

AMERICAN ACADEMY OF PEDIATRICS

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CANADIAN PAEDIATRIC SOCIETY

Fetus and Newborn Committee

Prevention and Management of Pain and Stress in the Neonate

ABSTRACT. This statement is intended for health care professionals caring for neonates (preterm to 1 month of age). The objectives of this statement are to:

1. Increase awareness that neonates experience pain;
2. Provide a physiological basis for neonatal pain and stress assessment and management by health care professionals;
3. Make recommendations for reduced exposure of the neonate to noxious stimuli and to minimize associated adverse outcomes; and
4. Recommend effective and safe interventions that relieve pain and stress.

ABBREVIATION. Sao₂, oxygen saturation.

The International Association for the Study of Pain has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”¹ The interpretation of pain is subjective. Each person forms an internal construct of pain through encountered injury. Several experts suggest that the neonate’s expression of pain does not fit within the strict definition of the International Association for the Study of Pain because of the requirement for self-report.²⁻⁴ This lack of ability to report pain contributes to the failure of health care professionals to recognize and treat pain aggressively during infancy and early childhood.⁵ Because neonates cannot verbalize their pain, they depend on others to recognize, assess, and manage their pain. Therefore, health care professionals can diagnose neonatal pain only by recognizing the neonate’s associated behavioral and physiological responses.⁶

Stress is defined as “a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation.”⁷ These responses can be specific to the stressor or can be generalized and nonspecific. Pain is always stressful, but stress is not necessarily painful; both require assessment, evaluation, and treatment. The signs of

pain and stress must be distinguished from signs of life-threatening conditions, such as hypoxemia or carbon dioxide retention, that require other forms of intervention.⁸

Studies indicate a lack of awareness among health care professionals of pain perception, assessment, and management in neonates.⁹⁻¹¹ When analgesics were used in infants, they often were administered based only on the perceptions of health care professionals or family members. Fear of adverse reactions and toxic effects often contributed to the inadequate use of analgesics. In addition, health care professionals often focused on treatment of pain rather than a systematic approach to reduce or prevent pain.^{12,13} More recent surveys have demonstrated increased awareness among health care professionals of pain in neonates and infants and its assessment and management.¹⁴⁻¹⁶ Several textbooks on pain in neonates and infants have been published,¹⁷⁻¹⁹ and measures for assessing pain have been developed and validated.²⁰⁻²⁴ However, despite the advances in pain assessment and management, prevention and treatment of unnecessary pain attributable to anticipated noxious stimuli remain limited.²⁵⁻²⁷ Several important concepts must be recognized to provide adequate pain management for the preterm and term neonate:

- Neuroanatomical components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate.²⁸⁻³²
- Exposure to prolonged or severe pain may increase neonatal morbidity.³³⁻³⁶
- Infants who have experienced pain during the neonatal period respond differently to subsequent painful events.³⁷⁻⁴¹
- Severity of pain and effects of analgesia can be assessed in the neonate.^{20-24,42-46}
- Neonates are not easily comforted when analgesia is needed.⁸
- A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain.⁴⁷

GENERAL PRINCIPLES

By late gestation, the fetus has developed the anatomic, neurophysiological, and hormonal compo-

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.
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nents necessary to perceive pain.^{11,28–32} Preterm and term infants demonstrate similar or even exaggerated physiological and hormonal responses to pain compared with those observed in older children and adults.^{11,33,35} Some studies suggest that pain experienced early in life by term infants may exaggerate affective and behavioral responses during subsequent painful events.^{37,38} Neonates who were exposed to numerous painful and noxious stimuli between postconceptual weeks 28 and 32 showed different behavioral and physiological responses to pain compared with neonates of a similar postconceptual age who had not had such experiences.⁴⁰ In addition, toddlers at 18 months corrected age who were of extremely low weight (<1000 g) at birth (and thus exposed to numerous noxious stimuli in the neonatal intensive care unit) were rated by parents as being less sensitive (reactive) to painful stimuli (eg, bumps, cuts, common hurts) and demonstrating more somatic complaints compared with full-term infants.^{41,48} In another study, children's judgment about pain at age 8 to 10 years were examined using pictures of children in potentially painful situations (medical, recreational, daily living, and psychosocial situations were used as the pain stimuli).³⁹ Two groups of children who had experienced different exposure to nociceptive procedures in the neonatal period were compared. Unlike infants of birth weight >2500 g, for extremely low birth weight infants (<1000 g), medical pain intensity was rated significantly higher than psychosocial pain at 8 to 10 years of age, at $P < .004$.³⁹ These clinical data support the experimental observations on the long-term effects of neonatal pain and stress.⁴⁹

Several validated and reliable pain measures exist to assess acute pain in term and preterm neonates.²⁴ Behavioral indicators of pain (eg, facial expression, body movements, crying), and physiological indicators of pain (eg, changes in heart rate, respiratory rate, blood pressure, oxygen saturation [Sao₂], vagal tone, palmar sweating, and plasma cortisol or catecholamine levels) can be used to assess and manage stress and pain in neonates. Composite measures of neonatal pain include the following: 1) the Premature Infant Pain Profile (PIPP) that includes facial actions, such as brow bulge, eyes squeezed shut, and nasolabial furrow, and physiological indicators, including heart rate and Sao₂ in the context of gestational age and neonatal state²²; 2) CRIES that assesses Crying, the Requirement for oxygen supplementation (for Sao₂ >95%), Increases in heart rate and blood pressure, facial Expression and Sleeplessness²³; and 3) the Neonatal Infant Pain Scale (NIPS), which assesses facial expression, cry, breathing patterns, movements of arms and legs, and state of arousal.²¹ Other assessment measures are unidimensional but include multiple indicators of facial expression in term and preterm neonates. One such measure is the Neonatal Facial Coding System²⁰ that was developed for use in pain research, but study continues of its clinical usefulness.⁴¹ However, there is a paucity of measures to evaluate pain in very low birth weight neonates or those who require mechanical ventilation.^{43,44} There remains a need to establish

the clinical usefulness of existing measures and to develop measures to assess potential pain in pharmacologically paralyzed neonates or neonates with chronic pain.⁸

Pain is managed most effectively by preventing, limiting, or avoiding noxious stimuli and providing analgesia.¹³ Modifying the environment and providing anxiolytics for circumstances expected to be stressful also may be useful. The environment should be as conducive as possible to the well-being of the neonate and the family.^{50,51} Unnecessary noxious stimuli (acoustic, visual, tactile, vestibular) of neonates should be avoided. Simple comfort measures, such as swaddling, nonnutritive sucking (pacifier), and positioning (when not contraindicated because of specific medical or surgical conditions) should be used whenever possible for minor procedures.^{52,53} Oral administration of sucrose reduces pain associated with painful procedures.^{54,55} However, these interventions alone may not alleviate moderate to severe pain, and analgesic treatment should be provided as indicated.

Painful or stressful procedures should be minimized and, when appropriate, coordinated with other aspects of the neonate's care. Furthermore, consideration of the least painful method is important. For example, when performed by trained personnel, obtaining blood by venipuncture may be less painful than heel lancing.^{56–58} Skillful placement of peripheral, central, or arterial lines reduces the need for repeated intravenous punctures or intramuscular injections. Thus, in some such cases, the risk-benefit balance may favor the more invasive indwelling catheters. Whenever possible, validated noninvasive monitoring techniques (eg, pulse oximetry) that are not tissue damaging should replace invasive methods.

The risks and benefits of pain management techniques must be considered on an individual basis within the context of the type and severity of the painful stimulus. Pharmacological analgesia should be chosen carefully based on comprehensive assessment of the neonate, efficacy and safety of the drug, the clinical setting, and experience of the personnel using the drug. Drug doses, including those for local anesthetics, should be calculated carefully based on the current or most appropriate weight of the neonate, and initial doses should not exceed maximal recommended amounts. Subsequent doses should be modified based on multiple factors, including the cause of the pain, previous response, clinical condition, concomitant drug use, and the known pharmacokinetics and pharmacodynamics of the sedative and analgesic drugs administered. Medications that might result in the loss of protective reflexes or cause cardiorespiratory instability should be used only by appropriately trained persons in an environment equipped to handle emergencies. Monitoring to ensure adequate oxygenation, ventilation, and cardiovascular stability should follow the guidelines of the American Society of Anesthesiologists,⁵⁹ the Canadian Anaesthetists Society,⁶⁰ and the American Academy of Pediatrics.⁶¹

Studies are lacking on the management of pain in

neonatal conditions associated with extensive tissue damage and those resulting in recurrent or chronic pain (eg, necrotizing enterocolitis, meningitis, fractured bones). The effects of the use of analgesics or sedation during the neonatal period on long-term neurodevelopmental and psychological outcomes has not been well studied.⁴⁹ No differences in intelligence, motor function, or behavior at 5 to 6 years of age were found between neonates who received morphine for sedation during mechanical ventilation and placebo-treated neonates.⁶²

PREVENTION OF ACUTE PAIN DURING OR AFTER SURGERY OR A PAINFUL PROCEDURE

General Anesthesia

Advances in anesthetic medications, techniques, and monitoring by trained personnel have increased the safety and efficacy of general anesthesia for preterm and term neonates. The state of general anesthesia makes the patient pain-free and amnesic during surgery; the same medications and techniques can be used to extend the period of analgesia postoperatively.⁶³

Regional Anesthesia

Regional techniques, such as peripheral nerve blocks and central neuraxis blockade (spinal, epidural), are sometimes used to provide anesthesia and analgesia for procedures on the trunk or limbs, as an adjunct to general anesthesia, and for postoperative analgesia.^{64–68} Examples of regional nerve blocks include ilioinguinal and iliohypogastric nerve blocks, penile block, digital block, local infiltration, and intercostal nerve blocks. The duration of such blocks can be extended by using vasoconstrictors (contraindicated in areas of end-arterial circulation, such as the penis, digit, and pinna of the ear). The duration of epidural blockade can be extended with the coadministration of opioids, clonidine, or both. Indwelling epidural catheters threaded from the caudal or lumbar region may provide analgesia for procedures above the diaphragm.^{18,69,70} These techniques should be used carefully by health care professionals trained in their use and with appropriate and careful observation. In neonates, intermittent administration of dilute local anesthetics with low-dose extradural opioids, such as fentanyl, offers less potential for the toxic effects of drugs than continuous infusion techniques with either drug alone. Careful calculation of doses is mandatory to avoid toxic effects for all uses of local anesthetic agents and for all other medications used to provide analgesia, sedation, and relief of anxiety. Accurate calculation is a particular concern in the care of preterm and term neonates in whom differences in protein binding and metabolism can result in local anesthetic drug accumulation and toxic effects.^{71,72}

Continuous caudal or epidural blockade may be administered for several days postoperatively by using a continuous infusion pump. Continuous infusions are best managed by pain specialists trained in appropriate pharmacology, frequent assessment of effects, and the recognition of adverse reactions.

Local Infiltration Anesthesia

Analgesia for procedures in superficial areas, (eg, chest tube insertion), usually can be managed with superficial infiltration with local anesthetic agents. Just as with regional nerve blocks, care must be taken to remain within maximal recommended total doses of local anesthetic agents. The addition of bicarbonate to local anesthetics can reduce the pain of local infiltration.⁷³ For topical use, a cream containing lidocaine and prilocaine decreases the pain associated with a variety of minor procedures, although it was not effective for heel-lance procedures.^{74–76} For the success of topical analgesia, at least 1 hour must have elapsed between application and the time of the procedure; the analgesia may last 1 to 2 hours.⁷⁶ Single applications of this cream have not been shown to cause clinically important methemoglobinemia in preterm and term neonates.⁷⁶ However, despite no data demonstrating additive risk, caution should be used when other agents capable of causing methemoglobinemia (eg, acetaminophen) are coadministered.⁷⁷

Opioids

A variety of opioids are available for pediatric use.^{78,79} Although most of these medications have not received formal approval for use in pediatric patients by the Food and Drug Administration, their use in children of all ages is indicated to treat the pain of procedures, as an adjunct to general anesthesia, for postoperative or postprocedural pain, and for the treatment of painful medical conditions. Such medications may be administered as single or intermittent boluses or as a continuous infusion. For prolonged use, continuous infusion is preferred to avoid large variations in plasma concentration. Whenever medications in this category are administered, there must be accompanying vigilance for potential adverse effects on the respiratory and cardiovascular systems. Such observations may be limited with a single administration but must be more intense with repeated doses, when administered by infusion, or when drug combinations are used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in airway management and in settings with the capacity for continuous monitoring of vital signs (ie, heart rate, blood pressure, respiratory rate, SaO_2).^{59–61} The need for continued treatment with the opioid to manage pain increases the possibility of tolerance that requires dose escalation to maintain analgesia and slow withdrawal of the drug to avoid abstinence syndrome.

The risk of adverse effects is directly related to rate of drug administration, total dose, and combination with other medications capable of central nervous system depression. Intravenous boluses of the synthetic opioids (eg, fentanyl, sufentanil, alfentanil) may be associated with glottic and chest wall rigidity.⁸⁰ The propensity for these adverse effects is reduced by avoiding rapid bolus injection. Administration should be by frequent small aliquots or by infusion over several minutes. The health care pro-

professional who administers opioids should be trained in the recognition and treatment of the adverse complications, including the use of bag-mask ventilation, an opioid antagonist to oppose the respiratory depression, or a muscle relaxant to treat glottic and chest wall rigidity.⁸⁰ The health care professional must have airway management skills and knowledge of the pharmacodynamics of the administered drugs to manage life-threatening events. When an opioid antagonist is administered, the analgesic effect of opioids also is antagonized. Opioid antagonists must be used with caution in neonates who have received prolonged treatment with opioids (>4 days). In this situation, an antagonist (eg, naloxone) may precipitate acute opioid withdrawal with seizures, hypertension, and other adverse clinical consequences.⁸¹

Concomitant use of opioids and benzodiazepines necessitates a decrease in the total dose of opioid and benzodiazepine. However, nonopioid medications should not be used in place of opioids because they do not possess analgesic properties. Moreover, the risk of respiratory depression may be additive or synergistic.

There are insufficient data to recommend one opioid over another. In general, meperidine is not recommended for prolonged administration owing to the possibility of the accumulation of toxic metabolites capable of causing seizures.⁸² When opioids or other sedating medications, such as benzodiazepines, are administered for a prolonged period, physical dependence and tolerance may develop, thus increasing the opioid or sedative requirements to maintain patient comfort.^{81,83-85} The long-term effects of opioids and sedatives have not been well established. However, the first concern of the health care professional should be the treatment of stress or pain, which later can be followed by managing the consequences of the stress or pain treatment.³³

When stress or pain medications are no longer deemed necessary, slow weaning of the patient from opioids and other sedatives over a prolonged period may be required.⁸¹ Such weaning may be a gradual reduction in daily drug dosage with frequent reassessment to ensure that the patient is free of pain and withdrawal symptoms or it may be a change to longer-acting oral medications, such as methadone, that can be tapered.^{81,83-85} The starting dose of methadone should be calculated to provide a dose equivalent to the dose of opioid the neonate is receiving. Methadone kinetics and dosing requirements for extremely premature neonates have not been studied adequately.

Titration of dose to observed clinical effect and administration of the lowest effective dose help to avoid toxic effects. Rectal administration of opioids has been described but is not generally recommended owing to irregular and unpredictable absorption.⁷⁷

Nonsteroidal Anti-inflammatory Drugs

Generally, this category of medications is used to treat less intense pain and as an adjunct to reduce the total dose of more potent analgesics, such as opioids.

Limited data are available on the pharmacokinetics of acetaminophen (paracetamol) in newborns.⁸⁶⁻⁸⁸ Acetaminophen does not reduce the response to pain due to heel-lance procedures⁸⁹ but may provide some reduction in pain after circumcision.⁹⁰ There are no studies in the newborn of the effectiveness and safety of ketorolac or ibuprofen to reduce pain.⁹¹

MANAGEMENT OF NONPAINFUL STRESS (ANXIETY) IN THE NEONATE

Behaviors associated with pain (eg, crying, grimacing, posturing, sweating, restlessness) also may accompany nonpainful care-giving procedures for low birth weight neonates.⁴⁵ Additional research is needed to better differentiate pain, stress, and variation in behavioral or sleep and awake states.⁹² A method to quantitate stress in preterm neonates has been developed to assist neonatal health care professionals to recognize and reduce stress in preterm neonates, although its clinical usefulness requires further evaluation.⁴⁶

Noxious environmental stimuli should be minimized. Only limited research addresses the short- and long-term efficacy and toxic effects of the pharmacological agents (sedatives and hypnotics) used to manage perceived neonatal anxiety. Thus, health care professionals must individualize decisions about the appropriateness of the use of these drugs based on extrapolation from adult experience and common sense. The following concepts must be kept in mind: 1) Sedatives and anxiolytics do not provide analgesia. If painful procedures are anticipated, analgesics should usually be administered. 2) Long-term use of many sedatives and hypnotics includes the risks of tolerance, dependency, and withdrawal. 3) Long-term outcome (particularly neurodevelopmental) for infants who have received long-term sedation is unknown, although the long-term effects of neonatal pain and stress were the focus of recent research.^{37-41,48} 4) Sedatives and hypnotics may cause respiratory and cardiovascular depression.⁹³⁻⁹⁷ Continuous pulse oximetry and frequent monitoring of vital signs is recommended strongly. 5) Use of combined therapy with a sedative or hypnotic and an opioid necessitates a decrease in dosage of each. Failure to reduce dosage when used in combination increases the risk of adverse effects, such as respiratory depression. In addition, certain combinations, such as fentanyl and midazolam, should not be given as rapid infusions because this combination is associated with severe systemic hypotension.⁹³⁻⁹⁷

Among older infants, benzodiazepines, barbiturates, chloral hydrate, and phenothiazines have been used for sedation and to relieve anxiety. Of these options, data are available for the use of benzodiazepines, chloral hydrate, and barbiturates in neonates. Of the benzodiazepines, midazolam has been approved for use in neonates, and a randomized, controlled trial has demonstrated sedative effects.⁹⁷ However, adverse hemodynamic effects and abnormal movements have been associated with its use in neonates.⁹⁴⁻⁹⁸ If used, a continuous infusion or administration of individual doses over at least 10 minutes is recommended to reduce the risk of adverse

effects. Data are insufficient to assess the efficacy and safety of lorazepam.⁹⁹⁻¹⁰³ Diazepam is not recommended owing to its long half-life, its long-acting metabolites, and concern about the benzyl alcohol content, although the dose of benzyl alcohol is far less than that associated with toxic effects.^{104,105} Chloral hydrate has been used extensively as a sedative-hypnotic in neonates¹⁰⁶ but it is metabolized to trichloroethanol, which competes for glucuronidation and may exacerbate hyperbilirubinemia.¹⁰⁷ In addition, another metabolite (trichloroacetic acid) persists for up to 1 week after a single dose.¹⁰⁸ Owing to a long half-life for trichloroacetic acid and trichloroethanol in premature neonates, repeated doses may be associated with adverse effects (eg, central nervous system depression, arrhythmias, and renal failure).¹⁰⁹ Thus, repeated doses should not be given. Phenobarbital has a long half-life, and barbiturates may increase the reaction to painful stimuli.¹¹⁰ Evidence of the effectiveness and safety of phenothiazines is lacking; these drugs are not recommended.

RECOMMENDATIONS

- To evaluate and reduce the stress and pain experienced by neonates, validated measures and assessment tools must be used consistently. The assessments should continue as long as the neonate requires treatment for stress or pain.
- Health care professionals should use appropriate environmental, nonpharmacological (behavioral), and pharmacological interventions to prevent, reduce, or eliminate the stress and pain of neonates.
- Pharmacological agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Health care institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates, including those receiving palliative care.
- Educational programs to increase the skills of health care professionals in the assessment and management of stress and pain in neonates should be provided.
- There is a need for development and validation of neonatal pain assessment tools that are easily applicable in the clinical setting.
- For research purposes, a minimal set of well-defined outcome measures, including short- and long-term effects of interventions aimed at reducing stress and pain in the neonate, should be identified to permit statistical synthesis of data (meta-analysis) and more accurate estimates of effect size.

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