Review

Managing Procedural Pain in the Neonate Using an Opioid-sparing Approach

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ABSTRACT

Purpose: Pain in the neonate is often challenging to assess but important to control. Physicians often must balance the need for optimal pain control with the need to minimize oversedation and prolonged opioid use. Both inadequate pain control and overuse of opioids can have long-term consequences, including poor developmental outcomes. The aim of this review is to introduce a comprehensive approach to pain management for physicians, nurses, and surgeons caring for critically ill neonates, focusing on nonopioid alternatives to manage procedural pain.

Findings: After review, categories of opioid-sparing interventions identified included (1) nonopioid pharmacologic agents, (2) local and regional anesthesia, and (3) nonpharmacologic alternatives. Nonopioid pharmacologic agents identified for neonatal use included acetaminophen, NSAIDs, dexmedetomidine, and gabapentin. Local and regional anesthesia included neuraxial blockade (spinals and epidurals), subcutaneous injections, and topical anesthesia. Nonpharmacologic agents uniquely available in the neonatal setting included skin-to-skin care, facilitated tucking, sucrose, breastfeeding, and nonnutritive sucking.

Implications: The use of various pharmacologic and interventional treatments for neonatal pain management allows for the incorporation of opioid-sparing techniques in neonates who are already at risk for poor neurodevelopmental outcomes. A multifactorial approach to pain control is paramount to optimize periprocedural comfort and to minimize the negative sequelae of uncontrolled pain in the neonate. (*Clin Ther*. 2019;41:1701–1713)

Key words: neonate, nonpharmacologic, opioid, opioid-sparing, procedural pain.

INTRODUCTION

The balance between the over- and under-treatment of neonatal procedural pain is challenging, because both insufficient pain control and excess opioid use can lead to poor developmental outcomes.[1] Neonatal physiologic and hormonal responses to pain can lead to increased neurologic morbidity and mortality; thus, timely and effective pain management is integral

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to comprehensive neonatal care.[2–4] Opioid analgesic agents have been historically a first-line treatment for procedural and postoperative pain management in neonatal intensive care units (NICUs) and surgical units. In a survey of hospitals in the United Kingdom, 93% of hospitals used morphine as a first-line medication for postoperative pain management in neonates undergoing elective intubation, sedation for ventilation, and postoperative pain management.[5] Although widespread and commonly used, opioid analgesic agents in the neonatal and infant population can have profound side effects, including adverse neurodevelopmental outcomes.[2,6–9] Furthermore, long-term opioid exposure can result in opioid-induced hyperalgesia, tolerance, and withdrawal.[10] Fortunately, nonopioid analgesia provides tolerable and efficacious pharmacologic alternative treatment to neonates and infants who have undergone surgery or a procedure in an intensive care setting. The aim of this article is to review nonopioid alternatives for procedural pain management in term and preterm neonates and infants.

Physiology of Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," but importantly, "inability to communicate verbally does not negate the possibility that an individual is experiencing pain and needs appropriate pain-relieving treatment."[2] The neural pathway of pain begins at sensory receptors that transmit the pain signal to the dorsal horn of the spinal cord, then up the spinothalamic tracts to supraspinal centers in the brainstem, thalamus, and cerebral cortex.[11] Tissues subjected to direct noxious stimuli resulting in damage cause nociceptive pain, whereby the painful response is experienced through pain receptors at the site of injury.[12] Examples include pain after surgery due to iatrogenic tissue violation or acute trauma such as from a sport-related injury.[12] Health care providers rely on physiologic ques (ie, increased heart rate or facial grimacing) or standardized neonatal pain scales (eg, Neonatal Pain, Agitation, and Sedation Scale (NPASS)) to assess pain in neonates. However, there is significant variation between practitioners when rating pain levels in neonates, leading to inconsistent delivery and use of pain medication.[4,13]

Risks of Uncontrolled Pain

Multiple studies report poor outcomes in neonates with undertreated pain that can have both short- and long-term consequences. Short-term effects of uncontrolled pain include changes in physiologic vital signs (eg, oxygen desaturations and increased heart rate), increased catabolism from these physiologic changes, delayed healing time, and greater postoperative morbidity and mortality.[14] Long-term effects of uncontrolled pain include impaired emotional bonding, developmental delay, and hypoactive/hyperactive response to pain, and stress.[15,16] Because of the many negative sequelae from uncontrolled pain in the neonate, proper assessment and treatment are imperative.

Traditionally, the most common therapy for moderate and severe pain control in critically ill children is opioid analgesic agents, providing efficacious and reliable relief for all age groups. Opioids are well known to produce both analgesia and sedation that can acceptably treat neonates and infants undergoing a variety of procedures. Despite the potential side effects of opioids, morphine, for instance, has a wide therapeutic window, and the deleterious effects are often experienced at higher doses or combined with other medications. The benefits of opioids such as morphine are particularly important for neonates subjected to severe pain and physiologic stress due to procedures. For the experienced provider and applicable clinical setting, opioids can be an effective therapy for pain control in the neonate.

Risks of Opioid Overuse

Although opioid analgesic agents routinely and effectively treat pain resulting from many common ICU procedures, opioid overuse is associated with poor neurodevelopmental outcomes in neonates. Risks from opioid overuse include death, prolonged hospitalization, and risk of future habituation in neonates.[17,18] Moreover, studies in neonates with prenatal opioid exposure report increased cognitive, motor, and behavioral delays compared with population norms.[19] Premature neonates in particular are at substantial risk of increased morbidity

associated with opioid exposure. Postnatal studies in preterm neonates exposed to opioids show decreased cerebellar volume, and poorer 18-month motor and cognitive scores are associated with increasing morphine exposure.[8]

Two randomized controlled trials have explored the relationship between opioid use and neurologic morbidity in neonates. In the NOPAIN (Neonatal Outcome and Prolonged Analgesia in Neonates) trial, researchers randomly assigned 67 premature neonates who required intubation and ventilatory support to receive a midazolam infusion, morphine infusion, or saline (placebo) infusion.[20] Infants randomly assigned to the morphine infusion group had significantly lower rates of death, grade III or IV intraventricular hemorrhage, and periventricular leukomalacia than infants randomly assigned to midazolam or saline infusions. Similarly, in the NEOPAIN (Neurologic Outcomes and Pre-emptive Analgesia in Neonates) trial, 898 intubated premature neonates were randomly assigned to either a morphine or saline (placebo) infusion.[21] Of note, both groups in the NEOPAIN trial were allowed open-label, or as needed, dosing of morphine. Unlike the smaller NOPAIN trial, there was no difference between groups for rates of death, intraventricular hemorrhage, or periventricular leukomalacia in the NEOPAIN trial. However, infants in both groups who received additional open-label morphine boluses did exhibit increased rates of death, intraventricular hemorrhage, and periventricular leukomalacia. The morphine group also exhibited increased hypotension, prolonged ventilation, and increased time to reach full enteral nutrition[22–24] Furthermore, long-term clinical characteristics and neurodevelopmental assessments of the morphine infusion group revealed significantly lower weight and head circumference and increased social problems.[2]

Opioid Alternatives

Fortunately, there are many nonopioid pain management strategies appropriate for neonatal and infant use (Table I). Nonopioid pharmacologic alternatives include acetaminophen, NSAIDs (eg, ketorolac, ibuprofen), dexmedetomidine, and gabapentin. Epidural and spinal blocks are routinely used for inguinal hernia repairs, orchiopexy, and circumcision.[25,26] Furthermore, neonates are a unique population in which nonpharmacologic alternatives such as nonnutritive suck with and without oral sucrose, facilitated tucking, or skin-to-skin care (SSC) can be broadly applied.[27]

NONOPIOID PHARMACOLOGIC AGENTS

Various classes of nonopioid pharmacologic agents exist and are emerging as both primary pain control regimens and helpful adjuncts that are beneficial when added to opioid pain control regimens. A summary of nonopioid pharmacologic alternatives is outlined in Table II.

Acetaminophen

Acetaminophen is one of the most commonly delivered drugs to neonates and young children as both an antipyretic and analgesic agent. As an alternative to opioids, acetaminophen has been shown to be an effective postprocedural analgesic agent for neonatal and pediatric populations.[28,29]

Table I. Summary of nonopioid therapies for neonates and infants.

Nonopioid Pharmacologic Agents	Local and Regional Anesthesia	Nonpharmacologic Alternatives
Acetaminophen	Neuraxial blockade (spinal, epidural)	Skin-to-skin care
NSAIDs*	Local anesthetic agents	Facilitated tucking
(ibuprofen, ketorolac)	(lidocaine, bupivacaine)	Oral sucrose/glucose
Gabapentin	Topical anesthetic agents (EMLA†)	Breastfeeding
Dexmedetomidine		Nonnutritive sucking

EMLA = Eutectic Mixture of Local Anesthetics.
* Note: Not approved for use in infants <6 months.
† Trademark: EMLA (Astra Pharmaceuticals, L.P, Wayne, Pennsylvania).

Table II. Commonly used nonopioid pharmacologic agents for neonates and infants in critical care and peri-procedural settings.

Nonopioid Pharmacologic Analgesic Agents	Routes	Advantages	Disadvantages
Acetaminophen	PO, IV, PR	Combined analgesic and antipyretic No respiratory depression PR and IV options for NPO patients Reduction of morphine requirements*	Precluded in patients with compromised liver function Enteral and rectal delivery with variable absorption
NSAIDs	PO, IV	No respiratory depression Anti-inflammatory and analgesic properties	Renal injury Gastrointestinal bleeding Ketorolac not FDA approved for neonates because of demonstrated bleeding risk
Gabapentin	PO	Improves feeding intolerance† Decreases use of benzodiazepines and opioids	Autonomic instability with abrupt withdrawal; symptoms include tachycardia or bradycardia, emesis, and irritability
Dexmedetomidine	IV, IM, intranasal, buccal	Sedative, analgesic, and anti-anxiolytic Rapid onset Limited respiratory depression Does not require intubation for procedural sedation	Currently only off-label use in neonates Requires continuous monitoring Side effects of hypotension and bradycardia

FDA = Food and Drug Administration; NPO = nothing by mouth; PR = per rectum.
* For infants receiving IV acetaminophen in major thoracic and abdominal surgery.
† For infants with visceral hyperalgesia in the setting of neurologic impairment and poor gastrointestinal motility.

Although the mechanisms of acetaminophen are not fully understood, analgesia results from a variety of proposed pathways, including potent inhibitor of prostaglandin synthesis acting within the central nervous system, peripherally acting along the serotonergic pathway by blocking chemoreceptors responsible for nociceptive impulses, producing a metabolite that acts as a ligand for a cannabinoid receptor, and effects on spinal neurotransmitter nitrous oxide.[30–32] Despite acetaminophen's widespread use for infants, the mechanisms of hepatotoxicity are well known and must be judiciously considered in neonates and avoided in those patients with compromised liver function.

Although the multifactorial mechanisms of action probably contribute to acetaminophen's analgesic effects, one must also consider the neonate's unique physiology, as their pharmacodynamics and pharmacokinetics differ substantially from older children and adults. If acetaminophen is administered by the oral route, the slow and variable gastric motility of a newborn paired with the immature ability to acidify gastric juices should be considered. Neonatal gastric motility is slower than in older

children, taking ~6–8 h for gastric emptying. Gastric acid secretions start to occur at day 8–10 of life and are less acidic than pediatric and adult populations.[33] Because acetaminophen is absorbed in the upper small bowel, slow gastric transit time can affect the bioavailability of acetaminophen compared with older children. Often enteral feeding and drug administration are not possible or may be delayed for pediatric patients in an ICU or perioperative setting. For these patients, alternative routes such as rectal and intravenous acetaminophen delivery may be more efficacious.

Rectal administration of medication is often appropriate for surgical patients, especially infants who may be ventilated and unable to tolerate oral intake. The rectum is a well-vascularized site, with two distinct venous drainage systems, enterohepatic and systemic, that can have variable implications on drug absorption. If administered high in the rectum, acetaminophen is subject to enterohepatic circulation, but if administered more distal systemic circulation avoids first-pass metabolism. Although variable in absorption site, bioavailability of medication per rectum is still higher in neonates than older patients, most likely because of less-mature first-pass metabolism in developing hepatic enzymes.[34] Limitations of rectal administration include fixed suppository dosing, loss of suppository with defecation, and the immaturity of the porta-rectal venous system contribute to variable absorption. In addition, prolonged absorption seems to occur in preterm neonates compared with term neonates, with rectal temperature as a possible contribution.[35]

Several studies have shown that rectal mode of delivery results in less-efficient absorption than the oral route, with a single dose unable to achieve a therapeutic plasma concentration for analgesia, thus requiring higher doses than oral route.[35,36] In a randomized trial that assessed oral versus rectal acetaminophen administration for children undergoing tonsillectomy, children who received an oral elixir had higher mean plasma concentrations of acetaminophen and lower pain scores postoperatively than with patients who received a suppository at the equivalent dose of 40 mg/kg.[37] Given the variability of acetaminophen absorption, delivery route in newborns can have inconsistent effects on periprocedural pain control.

Since the advent of intravenous acetaminophen, its use has been increasing in neonates and has favorably augmented postsurgical pain regimens.[38,39] Specifically, when oral or rectal formulations are not appropriate or not adequate for pain control, such as for an infant with ileus, intravenous acetaminophen provides beneficial analgesia. Intravenous acetaminophen is often used in conjunction with opioids for postoperative analgesia, because it can mitigate the cumulative usage of opioid analgesia.[38] A randomized study of neonates and infants undergoing major thoracic and abdominal surgery reported 66% less cumulative morphine doses administered in the first 48 h after surgery when IV acetaminophen was incorporated into the postoperative pain regimen.[40] Decreasing cumulative opioid use for infants and neonates undergoing major surgeries is particularly important to minimize the adverse effects of opioids.

Preterm infants are especially susceptible to opioid-related adverse effects. They often experience more painful and stressful procedures in the NICU than their term counterparts. The stress of surgery has been shown to induce greater white matter injury and lower scores on mental developmental index in small preterm infants.[41] In addition to the stress of surgery, opioid-related respiratory complications can result in devastating events for this at-risk population. Medications that limit respiratory distress episodes and are not associated with adverse neurodevelopmental outcomes are paramount as these can be devastating insults. Incorporating acetaminophen can have a significant effect on decreasing dosage for opioids, with infants receiving acetaminophen requiring fewer cumulative doses of morphine.[42] A significant decrease is important, because cumulative opioid dose is associated with worse neurodevelopmental outcomes at 2 years.[43] For preterm neonates subjected to critical procedures, it seems that intravenous acetaminophen is a preferred route of administration, given its predictable absorption and decrease in morphine requirements.

NSAIDs

With the focus of opioid analgesia minimization, NSAIDs have become a common adjunct in procedural analgesia. NSAIDs are widely used in

pediatric and adult populations after surgery, but the safety profile and efficacy in the neonatal population is only partially understood. NSAIDs are cyclooxygenase inhibitors that act by constricting prostaglandin synthesis. However, systemic toxicities such as renal injury and gastrointestinal bleeding are particularly worrisome in infants, and most NSAIDs are not approved for use in patients younger than 6 months. Historically, the most serious adverse effects of NSAID usage are encountered in neonates being treated for patent ductus arteriosus, who require higher doses and longer duration of NSAID usage than those for postoperative analgesia.[44]

Among NSAIDs, ketorolac is approved by the Food and Drug Administration for intravenous administration. Ketorolac is a potent inhibitor of prostaglandin synthesis, and an IV formulation makes it an attractive postsurgical analgesic agent. In a retrospective study of 18 infants in Italy, a single postoperative dose of 1 mg/kg ketorolac was found to achieve near total pain control in almost all patients without any renal, hepatic, or hematologic complications.[45] Despite this, although ketorolac has been used in the pediatric and adult population, its use in neonatal postoperative management is not currently advised because of bleeding events as a major side effect. In a retrospective cohort study of 57 postsurgical neonates and infants aged 0−3 months in the United States, 17.2% of patients experienced a bleeding complication after ketorolac administration.[46] Complications were more likely in neonates younger than 21 days and younger than 37 weeks of corrected gestational age. Given the concerns of bleeding and the contrasting findings between small, retrospective studies, extreme caution should be advised with NSAID use for periprocedural pain management in neonatal populations.

Dexmedetomidine

More recently, use of dexmedetomidine in perioperative pain management has gained popularity because of its favorable pharmacologic properties. Dexmedetomidine is a highly selective α2-agonist that provides sedation, analgesia, and antianxiolytic properties without appreciably compromising respiratory function.[47] The mechanism of analgesia is by inhibition of release of substance P and shares a potassium channel with opioid receptors.[48,49] Dexmedetomidine was initially used as an off-label sedative for infants undergoing open heart surgery because of its minimal effects on respiratory function at sedative doses. More recently, current indications have evolved, finding efficacy in the critical care setting of dexmedetodine to reduce opioid usage in neonates and pediatric patients and to facilitate extubation.[50,51]

Dexmedetomidine can be administered intravenously, intramuscularly, orally, buccally, and intranasally. Intranasal and buccal administrations are relatively noninvasive and have high bioavailability, which can be an especially useful option for pediatric patients undergoing surgery.[52] In patients undergoing tonsillectomy, premedication with intranasal dexmedetomidine markedly reduced the required dosage of postoperative analgesia.[53] Infusion routes are often necessary for surgical patient and for ICU sedation. A metanalysis of randomized controlled trials in adults assessing use of intraoperative dexmedetomidine for postoperative pain control found collectively that patients experienced lower postoperative pain, had lower consumption of opioid pain medication in the first 24 hours postoperatively, and had lower opioid-related adverse effects.[54] Although tolerability and efficacy have been validated in adult populations in which dexmedetomidine gained approval by the Food and Drug Administration, the use of dexmedetomidine in infants is still off-label. Currently, clinical experience with dexmedetomidine in infants is based on off-label use that is limited to case reports and small case series.[55,56] Further studies focused on neonates and infants may validate favorable efficacy for postoperative pain control in children as has been seen in older children and adults.

Gabapentin

Gabapentin is a γ-aminobutyric acid analogue that acts by binding the α_2-δ subunit on voltage-gated calcium channels, blocking the release of excitatory neurotransmitters in the central nervous system that cause pain.[57] The role of gabapentin in neonates and infants has been gaining attention because of its efficacy in treating refractory pain not responding to traditional analgesic agents and for its relatively tolerable side effect profile compared with opioids.

Gabapentin is increasingly used to treat multiple conditions in neonates and infants cared for in the NICU. Agitation and refractory pain are often

difficult to manage in critically ill infants undergoing procedures in the ICU. A retrospective study found that the addition of gabapentin to relieve pain and agitation in neonates and infants in the ICU was associated with decreased scores on the Neonatal Pain, Agitation, and Sedation Scale and reduced requirements for analgesic and sedative medications.[58] The upregulation of sensory input in visceral hyperalgesia is associated with pain and prolonged feeding intolerance in the neonatal patient population. There is growing retrospective evidence for term and preterm infants with refractory visceral hyperalgesia caused by neurologic and gastrointestinal morbidities, suggesting that gabapentin reduces chronic irritability and feeding intolerance and reduces benzodiazepine and opioids use.[59,60] For a certain subset of neonates and infants with either refractory pain or agitation or for the neurodevelopmentally impaired child with enteral feeding compromise, gabapentin may be a useful adjunct.

LOCAL ANESTHESIA

Neuraxial blockade

Neuraxial anesthesia is an alternative method to opioid analgesic agents for procedural and postoperative pain. This includes spinal and epidural blockade by percutaneously administered local anesthetic agents as a continuous infusion or single injection.[61] Local anesthetic agents such as bupivacaine, lidocaine, or ropivacaine are commonly administered as regional anesthesia.[61–63] These blocks allow for pain relief without the risks of systemic side effects of opioids such as cardiorespiratory impairment.[64] They allow for earlier extubation, decreased perioperative apnea and respiratory morbidity, decreased exposure to volatile anesthetic agents, lower perioperative response to stress, and better pain relief.[62] They can also be used as the sole anesthetic agent in awake patients for minor surgeries (inguinal hernia repair, circumcision, orchidopexy, hydrocele, hypospadias repair, rectal surgery, or lower extremity surgery) or for procedures (chest tubes, proctoscopy, colonoscopy, cystoscopy, or nonsurgical reduction of intussusception).[63,64] Placement of neuraxial blockade requires an experienced provider with good technique for appropriate placement and careful attention to pediatric analgesic dosing to prevent local anesthetic toxicity that may result in seizures or dysrhythmias.[62,63]

Topical Analgesic Agents

In the setting of procedures such as venipuncture, peripheral arterial puncture, and percutaneous central venous catheter insertion, topical agents such as Eutectic Mixture of Local Anesthetics (EMLA*) may be used to obtain local anesthesia.[65] EMLA is a combination of 2.5% prilocaine and 2.5% lidocaine that, on application to skin, allows for absorption of the two agents into the epidermal and dermal skin layers, resulting in anesthesia at the area of application.[66] It has been shown to reduce pain associated with lumbar puncture at the time of needle insertion and withdrawal and for venipuncture, particularly when used in combination with oral sucrose.[67–69] It was also found to be efficacious in decreasing pain associated with circumcision when combined with a regional block and/or oral sucrose.[70,71] However, care must be taken with regard to dosing, frequency of use, and time of administration especially in preterm infants, because it places the neonate at risk of methemoglobinemia, skin irritation, and toxicity.[72]

NONPHARMACOLOGIC ALTERNATIVES

Procedural pain can cause neonates significant distress, especially for infants in the NICU where they can average up to 14 procedures per day, often without analgesia.[73–75] As a result, nonpharmacologic interventions such as SSC, facilitated tucking, oral sucrose, breastfeeding, and nonnutritive sucking have been introduced as important mediators in managing neonatal distress in the hospital setting.[73,74,76] These nonpharmacologic therapies may be used alone or in combination with other interventions to address mild to moderate pain secondary to heel sticks, intravenous access, injections, circumcision, oral gastric tube insertion, and lumbar puncture.[18,77]

Skin-to-Skin Care and Facilitated Tucking

Skin-to-skin care (SSC) involves direct skin-to-skin contact between the neonate and the caregiver. This contact has been shown to increase oxytocin levels

* Trademark: EMLA (Astra Pharmaceuticals, L.P, Wayne, Pennsylvania).

and to decrease cortisol levels after 60 min of SSC.[78] SSC also decreases pain-related stress in neonates undergoing heel lancing and venipuncture and facilitates physiologic stability.[79–83] Furthermore, tolerability and feasibility of SSC for surgical infants, including intubated infants,[84–87] has also been established.[80] A comprehensive systematic review of barriers and enablers of SSC revealed that most barriers are at the hospital and staff level.[88] For critically ill infants and their caregivers, multidisciplinary endorsement of SSC from nursing and physician teams is paramount in an effort to minimize procedural pain.

Facilitated tucking involves gently holding the neonate in a flexed position while in a supine, prone, or decubitus position.[89] It may be used during small procedures resulting in mild pain such as heel sticks, venipuncture, and endotracheal suctioning, especially in premature infants.[90] Studies show that it can be combined with other interventions such as oral sucrose or nonnutritive sucking for improved efficacy.[89,91,92] However, its use as a sole method of pain management for repeated procedures is discouraged.

Oral Sucrose/Glucose, Breastfeeding, and Nonnutritive Sucking

Oral feeding and stimulation are simple bedside interventions for pain management in the neonate.[75] Both oral feeding and oral stimulation work by increasing endogenous endorphin levels in the neonate and improving pain.[93] Administration of oral sucrose/glucose was found to be effective in single event procedures such as heel stick, intramuscular injections, oral gastric tube insertion, and venipuncture and for echocardiography and retinalexaminations.[94] It is also effective in combination with EMLA with and without a local anesthetic block in relieving circumcision-associated pain.[70] However, it is unclear whether there are adverse outcomes related to dose–response or tolerance.

Breastfeeding and nonnutritive suckling are both evidence-based methods for pain relief in neonates undergoing painful procedures such as heel sticks, intramuscular injections, or venipuncture. In comparison to SSC, topical anesthetics, and music therapy, a systematic review of the literature by Benoit et al[95] found breastfeeding to be more effective than all other therapies and recommended that it be a first-

Managing Pain in Neonates Using an Opioid-Sparing Approach: Highlights

- Critically ill neonates frequently undergo numerous painful procedures. Pain in the neonate is often challenging to assess but important to control.
- Opioid analgesics are beneficial and historically reliable therapies for pain control and sedation, but can be limited by the risk of unwanted side effects and future dependence.
- Nonopioid pharmacologic agents can provide primary pain control, replacing traditional opioids and/or provide adjunctive modes of pain control that reduce opioid requirements.
- Local and regional anesthesia such as neuraxial spinal and epidural blockade, local subcutaneous anesthetics, and topical agents provide additional periprocedural pain control.
- Nonpharmacologic alternatives such as skin-to-skin care, sucrose/glucose, facilitated tucking, breastfeeding, and nonnutritive sucking used alone or in combination with other interventions can address mild to moderate pain and decrease neonatal distress during procedures.

Figure 1. Managing pain in neonates using an opioid-sparing approach: highlights.

line intervention for the aforementioned procedures.[95] Nonnutritive sucking also improves neonatal response to pain during minor procedures in the NICU. Most commonly, nonnutritive suckling used in combination with other nonpharmacologic pain management techniques is most effective. A prospective, randomized control trial of nonnutritive sucking, oral breast milk, and facilitated tucking conducted by Peng et al[96] found that the combined use of these modalities effectively reduced preterm infants' mild pain and moderate-to-severe pain during heel-stick procedures. These findings are further underscored in the systematic review and meta-analysis of oral sucrose in combination with nonnutritive suckling conducted by Liu et al[74] that the combined therapies can be an alternative for better prevention and management of procedure pain in NICU newborns.[74] In summary, most nonpharmacologic pain management techniques are best used in combination with each other to optimize infant comfort.

CONCLUSIONS

Opioids have historically provided sufficient pain control and sedation for critically ill neonates and infants undergoing procedures. Alternatives to opioid analgesic agents have emerged as both primary and adjunctive therapies with promising applications in critical care settings. Optimizing pain control with opioid-sparing techniques may reduce the risk of poor neurodevelopmental outcomes in infants and neonates. Strong evidence supports the use of nonopioid pharmacologic agents, regional anesthesia, and nonpharmacologic interventions. As outlined in Figure 1, a multimodal approach to pain management is paramount to optimize periprocedural discomfort and to minimize the negative sequelae of uncontrolled pain in the neonate.

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Drs. Squillaro, Mahdi, and Tran conceptualized and designed the study, analyzed and interpreted the data, and critically reviewed and revised the manuscript. Drs. Lakshmanan and Kim critically reviewed the manuscript for important intellectual content. Dr. Kelley-Quon conceptualized and designed the study, analyzed and interpreted the data, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Valeri BO, Holsti L, Linhares MBM. Neonatal pain and developmental outcomes in children born preterm: a systematic review. *Clin J Pain*. 2015;31:355–362. https://doi.org/10.1097/AJP.0000000000000114.
2. Ferguson SA, Ward WL, Paule MG, Hall RW, Anand KJS. A pilot study of preemptive morphine analgesia in preterm neonates: effects on head circumference, social behavior, and response latencies in early childhood. *Neurotoxicol Teratol*. 2012;34:47–55. https://doi.org/10.1016/j.ntt.2011.10.008.
3. Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. *Ann Neurol*. 2012;71(3):385–396. https://doi.org/10.1002/ana.22267.
4. Anand KJS. Pain assessment in preterm neonates. *Pediatrics*. 2007;119:605–607. https://doi.org/10.1542/peds.2006-2723.
5. McKechnie L, Levene M. Procedural pain guidelines for the newborn in the United Kingdom. *J Perinatol*. 2008;28:107–111. https://doi.org/10.1038/sj.jp.7211822.
6. Purcell-Jones G, Dormon F, Sumner E. The use of opioids in neonates. A retrospective study of 933 cases. *Anaesthesia*. 1987;42:1316–1320.
7. Yaster M, Deshpande JK. Management of pediatric pain with opioid analgesics. *J Pediatr*. 1988;113:421–429.
8. Zwicker JG, Miller SP, Grunau RE, et al. Smaller cerebellar growth and poorer neurodevelopmental outcomes in very preterm infants exposed to neonatal morphine. *J Pediatr*. 2016;172:81–87.e2. https://doi.org/10.1016/j.jpeds.2015.12.024.
9. de Graaf J, van Lingen RA, Simons SHP, et al. Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial. *Pain*. 2011;152:1391–1397. https://doi.org/10.1016/j.pain.2011.02.017.

10. Anand KJS, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics*. 2010;125:e1208—e1225. https://doi.org/10.1542/peds.2009-0489.
11. Yam M, Loh Y, Tan C, Khadijah Adam S, Abdul Manan N, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. *Int J Mol Sci*. 2018;19:E2164. https://doi.org/10.3390/ijms19082164.
12. Nicholson B. Differential diagnosis: nociceptive and neuropathic pain. *Am J Manag Care*. 2006;12(9 Suppl): S256—S262.
13. Ranger M, Johnston CC, Anand KJS. Current controversies regarding pain assessment in neonates. *Semin Perinatol*. 2007;31:283—288. https://doi.org/10.1053/j.semperi.2007.07.003.
14. Hall RW, Anand KJS. Short- and long-term impact of neonatal pain and stress: more than an ouchie. *Neoreviews*. 2005;6:e69—e75. https://doi.org/10.1542/neo.6-2-e69.
15. Victoria NC, Murphy AZ. Exposure to early life pain: long term consequences and contributing mechanisms. *Curr Opin Behav Sci*. 2016;7:61—68. https://doi.org/10.1016/j.cobeha.2015.11.015.
16. Marcus DA. A review of perinatal acute pain: treating perinatal pain to reduce adult chronic pain. *J Headache Pain*. 2006;7:3—8. https://doi.org/10.1007/s10194-006-0267-5.
17. Fodor A, Tímár J, Zelena D. Behavioral effects of perinatal opioid exposure. *Life Sci*. 2014;104:1—8. https://doi.org/10.1016/j.lfs.2014.04.006.
18. Carter BS, Brunkhorst J. Neonatal pain management. *Semin Perinatol*. 2017;41:111—116. https://doi.org/10.1053/j.semperi.2016.11.001.
19. Reddy UM, Davis JM, Ren Z, Greene MF. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes workshop invited speakers. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the eunice kennedy shriver national institute of child Health and human development, American college of obstetricians and gynecologists, American academy of pediatrics, society for maternal-fetal medicine, centers for disease control and prevention, and the march of dimes foundation. *Obstet Gynecol*. 2017;130:10—28. https://doi.org/10.1097/AOG.0000000000002054.
20. Anand KJS, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN traial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med*. 1999;153:331—338. https://doi.org/10.1001/archpedi.153.4.331.
21. Anand KJ, Hall RW, Desai N, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004;363:1673—1682. https://doi.org/10.1016/S0140-6736(04)16251-X.
22. Hall RW, Kronsberg SS, Barton BA, Kaiser JR, Anand KJ. NEOPAIN Trial Investigators Group. Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? secondary results from the NEOPAIN trial. *Pediatrics*. 2005;115:1351—1359. https://doi.org/10.1542/peds.2004-1398.
23. Menon G, Boyle EM, Bergqvist LL, McIntosh N, Barton BA, Anand KJS. Morphine analgesia and gastrointestinal morbidity in preterm infants: secondary results from the NEOPAIN trial. *Arch Dis Child Fetal Neonatal Ed*. 2008;93:F362—F367. https://doi.org/10.1136/adc.2007.119297.
24. Bhandari V, Bergqvist LL, Kronsberg SS, Barton BA, Anand KJ, NEOPAIN Trail Investigators Group. Morphine administration and short-term pulmonary outcomes among ventilated preterm infants. *Pediatrics*. 2005;116:352—359. https://doi.org/10.1542/peds.2004-2123.
25. Maitra S, Baidya DK, Pawar DK, Arora MK, Khanna P. Epidural anesthesia and analgesia in the neonate: a review of current evidences. *J Anesth*. 2014;28:768—779. https://doi.org/10.1007/s00540-014-1796-8.
26. Bhalla T, Sawardekar A, Dewhirst E, Jagannathan N, Tobias JD. Ultrasound-guided trunk and core blocks in infants and children. *J Anesth*. 2013;27:109—123. https://doi.org/10.1007/s00540-012-1476-5.
27. Lago P, Garetti E, Merazzi D, et al. Guidelines for procedural pain in the newborn. *Acta Paediatr*. 2009;98(6): 932—939.
28. Arana A, Morton NS, Hansen TG. Treatment with paracetamol in infants. *Acta Anaesthesiol Scand*. 2001;45:20—29.
29. Maitra S, Baidya DK, Khanna P, Ray BR, Panda SS, Bajpai M. Acute perioperative pain in neonates: an evidence-based review of neurophysiology and management. *Acta Anaesthesiol Taiwanica*. 2014;52:30—37. https://doi.org/10.1016/j.aat.2014.02.004.
30. Sharma CV, Mehta V. Paracetamol: mechanisms and updates. *Contin Educ Anaesth Crit Care Pain*. 2014;14:153—158. https://doi.org/10.1093/bjaceaccp/mkt049.
31. Ruggieri V, Vitale G, Pini LA, Sandrini M. Differential involvement of opioidergic and serotonergic systems in the antinociceptive activity of N-arachidonoyl-phenolamine (AM404) in the rat: comparison with paracetamol. *Naunyn Schmiedebergs Arch Pharmacol*. 2008;377:219—229. https://doi.org/10.1007/s00210-008-0284-9.
32. Walker SM. Neonatal pain. *Pediatr Anaesth*. 2014;24:39—48. https://doi.org/10.1111/pan.12293.
33. Bartelink IH, Rademaker CMA, Schobben AFAM, van den Anker JN.

Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet*. 2006;45:1077–1097. https://doi.org/10.2165/00003088-200645110-00003.
34. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos J. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics*. 2011;3:53–72. https://doi.org/10.3390/pharmaceutics3010053.
35. van Lingen RA, Deinum JT, Quak JM, et al. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 1999;80:F59–F63. https://doi.org/10.1136/fn.80.1.f59.
36. Hansen TG, O'Brien K, Morton NS, Rasmussen SN. Plasma paracetamol concentrations and pharmacokinetics following rectal administration in neonates and young infants. *Acta Anaesthesiol Scand*. 1999;43:855–859.
37. Anderson B, Kanagasundarum S, Woollard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care*. 1996;24:669–673. https://doi.org/10.1177/0310057X9602400606.
38. Agrawal S, Fitzsimons JJ, Horn V, Petros A. Intravenous paracetamol for postoperative analgesia in a 4-day-old term neonate. *Paediatr Anaesth*. 2007;17:70–71. https://doi.org/10.1111/j.1460-9592.2006.02004.x.
39. Palmer GM, Atkins M, Anderson BJ, et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth*. 2008;101:523–530. https://doi.org/10.1093/bja/aen208.
40. Ceelie I, de Wildt SN, van Dijk M, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA*. 2013;309:149–154. https://doi.org/10.1001/jama.2012.148050.
41. Filan PM, Hunt RW, Anderson PJ, Doyle LW, Inder TE. Neurologic outcomes in very preterm infants undergoing surgery. *J Pediatr*. 2012;160:409–414. https://doi.org/10.1016/j.jpeds.2011.09.009.
42. Härmä A, Aikio O, Hallman M, Saarela T. Intravenous paracetamol decreases requirements of morphine in very preterm infants. *J Pediatr*. 2016;168:36–40. https://doi.org/10.1016/j.jpeds.2015.08.003.
43. Kocek M, Wilcox R, Crank C, Patra K. Evaluation of the relationship between opioid exposure in extremely low birth weight infants in the neonatal intensive care unit and neurodevelopmental outcome at 2years. *Early Hum Dev*. 2016;92:29–32. https://doi.org/10.1016/j.earlhumdev.2015.11.001.
44. Johnston PG, Gillam-Krakauer M, Fuller MP, Reese J. Evidence-based use of indomethacin and ibuprofen in the neonatal intensive care unit. *Clin Perinatol*. 2012;39:111–136. https://doi.org/10.1016/j.clp.2011.12.002.
45. Papacci P, De Francisci G, Iacobucci T, et al. Use of intravenous ketorolac in the neonate and premature babies. *Paediatr Anaesth*. 2004;14:487–492. https://doi.org/10.1111/j.1460-9592.2004.01250.x.
46. Aldrink JH, Ma M, Wang W, Caniano DA, Wispe J, Puthoff T. Safety of ketorolac in surgical neonates and infants 0 to 3 months old. *J Pediatr Surg*. 2011;46:1081–1085. https://doi.org/10.1016/j.jpedsurg.2011.03.031.
47. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology*. 1992;77:1125–1133.
48. Kuraishi Y, Hirota N, Sato Y, Kaneko S, Satoh M, Takagi H. Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. *Brain Res*. 1985;359:177–182. https://doi.org/10.1016/0006-8993(85)91426-X.
49. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)*. 2001;14:13–21.
50. Dersch-Mills DA, Banasch HL, Yusuf K, Howlett A. Dexmedetomidine use in a tertiary care NICU: a descriptive study. *Ann Pharmacother*. 2019;53:464–470. https://doi.org/10.1177/1060028018812089.
51. Whalen LD, Di Gennaro JL, Irby GA, Yanay O, Zimmerman JJ. Long-term dexmedetomidine use and safety profile among critically ill children and neonates. *Pediatr Crit Care Med*. 2014;15:706–714. https://doi.org/10.1097/PCC.0000000000000200.
52. Tang C, Xia Z. Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic. *J Pain Res*. 2017;10:1899–1904. https://doi.org/10.2147/JPR.S139387.
53. Akin A, Bayram A, Esmaoglu A, et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Paediatr Anaesth*. 2012;22:871–876. https://doi.org/10.1111/j.1460-9592.2012.03802.x.
54. Schnabel A, Meyer-Frieem CH, Reichl SU, Zahn PK, Pogatzki-Zahn EM. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. *Pain*. 2013;154:1140–1149. https://doi.org/10.1016/j.pain.2013.03.029.
55. O'Mara K, Gal P, Wimmer J, et al. Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature

neonates. *J Pediatr Pharmacol Ther*. 2012;17:252–262. https://doi.org/10.5863/1551-6776-17.3.252.
56. Dilek O, Yasemin G, Atci M. Preliminary experience with dexmedetomidine in neonatal anesthesia. *J Anaesthesiol Clin Pharmacol*. 2011;27:17–22.
57. Rose MA, Kam PCA. Gabapentin: pharmacology and its use in pain management. *Anaesthesia*. 2002;57:451–462.
58. Sacha GL, Foreman MG, Kyllonen K, Rodriguez RJ. The use of gabapentin for pain and agitation in neonates and infants in a neonatal ICU. *J Pediatr Pharmacol Ther*. 2017;22:207–211. https://doi.org/10.5863/1551-6776-22.3.207.
59. Schwarz SM, Corredor J, Fisher-Medina J, Cohen J, Rabinowitz S. Diagnosis and treatment of feeding disorders in children with developmental disabilities. *Pediatrics*. 2001;108:671–676.
60. Edwards L, DeMeo S, Hornik CD, et al. Gabapentin use in the neonatal intensive care unit. *J Pediatr*. 2016;169:310–312. https://doi.org/10.1016/j.jpeds.2015.10.013.
61. Butterworth JF, Mackey DC, Wasnick JD. *Spinal, epidural, & caudal blocks. Morgan & Mikhail's Clinical Anesthesiology*. 5 ed. New York, NY: McGraw-Hill Medical; 2013.
62. Veneziano G, Tobias JD. Chloroprocaine for epidural anesthesia in infants and children. *Paediatr Anaesth*. 2017;27:581–590. https://doi.org/10.1111/pan.13134.
63. Bosenberg A, Flick RP. Regional anesthesia in neonates and infants. *Clin Perinatol*. 2013;40:525–538. https://doi.org/10.1016/j.clp.2013.05.011.
64. Marhofer P, Keplinger M, Klug W, Metzelder ML. Awake caudals and epidurals should be used more frequently in neonates and infants. *Paediatr Anaesth*. 2015;25:93–99. https://doi.org/10.1111/pan.12543.
65. Committee on Fetus and Newborn and Section on Anesthesiology, Pain Medicine. Prevention and management of procedural pain in the neonate: an update. *Pediatrics*. 2016;137, e20154271. https://doi.org/10.1542/peds.2015-4271.
66. Kumar M, Chawla R, Goyal M. Topical anesthesia. *J Anaesthesiol Clin Pharmacol*. 2015;31:450–456. https://doi.org/10.4103/0970-9185.169049.
67. Kaur G, Gupta P, Kumar A. A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Arch Pediatr Adolesc Med*. 2003;157:1065–1070. https://doi.org/10.1001/archpedi.157.11.1065.
68. Biran V, Gourrier E, Cimerman P, Walter-Nicolet E, Mitanchez D, Carbajal R. Analgesic effects of EMLA cream and oral sucrose during venipuncture in preterm infants. *Pediatrics*. 2011;128:e63–e70. https://doi.org/10.1542/peds.2010-1287.
69. Hui-Chen F, Hsiu-Lin C, Shun-Line C, et al. The effect of EMLA cream on minimizing pain during venipuncture in premature infants. *J Trop Pediatr*. 2013;59:72–73. https://doi.org/10.1093/tropej/fms040.
70. Sharara-Chami R, Lakissian Z, Charafeddine L, Milad N, El-Hout Y. Combination analgesia for neonatal circumcision: a randomized controlled trial. *Pediatrics*. 2017;140, e20171935. https://doi.org/10.1542/peds.2017-1935.
71. Al Qahtani R, Abu-Salem L, Pal K. Effect of lidocaine-prilocaine eutectic mixture of local anaesthetic cream compared with oral sucrose or both in alleviating pain in neonatal circumcision procedure. *Afr J Paediatr Surg*. 2014;11:56. https://doi.org/10.4103/0189-6725.129236.
72. Foster JP, Taylor C, Spence K. Topical anaesthesia for needle-related pain in newborn infants. *Cochrane Database Syst Rev*. 2017;2:CD010331. https://doi.org/10.1002/14651858.CD010331.pub2.
73. Hsieh KH, Chen SJ, Tsao PC, et al. The analgesic effect of non-pharmacological interventions to reduce procedural pain in preterm neonates. *Pediatr Neonatol*. 2018;59:71–76. https://doi.org/10.1016/j.pedneo.2017.02.001.
74. Liu Y, Huang X, Luo B, Peng W. Effects of combined oral sucrose and nonnutritive sucking (NNS) on procedural pain of NICU newborns, 2001 to 2016: a PRISMA-compliant systemic review and meta-analysis. *Medicine (Baltimore)*. 2017;96, e6108. https://doi.org/10.1097/md.0000000000006108.
75. Field T. Preterm newborn pain research review. *Infant Behav Dev*. 2017;49:141–150. https://doi.org/10.1016/j.infbeh.2017.09.002.
76. De Lima J, Carmo KB. Practical pain management in the neonate. *Best Pract Res Clin Anaesthesiol*. 2010;24:291–307. https://doi.org/10.1016/j.bpa.2010.04.001.
77. Thrane SE, Wanless S, Cohen SM, Danford CA. The assessment and non-pharmacologic treatment of procedural pain from infancy to school age through a developmental lens: a synthesis of evidence with recommendations. *J Pediatr Nurs*. 2016;31:e23–e32. https://doi.org/10.1016/j.pedn.2015.09.002.
78. Vittner D, McGrath J, Robinson J, et al. Increase in oxytocin from skin-to-skin contact enhances development of parent–infant relationship. *Biol Res Nurs*. 2018;20:54–62. https://doi.org/10.1177/1099800417735633.
79. Pados BF. Physiology of stress and use of skin-to-skin care as a stress-reducing intervention in the NICU. *Nurs Womens Health*. 2019;23:59–70. https://doi.org/10.1016/j.nwh.2018.11.002.
80. Kelley-Quon LI, Kenney BD, Bartman T, et al. Safety and feasibility of skin-to-skin care for surgical infants: a quality improvement project. *J Pediatr Surg*.

February 2019. https://doi.org/10.1016/j.jpedsurg.2019.02.016.
81. Mitchell AJ, Yates CC, Williams DK, Chang JY, Hall RW. Does daily kangaroo care provide sustained pain and stress relief in preterm infants? *J Neonatal Perinatal Med*. 2013;6:45–52. https://doi.org/10.3233/NPM-1364212.
82. Cong X, Ludington-Hoe SM, McCain G, Fu P. Kangaroo Care modifies preterm infant heart rate variability in response to heel stick pain: pilot study. *Early Hum Dev*. 2009;85:561–567. https://doi.org/10.1016/j.earlhumdev.2009.05.012.
83. Johnston CC, Stevens B, Pinelli J, et al. Kangaroo care is effective in diminishing pain response in preterm neonates. *Arch Pediatr Adolesc Med*. 2003;157:1084–1088. https://doi.org/10.1001/archpedi.157.11.1084.
84. Azevedo VMG, Xavier CC, Gontijo Fde O. Safety of kangaroo mother care in intubated neonates under 1500 g. *J Trop Pediatr*. 2012;58:38–42. https://doi.org/10.1093/tropej/fmr033.
85. Lorenz L, Dawson JA, Jones H, et al. Skin-to-skin care in preterm infants receiving respiratory support does not lead to physiological instability. *Arch Dis Child Fetal Neonatal Ed*. 2017;102:F339–F344. https://doi.org/10.1136/archdischild-2016-311752.
86. Ludington-Hoe SM, Ferreira C, Swinth J, Ceccardi JJ. Safe criteria and procedure for kangaroo care with intubated preterm infants. *J Obstet Gynecol Neonatal Nurs*. 2003;32:579–588. https://doi.org/10.1177/0884217503257618.
87. Swinth J, Anderson GC, Hadeed AJ. Kangaroo (skin-to-skin) care with a preterm infant before, during, and after mechanical ventilation. *Neonatal Netw*. 2003;22:33–38. https://doi.org/10.1891/0730-0832.22.6.33.
88. Seidman G, Unnikrishnan S, Kenny E, et al. Barriers and enablers of kangaroo mother care practice: a systematic review. *PLoS One*. 2015;10, e0125643. https://doi.org/10.1371/journal.pone.0125643.
89. Cignacco EL, Sellam G, Stoffel L, et al. Oral sucrose and "facilitated tucking" for repeated pain relief in preterms: a randomized controlled trial. *Pediatrics*. 2012;129:299–308. https://doi.org/10.1542/peds.2011-1879.
90. Hartley KA, Miller CS, Gephart SM. Facilitated tucking to reduce pain in neonates: evidence for best practice. *Adv Neonatal Care*. 2015;15:201–208. https://doi.org/10.1097/ANC.0000000000000193.
91. Perroteau A, Nanquette M-C, Rousseau A, et al. Efficacy of facilitated tucking combined with non-nutritive sucking on very preterm infants' pain during the heel-stick procedure: a randomized controlled trial. *Int J Nurs Stud*. 2018;86:29–35. https://doi.org/10.1016/j.ijnurstu.2018.06.007.
92. Liaw J-J, Yang L, Katherine Wang K-W, Chen C-M, Chang Y-C, Yin T. Non-nutritive sucking and facilitated tucking relieve preterm infant pain during heel-stick procedures: a prospective, randomised controlled crossover trial. *Int J Nurs Stud*. 2012;49:300–309. https://doi.org/10.1016/j.ijnurstu.2011.09.017.
93. Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol*. 2014;41:895–924. https://doi.org/10.1016/j.clp.2014.08.010.
94. Stevens B, Yamada J, Ohlsson A, et al. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2016 Jul 16:7:CD001069. https://doi.org/10.1002/14651858.CD001069.pub5.
95. Benoit B, Martin-Misener R, Latimer M, Campbell-Yeo M. Breast-feeding analgesia in infants: an update on the current state of evidence. *J Perinat Neonatal Nurs*. 2017;31(2):145–159. https://doi.org/10.1097/JPN.0000000000000253.
96. Peng HF, Yin T, Yang L, et al. Non-nutritive sucking, oral breast milk, and facilitated tucking relieve preterm infant pain during heel-stick procedures: a prospective, randomized controlled trial. *Int J Nurs Stud*. 2018;77:162–170. https://doi.org/10.1016/j.ijnurstu.2017.10.001.

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