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Prevention and Management of Procedural Pain in the Neonate: An Update

COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE

abstract

The prevention of pain in neonates should be the goal of all pediatricians and health care professionals who work with neonates, not only because it is ethical but also because repeated painful exposures have the potential for deleterious consequences. Neonates at greatest risk of neurodevelopmental impairment as a result of preterm birth (ie, the smallest and sickest) are also those most likely to be exposed to the greatest number of painful stimuli in the NICU. Although there are major gaps in knowledge regarding the most effective way to prevent and relieve pain in neonates, proven and safe therapies are currently underused for routine minor, yet painful procedures. Therefore, every health care facility caring for neonates should implement (1) a pain-prevention program that includes strategies for minimizing the number of painful procedures performed and (2) a pain assessment and management plan that includes routine assessment of pain, pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and measures for minimizing pain associated with surgery and other major procedures.

Previous guidance from the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society addressed the need to assess neonatal pain, especially during and after diagnostic and therapeutic procedures.[1,2] These organizations also provided recommendations on preventing or minimizing pain in newborn infants and treating unavoidable pain promptly and adequately.[1,2] This statement updates previous recommendations with new evidence on the prevention, assessment, and treatment of neonatal procedural pain.

BACKGROUND

Neonates are frequently subjected to painful procedures, with the most immature infants receiving the highest number of painful events.[3–5]

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Despite recommendations from the AAP and other experts, neonatal pain continues to be inconsistently assessed and inadequately managed.[2,3] A large prospective study from France in 2008 found that specific pharmacologic or nonpharmacologic analgesia was given before painful procedures in only 21% of infants, and ongoing analgesia was given in an additional 34%.[3] Thus, infants received analgesia for approximately half of the procedures performed, with wide variation among facilities.

The prevention and alleviation of pain in neonates, particularly preterm infants, is important not only because it is ethical but also because exposure to repeated painful stimuli early in life is known to have short- and long-term adverse sequelae. These sequelae include physiologic instability, altered brain development, and abnormal neurodevelopment, somatosensory, and stress response systems, which can persist into childhood.[5–15] Nociceptive pathways are active and functional as early as 25 weeks' gestation and may elicit a generalized or exaggerated response to noxious stimuli in immature newborn infants.[16]

Researchers have demonstrated that a procedure-related painful stimulus that results in increased excitability of nociceptive neurons in the dorsal horn of the spinal cord accentuates the infant's sensitivity to subsequent noxious and nonnoxious sensory stimuli (ie, sensitization).[17,18] This persistent sensory hypersensitivity can be physiologically stressful, particularly in preterm infants.[19–22] Investigators have demonstrated increased stress-related markers and elevated free radicals after even simple procedures, such as routine heel punctures or tape removal from central venous catheters,[23,24] which can adversely affect future pain perception.[8] Specific cortical pain processing occurs even in preterm infants; however, multiple factors interact to influence the nociceptive processing and/or behavioral responses to pain.[14,16,25–27] Noxious stimuli activate these signaling pathways but also activate the central inhibitory circuits, thus altering the balance between the excitatory and inhibitory feedback mechanisms. The immaturity of the dorsal horn synaptic connectivity and descending inhibitory circuits in neonates results in poor localization and discrimination of sensory input and poor noxious inhibitory modulation, thus facilitating central nervous system sensitization to repeated noxious stimuli.[25]

ASSESSMENT OF PAIN AND STRESS IN THE NEONATE

Reliable neonatal pain assessment tools are essential for the rating and management of neonatal pain, and their use has been strongly recommended by the AAP and by international researchers, including the International Evidence-Based Group for Neonatal Pain.[1,2,28] However, the effective management of pain in the neonate remains problematic because of the inability of the infant to report his or her own pain and the challenges of assessing pain in extremely premature, ill, and neurologically compromised neonates.[29] Thus, pain assessment tools reflect surrogate measures of physiologic and behavioral responses to pain. Although numerous neonatal pain scales exist (Table 1), only 5 pain scales have been subjected to rigorous psychometric testing with the patients serving as their own controls, measuring their physiologic and behavioral responses by using the scale in question (Neonatal Facial Coding System,[30,31] Premature Infant Pain Profile [PIPP],[32–34] Neonatal Pain and Sedation Scale,[35,36] Behavioral Infant Pain Profile,[37] and Douleur Aiguë du Nouveau-né[38]). Many of the current pain assessment tools have been tested against existing or newly developed tools and against each other to determine which is more reliable for a particular population and application, but more research is needed.[29,39]

Contextual factors such as gestational age and behavioral state may play a significant role in pain assessment and are beginning to be included in some assessment tools (eg, the PIPP-Revised).[40,41] New and emerging technologies to measure pain responses, such as near-infrared spectroscopy, amplitude-integrated electroencephalography, functional MRI, skin conductance, and heart rate variability assessment, are being investigated.[53,54] These innovations hold promise in the development of neurophysiologically based methods for assessing noxious stimuli processing at the cortical level in neonates while they are awake, sedated, or anesthetized. If the neurophysiologic measures prove to be reliable and quantifiable, these measures could be used in the future to simultaneously correlate with the physiologic and behavioral pain assessment scales to determine the most clinically useful tool(s).

Many of the tools developed to measure acute pain in neonates are multidimensional in nature and include a combination of physiologic and behavioral signs. These tools were most commonly developed to assess unventilated infants; only a few scales are validated to assess pain in infants who are ventilated through an endotracheal tube or receiving nasal continuous positive airway pressure.[42,55] Recently, investigators reported that 2 behaviorally based, one-dimensional pain assessment tools (the Behavioral Indicators of Infant Pain and the Neonatal Facial Coding System) were more sensitive in detecting behavioral cues related to pain in term neonates than the PIPP.[56]

It is unlikely that a single, comprehensive pain assessment

TABLE 1 Pain Assessment Tools for Neonates

Pain Assessment Tool	Number and GA of Infants Studied	Indicators	Intervention Studied	Validation Methodology	Intended Use
Neonatal Facial Coding System (NFCS)[30,31] (1998, 2003)	*N* = 40 24–32 wk GA 5–56 DOL	Brow lowering Eye squeeze Nasolabial furrowing Lip opening Vertical mouth stretch Horizontal mouth stretch Taut tongue Chin quiver Lip pursing	Postoperative abdominal or thoracic surgery	Patients served as controls Interrater reliability: 0.86 Construct validity: demonstrated Feasibility: established	Acute pain Prolonged pain Postoperative pain
Premature Infant Pain Profile (PIPP)[32–34] (1996, 1999)	*N* = 211, 43, 24 Age: 28–40 wk GA	GA Behavioral state Maximum HR % Decrease in O_2 sat Brow bulge Eye squeeze Nasolabial furrow	Heel lance	Patients served as controls Internal consistency: 0.71 Construct validity: established Interrater reliability: 0.93–0.96 Intrarater reliability: 0.94–0.98	Acute pain
Neonatal Pain Agitation and Sedation Scale (NPASS)[35,36] (2010) (http://www.n-pass.com/research.html)	*N* = 42 Age: 23–40 wk GA 1–100 DOL	Crying Behavioral state Facial expressions Extremities/tone Vital signs (HR, BP, RR, O_2 sat)	Heel lance	Validated against PIPP Interrater reliability: 0.86–0.93 Internal consistency: 0.84–0.89 Construct (discriminate) validity: established Convergent validity: correlation with the PIPP scores Spearman rank correlation coefficient of 0.75 and 0.72 Test-retest reliability: 0.87	Acute pain Prolonged pain Level of sedation
Behavioral Indicators of Infant Pain (BIIP)[37] (2007)	*N* = 92 Age: 24–32 wk GA	Behavioral state Facial expressions Hand movements	Heel lance	Validated against NIPS Internal consistency: 0.82 Interrater reliability: 0.80–0.92 Construct validity: 85.9 Concurrent validity: correlations between the BIIP and NIPS = 0.64. Correlations between the BIIP and mean HR also remained moderate between GAs: earlier born = 0.33, $P < .05$; later born, $r = 0.50$, $P < .001$	Acute pain
Douleur Aiguë du Nouveau-né (DAN)[38] (1997)	*N* = 42 Age: 24–41 wk GA	Facial movements Limb movements Vocal expression	Heel lance Venipuncture	Patients served as controls Internal consistency: 0.88 Interrater reliability: 91.2 (Krippendorf)	Procedural pain
Premature Infant Pain Profile–Revised (PIPP-R)[40,41] (2014)	*N* = 52, 85, 31 Age: 25–40 wk GA	Maximum HR % Decrease in O_2 sat Brow bulge Eye squeeze Nasolabial furrow GA and behavioral state assessed if pain response detected	Retrospective comparison of PIPP and PIPP-R scores	Validated against PIPP Construct validity: established Feasibility: established	Acute pain

TABLE 1 Continued

Pain Assessment Tool	Number and GA of Infants Studied	Indicators	Intervention Studied	Validation Methodology	Intended Use
Faceless Acute Neonatal Pain Scale (FANS)[42] (2010)	*N* = 53 Age: 30–35 wk GA	HR change Acute discomfort (bradycardia, desat) Limb movements Vocal expression (must be nonintubated)	Heel lance	Validated against DAN Interrater reliability: 0.92 (0.9–0.98) Internal consistency: Cronbach's $\alpha = 0.72$ The ICC between the FANS and DAN scores was 0.88 (0.76–0.93)	Acute pain Developed for use when the neonate's face is not completely visible related to respiratory devices
Neonatal Infant Pain Scale (NIPS)[43] (1993)	*N* = 38 Age: 26–47 wk GA	Facial expression Crying Breathing patterns Arm movements Leg movements State of arousal	Needle insertion	Validated against VAS Concurrent validity: correlations with VAS ranged from 0.53 to 0.84. Interrater reliability: 0.92–0.97 Internal consistency: Cronbach's α's were 0.95, 0.87, and 0.88 for before, during, and after the procedures, respectively	Acute pain Postoperative pain
Crying Requires Increased oxygen administration, Increased vital signs, Expression, Sleeplessness (CRIES)[44] (1995)	*N* = 24 Age: 32–60 wk GA 1382 observations	Crying Requires O_2 to maintain sat at 95% Increased blood pressure, HR Expression Sleep state	Postoperative pain	Validated against the Objective Pain Score Interrater reliability: 0.72 Construct validity: yes Discriminant validity: yes	Prolonged pain Postoperative pain
COMFORTneo[45] (2009)	*N* = 286 Age: 24.6–42.6 wk GA 3600 assessments	Alertness Calmness/agitation Respiratory response in ventilated patient Crying in spontaneously breathing patient Body movement Facial tension Body muscle tone	Tertiary NICU care, including ventilation	Validated against Numeric Rating Scale Internal consistency: Cronbach's $\alpha = 0.88$ for nonventilated, 0.84 for ventilated patients Interrater reliability: 0.79 Concurrent validity: Pearson product-moment correlation coefficient between COMFORTneo and NRS-pain = 0.54 Correlation coefficient: 0.75 (95% confidence interval: 0.70–0.79; $P <$ .0001)	Persistent or prolonged pain Level of sedation
COVERS Neonatal pain scale[46] (2010)	*N* = 21 Age: 27–40 wk GA	Crying FIO_2 requirement Vital signs (HR, BP, frequency of apnea/bradycardia Facial expression Resting state Body movements	Heel lance	Validated different GAs against CRIES, NIPS, and PIPP Concurrent validity: premature infants PIPP versus COVERS, $r = 0.84$; full-term infants NIPS versus COVERS, $r = 0.95$ Construct validity: baseline ($P < .05$); heel stick ($P < .05$); recovery ($P < .05$)	Acute pain

TABLE 1 Continued

Pain Assessment Tool	Number and GA of Infants Studied	Indicators	Intervention Studied	Validation Methodology	Intended Use
Pain Assessment in Neonates (PAIN)[47] (2002)	*N* = 196 neonates Age: 26–47 wk GA	Facial expression Cry Breathing pattern Extremity movement State of arousal F_{IO_2} required for sat >95% Increase in HR	Heel lance, suctioning, IV placement, circumcision, NG tube insertion, tape or IV removal	Adapted from NIPS and CRIES Inter-rater reliability: not established Correlation between the total scores on the two scales (NIPS and PAIN) was 0.93 ($P < .001$).	Acute pain
Pain Assessment Tool (PAT)[48,49] (2005)	*N* = 144 Age: 27–40 wk GA	Posture/tone Cry Sleep pattern Expression Color Respirations HR O_2 sat BP Nurse's perception	Ventilated and postoperative neonates	Validated against CRIES and VAS Interrater reliability: 0.85 Correlation between PAT and CRIES scores (r = 0.76) and (0.38) between the PAT score and VAS	Prolonged pain
Scale for Use in Newborns (SUN)[50] (1998)	*N* = 33 Age: 24–40 wk GA 0–214 DOL 68 procedures	CNS state Breathing Movement Tone Face HR changes Mean BP changes	Intubation PIV insertion	Validated against NIPS and COMFORT Coefficient of variation: 33 ± 8%	Acute pain
Échelle Douleur Inconfort Nouveau-Né (EDIN)[51] (2001)	*N* = 76 Age: 25–36 wk GA	Facial activity Body movements Quality of sleep Quality of contact with nurses Consolability	Acute and chronic ventilation; NEC, postoperative for PDA ligation	Patients served as controls Interrater reliability: coefficient range of 0.59–0.74 Internal consistency: Cronbach's α coefficients ranged from 0.86 to 0.94	Prolonged pain
Bernese Pain Scale for Neonates (BPSN)[52] (2004)	*N* = 12	Alertness	Heel lance	Validated against VAS and PIPP	Acute pain
	Age: 27–41 wk GA	Duration of crying		Concurrent and convergent validity: compared with VAS and PIPP was $r = 0.86$ and $r = 0.91$, respectively ($P < .0001$)	
	288 pain assessments	Time to calm Skin color Eyebrow bulge with eye squeeze Posture Breathing pattern		Interrater reliability: $r = 0.86–0.97$ Intrarater reliability: $r = 0.98–0.99$	

BP, blood pressure; CNS, central nervous system; desat, desaturation; DOL, days of life; F_{IO_2}, fraction of inspired oxygen; GA, gestational age; HR, heart rate; ICC, intraclass correlation coefficient; IV, intravenous (catheter); NEC, necrotizing enterocolitis; NG, nasogastric; PDA, patent ductus arteriosus; PIV, peripheral intravenous (line); RR, respiratory rate; sat, saturation; VAS, visual analog scale.

tool will be satisfactory for assessing neonatal pain for all situations and in infants of all gestational ages,[39,57] although initial validation studies have been published for the PIPP-Revised in infants with a gestational age of 25 to 41 weeks.[40,41] More research needs to be performed to assess the intensity of both acute and chronic pain at the bedside, to differentiate signs and symptoms of pain from those attributable to other causes, and to understand the significance of situations when there is no perceptible response to pain.[40,41] However, even with those limitations, one can use the available evidence to choose a pain assessment tool that is appropriate for the type of pain assessed (acute, prolonged, postoperative) and advocate for the competency of the neonatal care provider team with the specific use of that tool.[58] Table 1 lists commonly used pain assessment tools and the evidence used to test them.

NONPHARMACOLOGIC TREATMENT STRATEGIES

Pediatricians and health care professionals who work with neonates have the difficult task of balancing the need for appropriate monitoring, testing, and treatment versus minimizing pain and stress to the patient. Nonpharmacologic strategies for pain management, such as swaddling combined with positioning, facilitated tucking (holding the infant in a flexed position with arms close to the trunk) with or without parental assistance, nonnutritive sucking, and massage, have all shown variable effectiveness in reducing pain and/or stress-related behaviors related to mild to moderately painful or stressful interventions.[59–63] A meta-analysis of 51 studies of nonpharmacologic interventions used during heel lance and intravenous catheter insertion found that sucking-related and swaddling/facilitated-tucking interventions were beneficial for preterm neonates and that sucking-related and rocking/holding interventions were beneficial for term neonates, but that no benefit was evident among older infants.[64]

Skin-to-skin care (SSC), with or without sucrose or glucose administration, has been shown to decrease some measures of pain in preterm and term infants.[65] An analysis of 19 studies examining the effects of SSC on neonatal pain caused by single needle-related procedures found no statistical benefit for physiologic indicators of pain but did show benefit for composite pain score items.[65] However, some investigators have reported decreased cortisol concentrations and decreased autonomic indicators of pain in preterm infants during SSC, suggestive of a physiologic benefit.[66,67]

The effects of breastfeeding on pain response have also been investigated. A Cochrane systematic review published in 2012 found that breastfeeding during a heel lance or venipuncture was associated with significantly lower pain responses in term neonates (eg, smaller increases in heart rate and shorter crying time), compared with other nonpharmacologic interventions such as positioning, rocking, or maternal holding. Breastfeeding showed similar effectiveness to oral sucrose or glucose solutions.[68] This meta-analysis of 20 randomized controlled trials (RCTs)/quasi-RCTs also found that providing supplemental human milk via a pacifier or syringe seems to be as effective as providing sucrose or glucose for pain relief in term neonates.

Sensorial stimulation (SS), a method of gently stimulating the tactile, gustatory, auditory, and visual systems simultaneously, has shown effectiveness at decreasing pain during minor procedures such as heel lance.[69] SS is achieved by looking at and gently talking to the infant, while stroking or massaging the face or back, and providing oral sucrose or glucose solution before a painful procedure. A systematic review of 16 studies found that SS was more effective than sucrose when all elements of SS were used,[69] and 1 study suggested that SS may play an important role in nonpharmacologic management of procedural pain for neonates.[70]

PHARMACOLOGIC TREATMENT STRATEGIES

Sucrose and Glucose

Oral sucrose is commonly used to provide analgesia to infants during mild to moderately painful procedures. It has been extensively studied for this purpose, yet many gaps in knowledge remain, including appropriate dosing, mechanism of action, soothing versus analgesic effects, and long-term consequences.[71–73] A meta-analysis of 57 studies including >4730 infants with gestational ages ranging from 25 to 44 weeks concluded that sucrose is safe and effective for reducing procedural pain from a single event.[74]

Maximum reductions in physiologic and behavioral pain indicators have been noted when sucrose was administered ~2 minutes before a painful stimulus, and the effects lasted ~4 minutes.[74–76] Procedures of longer duration, such as ophthalmologic examinations or circumcision, may require multiple doses of sucrose to provide continual analgesic effect.[76] In animal studies, the analgesic effects of sucrose appear to be a sweet-taste-mediated response of opiate, endorphin, and possibly dopamine or acetylcholine pathways; however, the mechanism of action is not well understood in human neonates.[72,77–81] An additive analgesic effect has been noted when sucrose is used in conjunction with other nonpharmacologic measures, such as nonnutritive sucking and swaddling, especially for procedures such as ophthalmologic examinations

and immunizations.[74,78] Although the evidence that oral sucrose alleviates procedurally related pain and stress, as judged by clinical pain scores, appears to be strong, a small RCT found no difference in either nociceptive brain activity on electroencephalography or spinal nociceptive reflex withdrawal on electromyography between sucrose or sterile water administered to term infants before a heel lance.[73] This masked study did find, however, that clinical pain scores were decreased in the infants receiving sucrose, and several methodologic concerns limit the conclusions that can be drawn from the trial.[74]

Sucrose use is common in most nurseries; however, doses vary widely.[82] Although an optimal dose has not been determined,[74] an oral dose of 0.1 to 1 mL of 24% sucrose (or 0.2–0.5 mL/kg) 2 minutes before a painful procedure has been recommended, taking into account gestational age, severity of illness, and procedure to be performed.[71] The role and safety of long-term sucrose use for persistent, ongoing pain have not been systematically studied. One study in 107 preterm infants of <31 weeks' gestation found worse neurodevelopmental scores at 32, 36, and 40 weeks' gestational age in infants who had received >10 doses of sucrose over a 24-hour period in the first week of life, raising concerns about frequent dosing in newly born preterm infants.[83,84] In addition, 1 infant in that study developed hyperglycemia coincident with frequent sucrose dosing, which may have been related to the sucrose or to subsequently diagnosed sepsis.[83] When sucrose is used as a pain management strategy, it should be prescribed and tracked as a medication. More research is needed to better understand the effects of sucrose use for analgesia.[71,81,84]

Glucose has also been found to be effective in decreasing response to brief painful procedures. A meta-analysis of 38 RCTs that included 3785 preterm and term neonates found that the administration of 20% to 30% glucose solutions reduced pain scores and decreased crying during heel lance and venipuncture compared with water or no intervention. The authors concluded that glucose could be used as an alternative to sucrose solutions, although no recommendations about dose or timing of administration could be made.[85] As described for sucrose, however, glucose may not be effective for longer procedures. For example, an RCT found no effect of glucose on pain response during ophthalmologic examinations.[86]

Opioids, Benzodiazepines, and Other Drugs

The most common pharmacologic agents used for pain relief in newborns are opioids, with fentanyl and morphine most often used, especially for persistent pain. Analgesics and sedatives are known to be potent modulators of several G-protein–linked receptor signaling pathways in the developing brain that are implicated in the critical regulation of neural tissue proliferation, survival, and differentiation. Studies of appropriate dosing and long-term effects of these analgesics given during the neonatal period are woefully lacking and/or conflicting.[87,88] However, in their absence, it remains critical to achieve adequate pain control in newborns, both as an ethical duty and because painful experiences in the NICU can have long-term adverse effects.[7,10,19,20,89]

Studies evaluating pharmacologic prevention and treatment of mild to moderate pain have generally been limited to a specific procedure such as intubation. The AAP recommends routine pain management during procedures such as circumcision,[90] chest drain insertion and removal,[2] and nonemergency intubations.[91]

However, effective management strategies for pain and sedation during mechanical ventilation remain elusive. A recent systematic review reported limited favorable effect with selective rather than routine use of opioids for analgesia in mechanically ventilated infants.[92] Concerns have been raised for adverse short- and long-term neurodevelopmental outcomes related to the use of morphine infusions in preterm neonates.[92,93] However, a follow-up study in ninety 8- to 9-year-olds who had previously participated in 1 RCT comparing continuous morphine infusion with placebo found that low-dose morphine infusion did not affect cognition or behavior and may have had a positive effect on everyday executive functions for these children.[87]

A 2008 Cochrane systematic review found insufficient evidence to recommend the routine use of opioids in mechanically ventilated infants.[94] Although there appeared to be a reduction in pain, there were no long-term benefits favoring the treatment groups; and concerns for adverse effects, such as respiratory depression, increase in the duration of mechanical ventilation, and development of dependence and tolerance, were raised. Other short-term physiologic adverse effects of concern included hypotension, constipation, and urinary retention for morphine and bradycardia and chest wall rigidity for fentanyl.[94] Remifentanil, a shorter-acting fentanyl derivative, may be an alternative for short-term procedures and surgeries because it is not cleared by liver metabolism, but there are no studies examining its long-term effects.[95,96]

Benzodiazepines, most commonly midazolam, are frequently used in the NICU for sedation. However, because there is evidence of only minor additional analgesic effect, they may not provide much benefit. These agents can potentiate the respiratory

depression and hypotension that can occur with opioids, and infants receiving them should be carefully monitored.[97] Midazolam was associated with adverse short-term effects in the NOPAIN (Neonatal Outcome and Prolonged Analgesia in Neonates) trial.[98] A systematic review in 2012 found insufficient evidence to recommend midazolam infusions for sedation in the NICU and raised safety concerns, particularly regarding neurotoxicity.[97]

Alternative medications, such as methadone,[99] ketamine, propofol, and dexmedetomidine, have been proposed for pain management in neonates; however, few, if any, studies of these agents have been performed in this population, and caution should be exercised when considering them for use because of concerns about unanticipated adverse effects and potential neurotoxic effects.[100] Although the potential benefits of using methadone for the treatment of neonatal pain include satisfactory analgesic effects and enteral bioavailability as well as prolonged duration of action related to its long half-life and lower expense compared with other opiates, safe and effective dosing regimens have yet to be developed.[101] Ketamine is a dissociative anesthetic that, in lower doses, provides good analgesia, amnesia, and sedation.[102] Although ketamine has been well studied in older populations, further research is needed to establish safety profiles for use in neonates because of concerns regarding possible neurotoxicity.[103] Propofol has been used for short procedural sedation in children because of its rapid onset and clearance. The clearance of propofol in the neonatal population is inversely related to postmenstrual age, with significant variability in its pharmacokinetics in preterm and term neonates.[104] It has also been associated with bradycardia, desaturations, and prolonged hypotension in newborn infants.[105] Limited experience with dexmedetomidine in preterm and term infants suggests that it may provide effective sedation and analgesia. Preliminary pharmacokinetic data showed decreased clearance in preterm infants compared with term infants and a favorable safety profile over a 24-hour period.[106]

The use of oral or intravenous acetaminophen has been limited to postoperative pain control. Although intravenous acetaminophen has not been approved by the US Food and Drug Administration, preliminary data on its safety and efficacy are promising in neonates and infants and it may decrease the total amount of morphine needed to treat postoperative pain.[107–109] Nonsteroidal antiinflammatory medication use has been restricted to pharmacologic closure of patent ductus arteriosus because of concerns regarding renal insufficiency, platelet dysfunction, and the development of pulmonary hypertension.[110] An animal study suggests that cyclooxygenase-1 inhibitors are less effective in immature compared with mature animals, probably because of decreased cyclooxygenase-1 receptor expression in the spinal cord.[110] This decrease in receptor expression may explain the lack of efficacy of nonsteroidal antiinflammatory drugs in human infants.[111]

Topical Anesthetic Agents

Topical anesthesia may provide pain relief during some procedures. The most commonly studied and used topical agents in the neonatal population are tetracaine gel and Eutectic Mixture of Local Anesthetics (EMLA), a mixture of 2.5% lidocaine and 2.5% prilocaine. These agents have been found to decrease measures of pain during venipuncture, percutaneous central venous catheter insertion, and peripheral arterial puncture.[112–114] EMLA did not decrease pain-related measures during heel lance[113] but may decrease pain measures during lumbar puncture,[115] particularly if the patient is concurrently provided with oral sucrose or glucose solution.[116] Concerns related to the use of topical anesthetics include methemaglobinemia, prolonged application times to allow absorption for optimal effectiveness, local skin irritation, and toxicity, especially in preterm infants.[117,118]

CONCLUSIONS AND RECOMMENDATIONS

In summary, there are significant research gaps regarding the assessment, management, and outcomes of neonatal pain; and there is a continuing need for studies evaluating the effects of neonatal pain and pain-prevention strategies on long-term neurodevelopmental, behavioral, and cognitive outcomes. The use of pharmacologic treatments for pain prevention and management in neonates continues to be hampered by the paucity of data on the short- and long-term safety and efficacy of these agents. At the same time, repetitive pain in the NICU has been associated with adverse neurodevelopmental, behavioral, and cognitive outcomes, calling for more research to address gaps in knowledge.[5,8,22,89,119–122] Despite incomplete data, the pediatrician and other health care professionals who care for neonates face the need to weigh both of these concerns in assessing pain and the need for pain prevention and management on a continuing basis throughout the infant's hospitalization.

Recommendations

1. Preventing or minimizing pain in neonates should be the goal of pediatricians and other health care professionals who care for neonates. To facilitate this goal, each institution should

have written guidelines, based on existing and emerging evidence, for a stepwise pain-prevention and treatment plan, which includes judicious use of procedures, routine assessment of pain, use of both pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and effective medications to minimize pain associated with surgery and other major procedures.

2. Despite the significant challenges of assessing pain in this population, currently available, validated neonatal pain assessment tools should be consistently used before, during, and after painful procedures to monitor the effectiveness of pain relief interventions. In addition, the need for pain prevention and management should be assessed on a continuing basis throughout the infant's hospitalization.

3. Nonpharmacologic strategies, such as facilitated tucking, nonnutritive sucking, provision of breastfeeding or providing expressed human milk, or SS have been shown to be useful in decreasing pain scores during short-term mild to moderately painful procedures and should be consistently used.

4. Oral sucrose and/or glucose solutions can be effective in neonates undergoing mild to moderately painful procedures, either alone or in combination with other pain relief strategies. When sucrose or glucose is used as a pain management strategy, it should be prescribed and tracked as a medication; evidence-based protocols should be developed and implemented in nurseries, and more research should be conducted to better understand the effects of sucrose use for analgesia.

5. The pediatrician and other health care professionals who care for neonates must weigh potential and actual benefits and burdens when using pharmacologic treatment methods based on available evidence. Some medications can potentiate the respiratory depression and hypotension that can occur with opioids, and infants receiving them should be carefully monitored. Caution should be exercised when considering newer medications for which data in neonates are sparse or nonexistent.

6. Pediatricians, other neonatal health care providers, and family members should receive continuing education regarding the recognition, assessment, and management of pain in neonates, including new evidence as it becomes available.

7. To address the gaps in knowledge, more research should be conducted on pain assessment tools and pharmacologic and nonpharmacologic strategies to prevent or ameliorate pain. Studies on pharmacokinetics and pharmacodynamics of newer medications are needed to prevent therapeutic misadventures in the most vulnerable patients in pediatric practice.

LEAD AUTHORS

Erin Keels, APRN, MS, NNP-BC
Navil Sethna, MD, FAAP

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Jennifer Riefe, MEd

ABBREVIATIONS

AAP: American Academy of Pediatrics
PIPP: Premature Infant Pain Profile
RCT: randomized controlled trial
SS: sensorial stimulation
SSC: skin-to-skin care

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