the most important predictor of the high burden of neurodevelopmental impairments in preterm infants. Potentially modifiable neonatal predictors of brain dysmaturation and neurodevelopmental disabilities in this population include sepsis, retinopathy of prematurity, and chronic lung disease.[2,3]

With advances in neonatal intensive care and reductions in the burdens of the major morbidities that impact infants born preterm, "everyday" clinical exposures are now also recognized as key predictors of brain maturation in preterm infants. Pain is one such "everyday" clinical exposure. Increasing evidence suggests that pain is a central factor that predicts dysmaturation, especially in babies born very preterm and in those with many early exposures to pain. Preterm infants often spend months in the NICU, where they receive many painful procedures that are essential to life-saving care. Preterm infants exposed to more procedural pain demonstrated reduced white matter and corticospinal tract fractional anisotropy (FA) as well as lower *N*-acetyl-aspartate/ choline in subcortical gray matter, even when comprehensively accounting for neonatal illness severity and exposure to sedatives

and analgesics.[28,29] Importantly, the changes in white matter FA relate to changes in diffusivity aligned along the long axis of neurons in contrast to the changes in FA related to infection and mechanical ventilation, which are perpendicular to the axonal component of diffusion. These findings further bolster the independent association of procedural pain with brain dysmaturation. The observations related to procedural pain are also congruent with studies of neonatal stress. Greater neonatal stress predicts decreased frontal and parietal brain width and altered diffusion and functional connectivity in the temporal lobes.[30] More recent observations demonstrate that greater procedural pain, especially in early life, is associated with smaller thalamic volumes, specifically in the somatosensory thalamus, and poor functional outcomes to 3 years of age (Fig. 1).[25]

Pain in neonatal life has a long-term impact on the developing brain. In a cohort of preterm infants studied at 8 years of age, greater exposure to neonatal pain predicted thinner cortex in multiple brain regions, predominantly in the frontal and parietal lobes.[31] In other studies of this cohort, greater exposure to pain is also associated with smaller regional volumes in the limbic system and basal ganglia at 8 years of age.[32] The association of pain with lower FA in superior white matter persists to school age, and associates with IQ.[33] Furthermore, cumulative neonatal pain-related stress is also related to brain function as reflected in changes to background cortical rhythmicity at school age, which negatively predicts visual–perceptual abilities.[34]

Pain also intersects with other common neonatal morbidities and may be modified by patient-specific factors. For example, infants with infections are exposed to more painful procedures, and these painful procedures predict poor somatic growth and brain maturation in preterm infants from early life to term age.[25,28,35] Recent studies highlight that the relationship between pain and brain morphology is modulated by genes known to impact pain sensitivity, neuronal survival, and synaptic plasticity.[32]

ASSESSMENT OF PAIN AND AGITATION IN THE PRETERM INFANT

A structured systematic manner to evaluate neonatal pain and agitation during hospital stays is of great importance in order to

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target strategies to prevent short- and long-term consequences. The most commonly used assessment tools are clinical pain scoring systems. In using these clinical scoring systems to assess pain and agitation, it is first important to define the circumstances that the assessment is designed to capture. For the current neonatal pain assessment tools that will be outlined more fully below, the tools are designed to characterize responses to acute pain, such as postoperative pain, procedural pain, or acute agitation associated with handling. They were not created to characterize chronic pain or agitation associated with either chronic noxious experiences and/or deprivation of positive or nurturing experiences.

All neonatal pain assessment tools are comprised of one or several observable indicators:

- Physiological (e.g., heart rate, blood pressure, respiration rate, oxygen saturation)—objective, but may be influenced by factors other than pain or agitation.
- Behavioral (e.g., crying, facial expression, bodily reactions, calming down, skin color)—subjective; facial grimacing specific for pain but cry and bodily reactions may lack sensitivity. Some such as "calming down" are not well operationalized.
- Contextual (e.g., gestational age, awake/asleep)—objective, affect physiological and behavioral responses to painful stimuli, but do not indicate the presence of pain.

The five most commonly used neonatal assessment tools are outlined in Table 1. They include the Neonatal Facial Coding System-Revised,[36] Premature Infant Pain Profile-Revised,[37] Neonatal Pain, Agitation and Sedation Scale,[38] Neonatal Infant Pain Scale,[39] and Bernese Pain Scale Neonates.[40] These five scales were recently compared in 42 term and preterm infants who were predominantly >34 weeks gestational age in the setting of a painful procedure (venipuncture) and a stressful procedure (diaper change). Inter-rater reliability was very high (intraclass coefficients >0.96) with notably lowest internal consistency for stressful procedures.[41] The highest consistency was obtained on the NFCS-R. It did appear that standard physiological measures were not as consistently expressed as measures of pain in comparison to behavioral measures. It also appeared that behavioral measures of body tenseness and movement were more often reliably affected by pain than facial grimacing. The authors concluded that this study confirmed that psychometrically sound assessment tools exist for evaluation of newborn pain and that focus should shift to training, clinical utility, and an understanding of the appropriate management related to the scores.

While observational scoring systems represent the standard of pain assessment in clinical care, investigators have explored additional measures of pain or agitation. These have included electroencephalography, which has been shown to discriminate noxious painful stimuli from touch with the highest specificity.[42,43] Near-infrared spectroscopy (NIRS) has also been shown to detect noxious cortical activation from painful stimuli with oxygenated hemoglobin showing pain-associated increases in the contralateral somatosensory cortex.[44,45] Skin conductance has also been proposed as a tool for the measurement of autonomic function reflecting pain or stress.[46] Finally, salivary cortisol has been shown to increase after a painful or stressful experience in preterm and term born infants.[47]

A recent study compared measurements from NIRS, foot skin conductance, and salivary cortisol alongside the NFCS for pain evaluation in 113 3-day-old term born infants who underwent a single venipuncture. Given that all measures only mildly or moderately correlated with the NFCS, the authors concluded that the measures appeared to reflect differential physiological responses to pain with the NIRS, heart rate, and oxygen saturations representing an acute response to pain, while the skin conductance and salivary cortisol represented a more prolonged stressful response to pain.[48] This differential time course of physiologic response to pain may reflect differing neurological impact. Another review article recently summarized non-invasive monitoring of stress biomarkers in the newborn period and found that the most commonly used marker remained as cortisol in saliva (reflecting acute stress) or hair (reflecting chronic stress).[49] Further research is urgently needed to determine the optimal measures of acute and chronic pain and stress in infancy.

NONPHARMACOLOGIC TREATMENT OF PAIN AND AGITATION
The clear short- and long-term adverse effects of untreated pain and agitation in preterm infants require a multimodal approach, including both nonpharmacologic and pharmacologic strategies. Nonpharmacologic strategies with potential benefit prior to minor painful procedures include non-nutritive sucking, breast milk, music therapy, skin-to-skin contact, kangaroo care, and facilitated tucking.[16] These interventions consistently reduce behavioral responses to minor acute painful procedures, such as needle sticks. Uniquely, facilitated tucking improves both pain reactivity (immediately after the painful stimulus) and immediate regulation (at least 30 s after the painful stimulus) in preterm infants.[50] Unfortunately, despite over 70 randomized controlled trials including over 7000 infants and young children, low-quality evidence pervades this field of study, potentially contributing to underutilization of these interventions in clinical practice.[51] Trials generally include small samples, with few examining identical combinations of painful procedure, intervention, and assessment

Table 1. Neonatal Pain Assessment Scales.

	Tool	Score	Reliability
Neonatal Facial Coding System-Revised (NFCS-R)	Five domains of facial movement	0–5	High inter-rater and construct validity
Premature Infant Pain Profile-Revised (PIPP-R)	Two physiological, three behavioral two contextual items	0–18	Moderate consistency Good validity
Neonatal Pain, Agitation and Sedation Scale (N-PASS)	Five items: (1) crying; (2) behavior state; (3) facial expression; (4) tone of extremities; (5) vital sign changes (choice between HR, blood pressure, pulse, and oxygen saturation)	0–13 for preterm 0–10 for term	High consistency High validity Treatment recommended with score >3
Neonatal Infant Pain Scale (NIPS)	Six behavioral indicators	0–7	High consistency Limited validity data
Bernese Pain Scale Neonates (BPSN)	Three physiological and six behavioral indicators	0–27	High consistency High validity

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technique. These limitations prohibit any conclusions regarding the optimal nonpharmacologic bundle of care for preterm infants. The confluence of low-quality evidence for existing interventions and the ethical principles governing randomized controlled trials involving painful procedures creates a challenging environment for researchers.[52] Leveraging unique trial designs, such as non-inferiority trials, and broadening assessed outcomes to include both subjective and objective measurements of infant response hold the promise of expanding knowledge in this area of study without causing unnecessary pain and stress to fragile patients.

Often misclassified as nonpharmacologic, sucrose is widely utilized in clinical practice despite outstanding questions regarding mechanism, efficacy, and long-term impact in preterm infants.[53] Sucrose alters the behavioral response to painful stimuli by an unclear mechanism. Traditionally, stimulation of the endogenous opioid system was hypothesized, emphasizing the pharmacologic nature of sucrose. In rodents, ingestion of sucrose produces β-endorphin release in the hypothalamus, an effect blunted by opioid receptor antagonists.[54,55] However, neither property has been replicated in human subjects.[56,57] Mediation of dopaminergic, cholinergic, or serotonergic pathways have been proposed as potential alternative mechanisms of oral sucrose, although the role of these pathways has not been confirmed in preterm infants.[58–60]

Clinical trials document reduction of crying, facial grimacing, and motor activity after oral administration of sucrose prior to minor painful procedures. The effective dose varies substantially in trials (range, 0.05–3 mL of 12–50% sucrose), although a recent randomized trial suggests 0.1 mL of 24% solution reduces the behavioral response to heel lance as effectively as higher doses.[61] Despite significant influence on pain scores during skin-breaking procedures, oral sucrose does not consistently impact objective physiologic measures of pain. Specifically, oral sucrose does not decrease oxygen consumption or energy expenditure, has no impact on salivary or plasma cortisol concentrations, and has no effect on the neural activity of nociception-evoked circuits in the spinal cord or brain.[53,62,63] Most strikingly, sucrose does not prevent the development of remote hyperalgesia in infants.[64]

The limited understanding of the mechanism and objective efficacy of oral sucrose should promote great caution regarding long-term neurodevelopmental outcomes of preterm infants exposed repeatedly in the early stages of brain development. The true mechanism of action of oral sucrose clearly impacts the potential for adverse neurologic impact. Data regarding chronic opioid receptor stimulation clearly suggest the potential for negative neurologic impact.[65] Dopamine, acetylcholine, and serotonin play central roles in development of motor function and attention, which is noteworthy considering the context of the available data regarding the developmental impact of sucrose. Repeated exposure to sucrose in the first week of life (ten times daily) prior to handling or needle prick as compared to placebo results in long-term alterations in white and gray matter volumes in mice.[66] Mice that received sucrose prior to handling had poorer short-term memory in adulthood compared to controls, while the combination of sucrose and needle prick did not protect against impairment in short-term memory associated with repetitive pain.[17] In human preterm infants, sucrose (0.1 mL of 24% solution) for all invasive procedures in the first week of life had no impact on measures of motor development or attention/orientation at term-equivalent follow-up in a single randomized controlled trial.[67] However, increased sucrose exposure (greater than ten doses per day) was associated with poorer motor development and attention/orientation scores, an association not observed in the placebo group, suggesting this finding was not attributable to increased painful procedures.[67,68] Additionally, a retrospective study found no protective effect from glucose prior to painful procedures on brain growth, functional connectivity, and neuro-developmental impairments at 18 months of age.[23] In this

setting, randomized controlled trials of sucrose in preterm infants continue to be required, specifically examining short-term objective markers of efficacy and long-term neurodevelopmental effects.

PHARMACOTHERAPY FOR ANALGESIA AND SEDATION
Analgesic and sedative practices vary considerably among hospitals, even for infants with similar characteristics, illness severity, and procedure burden.[69,70] Provision of appropriate analgesia prior to invasive procedures prevents acute pain and clearly benefits the infant.[13] Appropriate anesthesia prior to major surgery decreases postoperative physiologic instability and the incidence of acute brain injury.[9] However, the optimal level of anesthesia and specific pharmacologic approach remains an area of highly active investigation beyond the scope of this review.[14] Pre-medication prior to non-emergent endotracheal intubation significantly decreases the time and number of attempts needed to complete the procedure and minimizes the risk of airway trauma.[71] However, investigation of the safety and efficacy of novel regimens utilized commonly in clinical practice should be prioritized.[15]

The role of sedation or analgesia delivered by continuous infusion has not been clarified for infants who require invasive mechanical ventilation, despite extensive investigation (Table 2). Currently, consensus exists that continuous analgesic or sedative medications should be avoided when the duration of mechanical ventilation is expected to be short.[72] Continuous analgesia and sedation are indicated when the infant's physiology demands strict ventilator synchrony and minimization of oxygen consumption.[72] However, in preterm infants requiring prolonged mechanical ventilation with comfort scale scores indicating the need for sedation approaches vary dramatically.[18]

Benzodiazepines, most commonly midazolam, bind to the γ-aminobutyric acid$_A$ (GABA$_A$) receptor complex, increasing the action of this inhibitory ion channel and resulting in sedation and anxiolysis. Clinical trials of continuous infusion midazolam therapy in preterm infants for sedation during mechanical ventilation have produced negative results. The pilot Neonatal Outcome and Prolonged Analgesia In Neonates (NOPAIN) trial documented an increase in severe IVH, periventricular leukomalacia, or death in infants randomized to midazolam therapy.[73] This finding was most likely driven by hypotension associated with bolus doses of midazolam, and the associated persistent decrease in mean cerebral blood flow velocity.[74] Long-term outcome data from preterm infants treated with continuous midazolam are not available. However, numerous preclinical studies have noted neuroapoptosis as well as long-term functional deficits and atypical behavioral patterns associated with benzodiazepines.[65] Hence, both acute and long-term neurologic complications limit the utility of benzodiazepines in preterm infants.

Opioids bind G protein-coupled mu opioid receptors, producing analgesia and sedation through inhibition of ascending pathways in the brain stem, inhibition of neuronal firing in the dorsal horn of the spinal cord, and depression of both presynaptic and postsynaptic neuronal membrane potentials peripherally. Clinical trials of opioid therapy for sedation during mechanical ventilation have produced mixed results. Despite the promising results of the NOPAIN trial with regard to morphine, the NEOPAIN trial failed to document benefit with regard to acute brain injury.[73,75] In addition, clear acute adverse effects occurred in infants randomized to morphine, including prolongation of the duration of mechanical ventilation, delayed tolerance of enteral feedings, and subtle tone abnormalities at 36 weeks postmenstrual age.[76–78] Long-term follow-up of infants enrolled in the NEOPAIN trial was limited;[79] however, robust follow-up of the European morphine trial revealed conflicting results with regard to neurodevelopment, with some detriment suggested at 5 years (lower scores on the

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Table 2. Advantages and disadvantages of available agents for sedation of preterm neonates during mechanical vecntilation.

Agent	Advantages	Disadvantages
Morphine	Increased ventilator synchrony Decreased adrenaline concentrations No impact on incidence of severe IVH, PVL, or death	Tachyphylaxis Hypotension Prolongation of mechanical ventilation Prolongation of time to full enteral feedings Reduced cerebellar growth at high doses
Fentanyl	Decreased adrenaline and cortisol concentrations Less impact on gastrointestinal motility compared to morphine	Rapid tachyphylaxis Prolongation of mechanical ventilation Delayed meconium passage Reduced cerebellar growth at high doses
Midazolam	Decreased sedation scores	Increased severe IVH, PVL, or death Hypotension Myoclonus Frequent delirium Potential for neuroapoptosis and delayed motor development
Dexmedetomidine	Decreased adjunctive sedation compared to fentanyl Decreased incidence of delirium compared to benzodiazepine Minimal respiratory depression Minimal impact on gastrointestinal motility Potential for neuroprotection after PVL, hypoxia–ischemia, or concurrent neurotoxic drug exposure	Potential hypotension

IVH intraventricular hemorrhage, *PVL* periventricular leukomalacia

visual analysis domain of intelligence quotient), but potential subtle benefits of randomization to morphine at 8–9 years of age (superior executive functions as assessed by parent report, although no difference by teacher report or standardized assessment by the study team).[80–82]

The long-term outcomes of children in the European morphine trial must be interpreted in the context of the morphine dosing utilized in the trial (100 μg/kg bolus, followed by 10 μg/kg/h for 7 days or less; median duration of invasive mechanical ventilation in the treatment group was 77 h). A retrospective study of children with similarly low-level morphine exposure during neonatal intensive care (median cumulative dose = 0.79 mg/kg) documents correlations between morphine exposure and brain morphology and behavioral dysregulation in infancy, but no correlation with cognitive or motor outcome at 2 years of age, or with brain morphology or developmental outcome at 7 years of age.[83] In contrast, a retrospective study with higher-level exposure (median cumulative dose = 1.905 mg/kg) noted a strong correlation between morphine exposure and reduced cerebellar volume, poorer cognitive and motor outcomes, and behavioral problems in infancy.[22,84] Interestingly, genetic variability impacting the metabolism of morphine modulates the association between exposure and behavioral problems in this cohort.[84]

Data regarding a pharmacokinetically different opioid emphasizes the importance of considering the degree of exposure when evaluating the potential long-term implications of therapy. Historic data suggest substantial accumulation of fentanyl in preterm infants treated with dosing commonly utilized in clinical practice, even after a robust loading dose.[85] A randomized controlled trial suggests both acute and long-term adverse effects from fentanyl infusion, including prolonged duration of mechanical ventilation and an association with neurodevelopmental adverse effects at 24 months corrected age.[86,87] A retrospective cohort study adds to concern, associating increased cumulative fentanyl exposure with reduced cerebellar growth at term-equivalent age.[88] Importantly, a recent, robust pharmacokinetic study suggests potentially more appropriate doses of fentanyl as continuous infusion in young, preterm infants.[89] This approach has the potential to mitigate some of the adverse effects of fentanyl; however, some degree of acute and long-term adverse

effects appear to be inherent to exposure to any continuous infusion opioid in preterm infants.

α2-receptor agonists currently represent an interesting prospect to address the sedation needs of chronically mechanically ventilated preterm infants while minimizing both short- and long-term adverse effects. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that provides analgesia, anxiolysis, and sedation via reduction in sympathetic outflow from the locus coeruleus and release of substance P from the dorsal horn of the spinal cord. Clinical data in preterm infants are limited, but suggest the potential for short-term benefits compared to opioids, given the lack of respiratory depression and lack of impact on gastrointestinal motility.[90,91] In contrast to benzodiazepines and opioids, preclinical data examining α2-agonists suggests neuroprotection of the immature brain.[92] Extensive clinical research is required to define optimal dosing of dexmedetomidine in preterm infants and to clarify the safety and efficacy profile of this agent.

CLINICAL APPROACH TO PAIN AND AGITATION IN PRETERM INFANTS

Judicious utilization of laboratory assessments and procedures is a fundamental component of neonatal intensive care. Pain should be avoided and, when encountered, treated with a stepwise algorith, including standardized nonpharmacologic and pharmacologic interventions.

A systematic scoring system should be utilized prior to, during, and following acute painful procedures for all infants requiring neonatal intensive care in addition to regular scoring at care times. Standardized training for scoring and guidelines on the management of the score with regard to interventions for comfort should be developed by each NICU.

Nonpharmacologic interventions, such as facilitated tucking, should be consistently utilized prior to mild to moderately painful procedures.

If sucrose is utilized to mitigate behavioral responses to minor painful procedures, clinicians should administer the lowest effective dose less than ten times every 24 h in conjunction with

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nonpharmacologic interventions.

Anesthesia should be provided to prevent intraoperative pain and stress responses from major surgery. Rapidly acting opioid agents with a relatively short duration of action (fentanyl or remifentanil) should be provided prior to moderate painful procedures, including intubations.

Stress should be minimized during invasive mechanical ventilation by providing appropriate containment of the infant and an optimal sensory environment, including appropriate levels of light, noise, and maximal parent presence. Currently, no pharmacologic therapy has demonstrated safety and effectiveness for preterm infants requiring prolonged, invasive mechanical ventilation. Low-dose morphine (≤10 µg/kg/h and/or 50 µg/kg/dose as needed at least 5 min prior to agitating stimuli) may be utilized selectively on the basis of clinical judgment. Morphine may be titrated cautiously on the basis of pain scale scores and/or physiologic indicators of discomfort, carefully considering both short- and long-term risk:benefit ratio. In the setting of insufficient sedation from morphine, dexmedetomidine infusion may be considered, titrated carefully to effect while monitoring closely for adverse reactions.

FUTURE AREAS OF INVESTIGATION

Quantifying the impact of pain on brain development is complex. Given that severity of illness can be associated with increased need for painful interventions, it can be difficult to resolve the contribution of pain itself from the comorbid conditions resulting in painful stimuli. The subjective nature of most clinical pain assessment tools introduce a source of variability into comparative studies aimed to address pain in the newborn. Additionally, the known direct and indirect adverse pharmacological effects of sedative and analgesic medications on neuronal injury must be weighed against the clear adverse effects of untreated pain and agitation on the developing brain. Future research directions must address these three critical areas using a combination of preclinical models and pragmatic clinical studies. Development of objective measures of pain will need to interrogate physiological signals/responses to pain. Such tools would enable comparative studies of nonpharmacologic therapies and sucrose, which must also evaluate the long-term neurodevelopmental effects of these interventions. Rigorous clinical studies utilizing short- and long-term objective makers of safety and efficacy are also vital to address optimal dose, timing, and cumulative exposure to pharmacological agents. Anesthesia/analgesia is clearly indicated and clearly improves outcomes in the setting of major acute painful stimuli, although uncertainty about the optimal approach remains a source of variability in clinical practice and requires further investigation. The approach to preterm infants requiring long-term sedation/analgesia for mechanical ventilation is equally unclear, with major adverse effects inextricably linked to high-level exposure to both benzodiazepines and opioids. The potential promising role of dexmedetomidine in this population warrants careful investigation.

AUTHOR CONTRIBUTIONS

C.M., T.E.I. and S.P.M. drafted sections of the article. M.E-D. and A.N.M. revised it critically, contributing important intellectual content to the final manuscript. All authors provided final approval of the version to be published.

ADDITIONAL INFORMATION

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