American Academy of Pediatrics
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POLICY STATEMENT

Prevention and Management of Pain in the Neonate: An Update

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

AMERICAN ACADEMY OF PEDIATRICS
Committee on Fetus and Newborn, Section on Surgery, and Section on Anesthesiology and Pain Medicine

CANADIAN PAEDIATRIC SOCIETY
Fetus and Newborn Committee

ABSTRACT

The prevention of pain in neonates should be the goal of all caregivers, 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 our 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. Every health care facility caring for neonates should implement an effective pain-prevention program, which includes strategies for routinely assessing pain, minimizing the number of painful procedures performed, effectively using pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and eliminating pain associated with surgery and other major procedures.

INTRODUCTION

Objectives

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

1. emphasize that despite increased awareness of the importance of pain prevention, neonates in the NICU continue to be exposed to numerous painful minor procedures daily as part of their routine care;
2. present objective means of assessing neonatal pain by health care professionals;
3. describe effective strategies to prevent and treat pain associated with routine minor procedures; and
4. review appropriate methods to prevent and treat pain associated with surgery and other major procedures.

Background

The prevention of pain in neonates is an expectation of parents.[1] However, there are major gaps in our knowledge regarding the most effective way to accomplish this. Although it may not be possible to completely eliminate pain in neonates, much can be done to reduce the amount and intensity of pain. The prevention of

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Key Words
pain, neonates

Abbreviations
IVH—intraventricular hemorrhage
PVL—periventricular leukomalacia
ROP—retinopathy of prematurity

pain is important not only because it is an ethical expectation but also because repeated painful exposures can have deleterious consequences.[2–21] These consequences include altered pain sensitivity[5,7–9] (which may last into adolescence[15]) and permanent neuroanatomic and behavioral abnormalities, as found in animal studies.[5,14] It seems that altered pain sensitivity can be ameliorated if effective pain relief is provided.[7,17] There is growing concern that the long-term consequences of repeated pain in vulnerable neonates may also include emotional, behavioral, and learning disabilities[3,4,6,10,13,16]; however, there are no definitive data in humans. During the last few years, there has been considerable interest in the diagnosis and treatment of acute pain in the neonate, but there has been little published on the related subjects of stress and chronic pain in this population. In the original statement, stress and chronic pain were briefly discussed in addition to acute pain.[2] However, neither chronic pain nor stress has been specifically defined for the neonate, and only an intuitive understanding of these concepts is possible. Therefore, this updated statement deals primarily with acute pain prevention.

Neonates at greatest risk of neurodevelopmental impairment as a result of preterm birth (ie, the smallest and sickest neonates) are also those most likely to be exposed to the greatest number of painful stimuli in the NICU,[18] creating a "double-hit" phenomenon. Although effective pain relief is now usually provided for neonates during and after a major surgical procedure,[21] pain-reducing therapies are often underused for the numerous minor procedures that are a part of routine medical and nursing care for neonates.[20,21] Because the most effective and safest ways to prevent pain in the neonate are unknown, striking a proper balance between effective pain relief and avoidance of serious adverse effects from pain medications is a major challenge for caregivers. The subject of pain in the neonate was recently the focus of the Newborn Drug Development Workshop sponsored by the National Institute of Child Health and Human Development and the US Food and Drug Administration. The reader is referred to their publications for a detailed review and their discussions.[22–24]

ASSESSMENT OF PAIN AND STRESS IN THE NEONATE

Optimal pain management requires competent pain assessment, which can be especially difficult to perform in neonates. The pain-assessment tool used should be multidimensional, including measurements for both physiologic and behavioral indicators of pain, because neonates cannot self-report.[25–29] Physiologic indicators of pain include changes in heart rate, respiratory rate, blood pressure, oxygen saturation, vagal tone, palmar sweating, and plasma cortisol or catecholamine concentrations. Behavioral indicators include changes in facial expressions, body movements, and crying, but these may be absent in some neonates who are neurologically impaired or pharmacologically paralyzed.

When pain is prolonged, striking changes occur in the infant's physiologic and behavioral indicators. During episodes of prolonged pain, neonates enter a state of passivity with few, if any, body movements; an expressionless face; decreased heart rate and respiratory variability; and decreased oxygen consumption, all suggestive of a marked conservation of energy. Prolonged or repeated pain also increases the response elicited by future painful stimuli (hyperalgesia) and even by usually nonpainful stimuli (allodynia). Therefore, pain scales that are used in postoperative neonates should be sensitive to the changes in response that can occur when pain is prolonged.[27]

The most commonly used assessment tools are listed in Table 1.[30–45] For each tool, the physiologic and behavioral indicators of pain are described, the population for which they have been validated are delineated, and unique aspects are listed. Whatever assessment tools are used, continual multidisciplinary training of staff in the recognition of neonatal pain and in the use of the chosen pain-assessment tools should be provided.[26] Although in recent years, increased interest and research in the assessment of pain and stress in the neonate has occurred, there remains a need to develop a tool to measure pain in pharmacologically paralyzed and severely neurologically impaired infants.[40]

REDUCING PAIN FROM BEDSIDE CARE PROCEDURES

Neonates in the NICU often experience painful procedures during routine care,[10,21] such as needle insertions,[46–51] suctioning,[47,52,53] gavage-tube placement,[51,52,54] and tape removal,[52] as well as stressful disruptions, including diaper changes,[54] chest physical therapy,[54] physical examinations,[51] nursing evaluations,[52] and exposure to environmental stimuli.[20] Despite increased awareness by caregivers that neonates in the NICU frequently experience pain, effective pain relief for these routine procedures is often underused.[20,21,55] As discussed more completely later, the continuous infusion of morphine in ventilated preterm neonates may not effectively prevent acute pain from minor painful procedures and may increase adverse events.[56,57] However, there are other effective methods of preventing minor procedural pain in neonates, which should be used routinely. As part of a comprehensive pain-prevention program,[19,58,59] each neonatal unit should develop strategies to minimize the number of minor painful or stressful procedures and provide effective nonpharmacologic and/or pharmacologic pain relief for all procedures.

Reduction of Painful Events

Clearly, the most effective way of reducing minor procedural pain in the neonate is to reduce the number of procedures performed.[58] There currently is a paucity of

TABLE 1 **Pain-Assessment Tools**

Assessment Tool	Physiologic Indicators	Behavioral Indicators	Gestational Age Tested	Assesses Sedation	Scoring Adjusts for Gestational Age	Nature of Pain Assessed
PIPP: Premature Infant Pain Profile	Heart rate, oxygen saturation	Brow bulge, eyes squeezed shut, nasolabial furrow	28–40 wk	No	Yes	Procedural and postoperative pain
CRIES: Crying, Requires Oxygen Saturation, Increased Vital Signs, Expression, Sleeplessness	Heart rate, oxygen saturation	Crying, facial expression, sleeplessness	32–36 wk	No	No	Postoperative pain
NIPS: Neonatal Infant Pain Scale	Respiratory patterns	Facial expression, cry, movements of arms and legs, state arousal	28–38 wk	No	No	Procedural pain
N-PASS: Neonatal Pain Agitation and Sedation Scale	Heart rate, respiratory rate, blood pressure, oxygen saturation	Crying, irritability, behavior state, extremities tone	0–100 d of age and adjusts score on the basis of gestational age	Yes	Yes	Ongoing and acute pain and sedation
NFCS: Neonatal Facing Coding System	None	Facial muscle group movement	Preterm and term neonates, infants at 4 mo of age	No	No	Procedural pain
PAT: Pain Assessment Tool	Respirations, heart rate, oxygen saturation, blood pressure	Posture, tone, sleep pattern, expression, color, cry	Neonates	No	No	Acute pain
SUN: Scale for Use in Newborns	Central nervous system state, breathing, heart rate, mean blood pressure	Movement, tone, face	Neonates	No	No	Acute pain
EDIN: Echelle de la Douleur Inconfort Nouveau-Ne' (Neonatal Pain and Discomfort Scale)	None	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	25–36 wk (preterm infants)	No	No	Prolonged pain
BPSN: Bernese Pain Scale for Neonates	Heart rate, respiratory rate, blood pressure, oxygen saturation	Facial expression, body posture, movements, vigilance	Term and preterm neonates	No	No	Acute pain

research regarding effective ways to accomplish this, but strategies for reducing the number of procedures that neonates experience should be developed and their effectiveness should be tested.[55] Such an approach might include reducing the number of bedside disruptions in care.[55,60,61] Other strategies might include bundling interventions, eliminating unnecessary laboratory or radiographic procedures, using transcutaneous measurements when possible, and minimizing the number of repeat procedures performed after failed attempts.[58]

Nonpharmacologic Pain Prevention for Minor Procedures

A variety of nonpharmacologic pain-prevention and -relief techniques have been shown to effectively reduce pain from minor procedures in neonates. These include use of oral sucrose/glucose,[62–76] breastfeeding,[77] nonnutritive sucking,[49,78] "kangaroo care" (skin-to-skin contact),[55,58] facilitated tuck (holding the arms and legs in a flexed position),[79] swaddling,[80] and developmental care, which includes limiting environmental stimuli, lateral positioning, the use of supportive bedding, and attention to behavioral clues.[61] These measures have been shown to be useful in preterm and term neonates in reducing pain from a heel stick,[68,70–73,79,80] venipuncture,[62,64,65,67,74,77,81] and subcutaneous injections[81] and are generally more effective when used in combination than when used alone.[63,65,68,69,80,82] Concentrated oral sucrose has been widely studied. Oral sucrose eliminates the electroencephalographic changes associated with a painful procedure[83] in a neonate, but the mechanism of pain relief by sucking oral sucrose is not known for certain. In one study, endogenous endorphin concentrations did not increase with administration of oral sucrose as originally proposed.[84] Although the intraoral administration of sucrose to preterm infants without suckling is effective, intragastric administration is not.[72] Concentrated oral glucose has also been used and diminishes the pain response of venipuncture, but it does not decrease oxygen consumption or energy expenditure, suggesting there may still be a stress response.[85]

A wide range of oral sucrose doses have been used in neonates for pain relief, but an optimal dose has not been established.[75,86] The dosage range of sucrose for reducing pain in neonates is 0.012 to 0.12 g (0.05–0.5 mL of 24% solution).[75,86] Some authors have suggested that multiple doses for a procedure (2 minutes before and 1–2 minutes after) are more effective than a single dose.[73,75] The long-term safety of multiple doses of oral sucrose for painful procedures in neonates has not been established.[87] Additional research is needed to fully understand the mechanism of action, optimal dose, and safety of repeated doses of oral sucrose in neonates; nevertheless, available data suggest that this is an effective means of alleviating pain for many minor neonatal procedures. Because oral sucrose reduces but does not eliminate pain in neonates, it should be used with other nonpharmacologic measures to enhance its effectiveness.

Topical Anesthetic Pain Prevention for Minor Procedures

Topical anesthetics can effectively reduce pain from some procedures such as a venipuncture,[62,88–90] lumbar puncture,[91] and intravenous catheter insertion[91] in term and preterm neonates. These agents must be applied for a sufficient length of time before the procedure (usually 30 minutes for neonates), and they are not effective for a heel-stick blood draw,[92,93] because the pain from heel sticks is primarily from squeezing the heel and not from the lancet.[48] Other nonpharmacologic means of alleviating pain mentioned previously should be used for heel sticks. Topical anesthetics were not effective for peripheral intravenous central catheter placement in one trial.[94] There is a risk of methemoglobinemia after use of topical lidocaine-prilocaine cream in certain situations.[95,96] The risks can be minimized if used no more than once daily, on intact skin only, and not with other drugs known to cause methemoglobinemia.[97,98]

Prolonged Mechanical Ventilation

Many preterm neonates receiving intensive care undergo prolonged mechanical ventilation, and its use defines a population of patients experiencing numerous minor painful procedures as described previously. The routine use of continuous pain medication and sedatives for ventilated preterm neonates has been evaluated.[24] Two large randomized, controlled trials of the continuous use of intravenous morphine primarily as a potential means of decreasing poor neurologic outcome in preterm neonates receiving mechanical ventilation were published recently.[56,57] In both studies, additional open-label morphine was allowed if infants were considered to be in pain. In the first study,[56] continuous morphine infusion was used for 7 days or less as clinically needed. In this study, morphine had no apparent analgesic effect and did not alter the risk of a poor neurologic outcome (severe intraventricular hemorrhage [IVH], periventricular leukomalacia [PVL], or death). In the second study,[57] a continuous morphine infusion was used for up to 14 days. In this study, morphine use reduced pain scores slightly but did not alter the risk of severe IVH, cystic PVL, or a composite outcome (severe IVH, cystic PVL, or death within 28 days). In a subsequent analysis, the authors concluded that the use of morphine prolonged the duration of mechanical ventilation.[99] No large studies on the continuous infusion of fentanyl in ventilated preterm infants have been published, but the literature includes many smaller studies that have recently been reviewed.[24] In these studies, fentanyl seemed to result in increased ventilator settings.[24] Concern about adverse respiratory effects of continuous opioid infusions in chronically ventilated preterm infants and lack

of a demonstrated long-term benefit suggest that their routine use cannot be recommended at this time.

Midazolam has been evaluated as a sedative in mechanically ventilated preterm infants. A *Cochrane Database Systematic Review*[100] recently concluded that there were insufficient data to promote use of midazolam because of a lack of demonstrated benefit and concern for an increased risk of poor neurologic outcome. This conclusion was supported by another recent review.[24] Ketamine hydrochloride was evaluated in a randomized, controlled trial for relief of procedural pain associated with endotracheal suctioning in ventilated preterm neonates.[101] However, these authors concluded that ketamine was only modestly effective at reducing pain scores and did not alter physiologic responses in heart rate and systemic blood pressure.

REDUCING PAIN FROM SURGERY

Pain is an inevitable consequence of surgery at every age. Pain is of particular importance in the neonate because of the evidence of improved clinical outcomes, including decreased mortality, when adequate pain control is achieved.[19,102] Tissue injury, which occurs during all forms of surgery, elicits profound physiologic responses. The more marked these responses to surgery, the greater the morbidities and mortality.[103] Thus, minimizing the endocrine and metabolic responses to surgery by decreasing pain has been shown to significantly improve outcomes in neonatal surgery. Although it would now be considered unethical to perform surgery without anesthesia, the appropriate levels of anesthesia for various surgical procedures have not been well investigated. Improving pain management and improving outcomes in the neonate require a coordinated strategy of pain reduction, which must be multidimensional, requires a team approach, and should be a first priority in perioperative management. Despite fears that analgesics (opiates in particular) may lead to hypotension or respiratory depression and an increase in postoperative complications, such effects have never been shown in randomized, controlled trials. Indeed, postoperative inotrope requirements were decreased by high-dose opioids in neonates after cardiac surgery,[104] and postoperative respiratory compromise associated with the pain of a thoracotomy can be relieved by adequate analgesia.[105,106]

Because of the physiologic and metabolic immaturity of the neonate, doses of medications that are effective for the reduction of pain may be close to the doses that cause toxicity. Therefore, the concept of a "balanced analgesia" has arisen, whereby several approaches to pain reduction can be used simultaneously to decrease the dosage required of each medication and, thereby, reduce toxicity. Early and effective pain treatment is associated with a lower total dose of medications, although therapy should be guided by ongoing pain assessment. The developmental pharmacology of the agents used must also be kept in mind. For example, fentanyl, a drug that is metabolized rapidly in older infants, has a half-life averaging approximately 10 hours in the neonate,[107] and clearance is even lower in preterm infants.[108] The residual effects of intraoperative medications also need to be considered. Muscle relaxants completely prevent behavioral pain responses and may last for several hours postoperatively.

As far as possible, stress and preoperative pain should be relieved before surgical interventions. An infant who is stressed and disturbed, unclothed, hypothermic, overstimulated by noise and light, and already experiencing pain will have elevated basal concentrations of adrenal cortical and medullary hormones and will be susceptible to further stress and complications postoperatively. However, there has been little direct investigation of the effects of preoperative analgesia in neonates. A full discussion of intraoperative strategies to reduce pain in neonates is beyond the scope of this statement. However, anesthesia of sufficient depth to prevent intraoperative pain and stress responses must be provided to decrease postoperative analgesic requirements. For some procedures, regional anesthesia is an effective way of controlling intraoperative pain in neonates, but a detailed discussion about regional anesthesia is also beyond the scope of this statement.

Postoperatively, opioids can be given by continuous infusion or by regular bolus. Randomized trials do not show any substantial benefit of continuous infusion of opioids over intermittent dosing, probably because of the long half-life of many of these agents in the neonate.[109] More recently developed rapidly metabolized agents given by infusion hold promise for nurse-controlled anesthesia using a pump (the nurse providing additional boluses of medication as needed). This technique has not been widely investigated but holds promise for reducing the total dose of and complications from opioids.

Intravenous nonsteroidal antiinflammatory agents such as ketorolac and ketoprofen are well established as a means of reducing postoperative opioid requirements in adults. A small number of randomized, controlled trials in children have also shown effective analgesia, with a reduction in morphine requirements leading to reduced postoperative vomiting compared with an opioid-based analgesic.[110] However, bleeding time may be increased,[111] and some reports[112] show an increase in postoperative clinical bleeding, although there are no randomized, controlled trials that have included neonates. A case series of infants younger than 6 months after abdominal surgery suggested a reduction in morphine requirements when ketorolac was used.[113] Lacking any substantial evidence in the neonatal period, nonsteroidal antiinflammatory agents cannot be recommended for use as an adjunct to postoperative anesthesia outside a prospective clinical trial.

Acetaminophen administered orally postoperatively

has been shown to reduce morphine requirements after tonsillectomy.[114] It is associated with less postoperative vomiting than with an opioid-based analgesic[115] and does not affect coagulation. Studies in neonates seem to be limited to use for circumcision, in which it is ineffective for operative and immediate postoperative pain but decreases later postoperative pain scores at 6 hours.[116] Acetaminophen should not be used alone for severe pain but can be considered for use during the later postoperative period, after minor procedures, or as an adjunct to other measures. Dosing guidelines based on extensive literature review have been developed,[117] and a population kinetic study with a large sample size produced similar guidelines.[118] However, rectal acetaminophen should be used cautiously because of erratic absorption.

Although there are few data specific to the neonate, regional analgesia can provide effective postoperative pain relief in some situations.[119,120] There has been little systematic study of ancillary comfort measures in the postoperative neonate. Despite the importance of good pharmacologic treatment, the nonpharmacologic means of reducing pain in neonates discussed previously can also be used postoperatively and should be part of a coordinated effort to reduce the pain and stress experienced by infants during the postoperative period.

REDUCING PAIN FROM OTHER MAJOR PROCEDURES

Intercostal Drains

Insertion of a chest drain for pneumothorax or pleural fluid drainage is a painful procedure that is sometimes required in an emergency situation. There have been no prospective studies of analgesia for the insertion of chest tubes in the neonate. The recommendations, therefore, are based on general principles.[19] Infiltration of the skin site with a local anesthetic before incision has long-lasting effects on pain responses (see above) and should be used routinely unless there is life-threatening instability. Slow infiltration reduces pain from lidocaine infiltration.[121] Although there are no available data on the use of opioids before or after chest-tube insertion for pain prevention, this seems to be a reasonable approach. Nonpharmacologic means of reducing pain in neonates should be used also.

Chest-Drain Removal

Removal of the chest drain is also known to be very painful.[122] A prospective study of methohexital for chest-tube removal in the neonate has demonstrated good pain control without significant respiratory compromise.[123] In older children, low-dose morphine and topical lidocaine-prilocaine cream were equally effective.[122]

Intubation

The experience of being intubated is unpleasant[124,125] and painful.[21] Morphine seems not to reduce the occurrence of severe hypoxia with bradycardia during intubation, probably because of the delayed onset of action.[126] Opioids with a more rapid onset of action, such as fentanyl, are probably preferable.[127] In a randomized trial, thiopentone was shown to reduce apparent pain in neonates undergoing intubation.[128] Methohexital in an uncontrolled study was associated with smooth intubating conditions and no apparent distress during intubation.[129] Studies on medications for use during endotracheal intubation are needed to address the requirements for analgesia, prevention of adverse physiologic responses (particularly bradycardia), and pharmacologic paralysis. This complex issue will be discussed further in a forthcoming statement from the American Academy of Pediatrics and Canadian Paediatric Society on the use of medications for elective intubation of neonates.

Retinal Examination and Surgery for Retinopathy of Prematurity

Retinal examinations for retinopathy of prematurity (ROP) are painful,[130,131] and the pain is not completely relieved by use of oral sucrose.[132,133] Topical anesthetics are used often, but their effectiveness is limited.[134] Retinal surgery is also painful and leads to substantial physiologic disturbance that is not adequately treated with topical anesthesia.[130] There are limited data on the effective prevention of pain from ROP surgery. One small uncontrolled study suggested that continuous intravenous infusion of remifentanil effectively reduced pain from laser therapy for ROP.[135]

Circumcision

Pain relief for circumcision should always be provided. The American Academy of Pediatrics has published a separate statement on this subject.[136]

RECOMMENDATIONS

Assessment of Pain and Stress in the Neonate

1. Caregivers should be trained to assess neonates for pain using multidimensional tools.
2. Neonates should be assessed for pain routinely and before and after procedures.
3. The chosen pain scales should help guide caregivers in the provision of effective pain relief.

Reducing Pain From Bedside Care Procedures

1. Care protocols for neonates should incorporate a principle of minimizing the number of painful disruptions in care as much as possible.
2. Use of a combination of oral sucrose/glucose and other nonpharmacologic pain-reduction methods (nonnutritive sucking, kangaroo care, facilitated tuck,

swaddling, developmental care) should be used for minor routine procedures.

3. Topical anesthetics can be used to reduce pain associated with venipuncture, lumbar puncture, and intravenous catheter insertion when time permits but are ineffective for heel-stick blood draws, and repeated use of topical anesthetics should be limited.
4. The routine use of continuous infusions of morphine, fentanyl, or midazolam in chronically ventilated preterm neonates is not recommended because of concern about short-term adverse effects and lack of long-term outcome data.

Reducing Pain From Surgery

1. Any health care facility providing surgery for neonates should have an established protocol for pain management. Such a protocol requires a coordinated, multidimensional strategy and should be a priority in perioperative management.
2. Sufficient anesthesia should be provided to prevent intraoperative pain and stress responses to decrease postoperative analgesic requirements.
3. Pain should be routinely assessed by using a scale designed for postoperative or prolonged pain in neonates.
4. Opioids should be the basis for postoperative analgesia after major surgery in the absence of regional anesthesia.
5. Postoperative analgesia should be used as long as pain-assessment scales document that it is required.
6. Acetaminophen can be used after surgery as an adjunct to regional anesthetics or opioids, but there are inadequate data on pharmacokinetics at gestational ages less than 28 weeks to permit calculation of appropriate dosages.

Reducing Pain From Other Major Procedures

1. Analgesia for chest-drain insertion comprises all of the following:
   a. general nonpharmacologic measures;
   b. slow infiltration of the skin site with a local anesthetic before incision unless there is life-threatening instability (if there was inadequate time to infiltrate before insertion of the chest tube, local skin infiltration after achieving stability may reduce later pain responses and later analgesic requirements); and
   c. systemic analgesia with a rapidly acting opiate such as fentanyl.
2. Analgesia for chest-drain removal comprises the following:
   a. general nonpharmacologic measures and
   b. short-acting, rapid-onset systemic analgesic.
3. Although there are insufficient data to make a specific recommendation, retinal examinations are painful, and pain-relief measures should be used. A reasonable approach would be to administer local anesthetic eye drops and oral sucrose.
4. Retinal surgery should be considered major surgery, and effective opiate-based pain relief should be provided.

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