Pain Interventions in Premature Infants

What Is Conclusive Evidence and What Is Not

Lina Kurdahi Badr, RN, DNSc, CPNP, FAAN
From the UCLA, N. Hollywood, CA.

Address correspondence to
Lina Kurdahi Badr, RN, DNSc, CPNP, FAAN, UCLA, 4828 Denny Ave, N. Hollywood, CA 91601. E-mail: lbadr@apu.edu.


Abstract and Introduction

Abstract
This article is the second of a two-part series that focuses on interventions to decrease pain related to common procedures in the neonatal intensive care unit. In part one, the focus was on the etiology of pain, sources of pain, short- and long-term consequences, and currently used assessment tools. In this part, an introduction of evidence-based practice is discussed, along with current pharmacologic and nonpharmacologic management strategies. Recommendations are offered on what is considered conclusive evidence and what is not.

Introduction
Every practicing nurse has heard the phrase "evidence-based practice" (EBP); yet, it remains unclear to most what is meant by that phrase. Is practice based on evidence conclusive or is it what we know best from what is available to us now? Unfortunately, although nursing care aims to provide the best patient care based on best research evidence with clinical expertise and patient values, [1–3] conclusive evidence to most nursing practices is nonexistent.

Evidence-based practice is not new. It is traceable to the 1700s but not defined and used until the 1980s. Initially, the term referred to the critical appraisal of published research and current literature. [1–4] Then, the term was adopted by organizations that devoted themselves to advancing EBP such as the Cochrane library and the Agency for Healthcare. [5] Currently, almost every health professional, organization, or discipline has espoused the term. However, despite the explosion in using the term and the number of publications addressing it, EBP remains misunderstood by most academicians, practitioners, organizations, and patients. [6–8]

In nursing, the term surfaced more than two decades ago when Hunt wrote nursing should become a research-based profession. [2] However, to date, few nursing practices or protocols are based on conclusive evidence. Nurses continue to perform tasks based on tradition or what they had learned in nursing school or from their colleagues. Rarely do nurses question the basis for most their actions. [9–11] A good example related to the former statement is the bathing of premature infants. Over a decade ago, a study documented the negative consequences of bathing on premature infants, [12] followed by a quasi-experimental study documenting that preterm infants not bathed for 4 days did not have any negative sequelae in terms of infection or skin flora. [13] Yet, to date and in most neonatal intensive care units (NICUs), nurses still bathe premature infants daily, and no one has replicated the study to provide further support to these findings.

Although most nurses base their practice on tradition, others, especially those working in Magnet and university hospitals, may be eager to base their practice on research. However, many do not know how to implement research findings into clinical practice nor are they cognizant of what constitutes sufficient evidence to sanction a change in practice. [14] In addition, registered nurses may not be well equipped or have the resources or time to critically appraise the findings from research. [10,13,14]

To base practice on evidence means to bring together pertinent, trustworthy information by systematically acquiring, analyzing, and transferring research findings into clinical care. Best evidence is when a practice is based on conclusions from systematic reviews, [4] meta-analysis, [4] or guidelines based on research results [4] that have evolved through a methodological, rational accumulation, analysis, and understanding of published studies. [17–19]

This article will present published studies related on current interventions to reduce pain in preterm infants and to decipher what is "conclusive evidence" and what remains "controversial." Conclusive evidence refers to sufficient randomized, controlled trials (RCTs) with a systemic review and or a meta-analysis indicating that the evidence for a certain practice or
intervention is sufficient. In this category, emphasis is on experimental studies to document the efficacy of treatments against untreated control groups. For example, offering sucrose during a painful procedure currently provides conclusive evidence regarding efficacy and safety.

Controversial evidence is based on research findings better termed research based evidence\textsuperscript{[5,6]} that entails making decisions about how to provide care by integrating the best available evidence with practitioner expertise and other resources, but there have not been sufficient experimental studies to provide conclusive evidence. An example is massage therapy to reduce pain during painful procedures in premature infants. Most researchers prefer using the term levels of evidence, which indicates the strength or weakness of the published research.\textsuperscript{[18,19]} For practical purposes, this article will use the terms conclusive evidence and controversial evidence.

It is worth noting that evaluating the quality of published research can be a daunting task requiring meticulous reading, critiquing with background knowledge, and education. Few practitioners recognize that, in most published studies, conclusions are unjustified by the research design or results http://en.wikipedia.org/wiki/Evidence-based_practice-cite_note-10, omission of important results are common, and almost one fourth of what is published has inappropriate or incomplete statistical analysis.\textsuperscript{[20-23]}

To meet the objectives of this article, electronic searches were conducted using the following databases: PubMed, Ovid, ScienceDirect, PsychINFO, and CINAHL, with the following search words: preterm infant's pain responses, interventions to reduce pain in infants, randomized clinical trials (RCTs), systematic reviews, and Cochrane reviews related to preterm pain. The literature search covered the period from 1984 to 2012. Studies that exclusively examined full-term infants were not included in this review because previous reviews have addressed this population.\textsuperscript{[24-27]} Abstracts in French, German, and Spanish were not excluded if pertinent. Search results that met these criteria yielded 112 studies and reviews on pain management.

**Pain Interventions**

Pain management in the NICU remains a difficult task for all health professionals. Several pharmacologic and nonpharmacologic interventions have been investigated for the management of pain with limited evidence or rationale for the choice of treatment. Because infant pain responses are not simply those of an immature adult but stem from a different underlying structural and functional connectivity within the central nervous system, interventions especially pharmacologic ones have not been adequately tested with this population.\textsuperscript{[28-32]} The most commonly used pharmacologic interventions will be described followed by the nonpharmacologic or behavioral interventions that are more varied.

**Pharmacologic Interventions**

Pharmacologic management is limited because of the availability of only a few analgesics that have been tested in infants and because of the uncertainty about their safety and long-term effects. Analgesics include a variety of medications from the use of anesthetic creams\textsuperscript{[33,34]} to mild analgesics such as acetaminophen (paracetamol)\textsuperscript{[35]} to the use of opiates such as morphine.\textsuperscript{[30]} It is worth noting that although in some NICUs, 70% to 99% of infants are assessed and receive sedatives or analgesics before painful procedures,\textsuperscript{[36-39]} in others, sedation is minimal or not used at all.\textsuperscript{[40,41]} This is especially true for NICUs in developing counties where the fear of sedation and addiction prevails.\textsuperscript{[40]}

**Local or Surface Analgesics**

Local anesthetics are useful for the management of procedure-related acute pain, but they are not effective for heel stick draws. They can be injected subcutaneously or applied topically.\textsuperscript{[34,35,42]} Two topical anesthetics are currently available: the mixture of lidocaine/prilocaine 5% cream (EMLA) and tetracaine 4% gel (Ametop). Ametop has a faster onset time than EMLA (30–40 minutes), but its use in premature infants is controversial.\textsuperscript{[44]} The EMLA needs to be applied 1 to 2 hours before the procedure to achieve clinical efficacy. Local analgesics prevent the transmission of painful stimuli by nociceptors, by their action on sodium channels, and have been found to be effective especially in combination with sucrose.\textsuperscript{[33,43]} Although the safety of ELMA (once per day) on preterm infants has been documented, its efficacy on the very low birth weight (VLBW) infant and the long-term consequences of repeated doses have not been studied.\textsuperscript{[44]}

Acetaminophen (paracetamol) is a well-known analgesic in children without significant side effects; it is given orally or rectally and has been recently tested using the intravenous route in preterm infants to reduce the use of opiates.\textsuperscript{[45]} There is no consensus on dosage regimens for intravenous administration of paracetamol in infants. Some researchers suggest a maintenance dose of 20 mg/kg every 12 hours for infants younger than 31 weeks' gestational age (GA) after a loading dose of 30 mg/kg.\textsuperscript{[36,46]} It is effective for moderate pain but not for acute procedural pain. Some reports associate acetaminophen use in the first year of life with an increased risk of asthma and eczema.\textsuperscript{[41]}

---

\textsuperscript{[5,6]} For practical purposes, this article will use the terms conclusive evidence and controversial evidence.

\textsuperscript{[18,19]} For practical purposes, this article will use the terms conclusive evidence and controversial evidence.

\textsuperscript{[20-23]} The most commonly used pharmacologic interventions will be described followed by the nonpharmacologic or behavioral interventions that are more varied.

\textsuperscript{[24-27]} Abstracts in French, German, and Spanish were not excluded if pertinent. Search results that met these criteria yielded 112 studies and reviews on pain management.

\textsuperscript{[28-32]} The most commonly used pharmacologic interventions will be described followed by the nonpharmacologic or behavioral interventions that are more varied.

\textsuperscript{[33,34]} To meet the objectives of this article, electronic searches were conducted using the following databases: PubMed, Ovid, ScienceDirect, PsychINFO, and CINAHL, with the following search words: preterm infant's pain responses, interventions to reduce pain in infants, randomized clinical trials (RCTs), systematic reviews, and Cochrane reviews related to preterm pain. The literature search covered the period from 1984 to 2012. Studies that exclusively examined full-term infants were not included in this review because previous reviews have addressed this population. Abstracts in French, German, and Spanish were not excluded if pertinent. Search results that met these criteria yielded 112 studies and reviews on pain management.

\textsuperscript{[35]} It is worth noting that although in some NICUs, 70% to 99% of infants are assessed and receive sedatives or analgesics before painful procedures, in others, sedation is minimal or not used at all. This is especially true for NICUs in developing counties where the fear of sedation and addiction prevails.

\textsuperscript{[36-39]} It is worth noting that although in some NICUs, 70% to 99% of infants are assessed and receive sedatives or analgesics before painful procedures, in others, sedation is minimal or not used at all. This is especially true for NICUs in developing counties where the fear of sedation and addiction prevails.

\textsuperscript{[33,34]} Two topical anesthetics are currently available: the mixture of lidocaine/prilocaine 5% cream (EMLA) and tetracaine 4% gel (Ametop). Ametop has a faster onset time than EMLA (30–40 minutes), but its use in premature infants is controversial.

\textsuperscript{[44]} The EMLA needs to be applied 1 to 2 hours before the procedure to achieve clinical efficacy. Local analgesics prevent the transmission of painful stimuli by nociceptors, by their action on sodium channels, and have been found to be effective especially in combination with sucrose.

\textsuperscript{[33,43]} Although the safety of ELMA (once per day) on preterm infants has been documented, its efficacy on the very low birth weight (VLBW) infant and the long-term consequences of repeated doses have not been studied.

\textsuperscript{[44]} It is effective for moderate pain but not for acute procedural pain. Some reports associate acetaminophen use in the first year of life with an increased risk of asthma and eczema.

\textsuperscript{[41]} It is effective for moderate pain but not for acute procedural pain. Some reports associate acetaminophen use in the first year of life with an increased risk of asthma and eczema.
Opioids are the most popular analgesics for pain in preterm infants. \[31,36\] Opiates have been shown to reduce physiologic instability in the newborn in several ways. Studies have noted that when opiates are used, there is less hypoxemia, less blood pressure fluctuation, reduced behavioral stress responses, and elevated ventilator synchrony. Side effects of opioids include respiratory depression, bronchospasm, reduced gastrointestinal motility, urinary retention, and pruritus. \[31,36\]

Morphine is the most commonly used opioid especially in ventilated infants. The mean onset of the analgesic effect of morphine in premature infants is 5 minutes, and the peak is at 15 minutes. The side effects of morphine are hypertension, bradycardia, bronchospasm, and a delay in the attainment of full enteral feeding. It has a ceiling effect when a therapeutic level is reached; higher doses will not produce further sedation. Anand \[31\] suggests that a ceiling effect is reached by using doses up to 0.5 mg/kg. Although the short-term safety of morphine has been documented in several studies, there remains insufficient evidence to recommend routine use especially in ventilated infants and in VLBW infants. In addition, long-term neurodevelopmental consequences are not well established. \[16,47,48,49\]

A multicenter RCT that a large sample (N = 898) found that ventilated infants who received morphine had less signs of pain but may be at risk for intraventricular hemorrhage. \[50\] Furthermore, although some studies report the benefits of morphine in reducing acute pain (eg, Angeles et al \[50\] and Tadio et al \[51\]), others note minimal or no efficacy (eg, Simons et al \[52\] and Frank et al). \[52\] It is possible that the discrepancy in results is due to other variables not assessed such the use of dexamethasone among other contextual factors. Thus, further evidence is needed to document the efficacy of opioid (morphine) therapy to relieve acute pain in preterm infants, especially in VLBW infants and in terms of long-term neurodevelopment.

Fentanyl (FE) is as another opioid that is commonly used in the NICU. It is as effective as morphine in terms of analgesia and has fewer side effects especially in terms of reduced gastrointestinal motility or negative cardiovascular effects. Fentanyl has a rapid onset of action (2–3 minutes) and a short duration of action (60 minutes with bolus doses) with a wide therapeutic effect. Fentanyl has not been studied as extensively as morphine, but it has been shown to limit pain especially in ventilated infants. It should be used with caution, however, as premature infants may develop tolerance and chest wall rigidity. \[15,20\]

Propofol has been used for short-term sedation. It has a rapid onset of action and rapid termination. \[54\] Because serious side effects and neurotoxicity have been reported in pediatric patients, its use has been limited. \[55\] However, also because of its fast acting properties, it has been used in neonates with some success. \[56\] Propofol is a hypnotic agent without analgesic effects, thus adding an analgesic is required for painful procedures. A recent meta-analysis by Shah and Shah \[57\] found only one RCT using propofol with 63 infants, where no clinically significant side effects were observed between infants who received propofol and those who received morphine. They concluded that no practice recommendation can be made based on the available evidence.

Methadone is being studied as a possible drug to reduce pain in neonates. It is as potent as morphine but may have fewer complications. Methadone has an additive analgesic effect, and infants are less likely to develop tolerance as with morphine or FE. Methadone has a slow onset of action (20 minutes with intravenous (IV), 30–60 minutes with oral) and prolonged elimination half-life (children, 19 hours; neonates, 41 hours). \[58\]

Behavioral interventions to reduce mild to moderate pain in the NICU have been the focus of extensive studies in the past two decades. The underlying mechanism of how these interventions work is the gate control theory. \[59\] The theory proposes that stimuli or interventions traveling the ascending pathways to the brain may inhibit nociceptive signals or transmission, reducing the amount of pain the infant is exposed to. The more intense or various these stimuli are, the more effective they can be in blocking the perception of pain. Other explanations for the mechanisms underlying the success of behavioral interventions are the release of endomorphins and oxytocin. \[60\] The interventions reviewed in this section were used on preterm infants and include tucking, swaddling, massage, kangaroo care (KC), multisensory stimulation, rocking, nonnutritive sucking (NNS), sucrose solutions, breastfeeding, music therapy, and olfactory stimulation (see Table 1).

### Table 1. Behavioral Interventions and Outcomes of Studies on Pain in Preterm Infants (Excluding Studies Using Sucrose)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Design</th>
<th>Authors/Year/Reference</th>
<th>Subjects</th>
<th>Outcomes</th>
<th>Painful Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA, 33 HR/SO [61]</td>
<td>N = 30 HR/SO</td>
<td>2 Heel stick</td>
</tr>
<tr>
<td>RCT three groups</td>
<td>Carbajal et al (2011) [63]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Design</td>
<td>Study (Year)</td>
<td>N</td>
<td>GA (wk)</td>
<td>Interventions (Abbrev.)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
<td>-------------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Swaddling</td>
<td>Neu and Browne (1997)</td>
<td>GA, 32</td>
<td>15</td>
<td></td>
<td>NFCS</td>
</tr>
<tr>
<td>RCT (three groups):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) moderate</td>
<td>Diego and Hernandez-Reif (2009)</td>
<td>GA, 22</td>
<td>56</td>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>b) light</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kangaroo</td>
<td>Johnston et al (2003)</td>
<td>GA, 32</td>
<td>74</td>
<td></td>
<td>PIPP</td>
</tr>
<tr>
<td>RCT (three groups):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>GA</td>
<td>HRV</td>
<td>Behaviors</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Ludington-Hoe et al (2005)</td>
<td>RCT</td>
<td>24</td>
<td>27</td>
<td></td>
<td>Crying time</td>
</tr>
<tr>
<td>Kostandy et al (2008)</td>
<td>RCT/crossover</td>
<td>30</td>
<td>32</td>
<td></td>
<td>Heel stick</td>
</tr>
<tr>
<td>Akcan et al (2009)</td>
<td>RCT</td>
<td>50</td>
<td>26</td>
<td></td>
<td>NFCS crying</td>
</tr>
<tr>
<td>Castral et al (2008)</td>
<td>RCT</td>
<td>59</td>
<td>28</td>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>RCT (three groups):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Behavioral state</td>
</tr>
<tr>
<td>a) sucrose</td>
<td>Freire et al (2008)</td>
<td>95</td>
<td>28</td>
<td></td>
<td>saturation</td>
</tr>
<tr>
<td>b) KC</td>
<td></td>
<td>30</td>
<td>36</td>
<td></td>
<td>HRV</td>
</tr>
<tr>
<td>c) control</td>
<td></td>
<td>36</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston et al (2009)</td>
<td>RCT/crossover</td>
<td>90</td>
<td>34</td>
<td></td>
<td>Neurobehavioral</td>
</tr>
<tr>
<td>Bernardini et al (2011)</td>
<td>RCT</td>
<td>28</td>
<td>36</td>
<td></td>
<td>PIPP, ECG, HR</td>
</tr>
<tr>
<td>Carbajal et al (2011)</td>
<td>RCT</td>
<td>150</td>
<td>32</td>
<td></td>
<td>Levels of cytokins</td>
</tr>
<tr>
<td>Field and Godson (1984)</td>
<td>RCT</td>
<td>148</td>
<td>29</td>
<td></td>
<td>Physiologic measures</td>
</tr>
<tr>
<td>Liaw et al (2010)</td>
<td>RCT</td>
<td>104</td>
<td>40</td>
<td></td>
<td>PIPP, HR, RR, Spo</td>
</tr>
</tbody>
</table>
Facilitated Tucking

Facilitated tucking (FT) refers to positioning infants with extremities flexed and close to the trunk with blanket rolls in a restricted mode. This position has been noted to facilitate self-regulation and decrease crying time in many research studies and has recently been used as an intervention to decrease pain during stressful procedures.\textsuperscript{[61–63]} Facilitated tucking was tested in seven studies with samples ranging between 12 and 150 premature and very premature infants. Six were RCTs with three using the crossover design.\textsuperscript{[61–67]} Facilitated tucking as a behavioral intervention during a heel stick procedure, endotracheal suctioning, or routine nursing interventions was effective in relieving pain, leading to significant reductions on pain assessment scores (the premature infant pain profile [PIPP], the Neonatal Infant Pain Scale [NIPS], and the CRIES). Two studies reported a shorter mean sleep disruption time and less crying time. No significant reductions in oxygen saturation (SO\textsubscript{2}) levels were reported in any of the studies, and only one study noted a lower mean heart rate (HR) in the intervention group.\textsuperscript{[62]} The study by Liaw et al\textsuperscript{[66]} noted less frequencies of abnormal SO\textsubscript{2} and HR, although there were no significant differences between groups. It is worth mentioning that with the exception of two studies,\textsuperscript{[62,65]} the authors used validated assessment tools of pain.

The most recent studies by Gitto et al\textsuperscript{[63]} and Liaw et al\textsuperscript{[66]} reported conflicting results when using FT. Carbajal et al\textsuperscript{[63]} randomly divided 150 preterm infants to three different treatment groups, (a) FE, (b) FT, and (c) sensorial saturation (SS), and found that FT was not as effective as the other two interventions and that cytokines levels, which are markers of stress, were significantly higher in the FT group. Liaw et al\textsuperscript{[66]} had 34 infants randomly divided into three groups with three sequences of interventions during a heel stick (a) routine care, NNS, and FT; (b) NNS, FT, and routine care; and (c) FT, routine care, and NNS). In addition to the PIPP, infant behaviors and physiologic signals by electrocardiogram monitors were assessed. Although the group that received FT and NNS had lower PIPP scores, behavioral and physiologic measures (HR, respiratory rate [RR], and SO\textsubscript{2}) were not significantly between the sequences of interventions. Based on the above, there is not sufficient evidence to the benefits of FT.

Swaddling

Swaddling involves wrapping an infant in a blanket with minimal restraint; limbs are flexed, and hands are accessible for exploration. It is also called binding or bundling and was a very common infant care practice before the 18th century.\textsuperscript{[92]} Although most developing counties have not used this practice for many years, it appears to be gaining momentum as several studies have found that swaddling has a soothing effect on infants and decreases crying time.\textsuperscript{[69]} In fact, four studies from Thailand concluded that swaddling full-term infants manifested less pain during a heel stick procedure.\textsuperscript{[69]} In terms of using swaddling to decrease pain in preterm infants, only three earlier studies were found. One study reported that swaddling infants especially those with higher GAs had faster recovery in HR and SO\textsubscript{2} during a heel stick procedure, whereas in infants 27 to 30 weeks' postconceptional age, recovery after heel stick was not influenced by swaddling.\textsuperscript{[69]} Another case control study with 14 preterm infants showed less physiologic distress, better motor organization, and more effective self-regulatory ability in premature infants who were swaddled during a weighing procedure.\textsuperscript{[68]} The study by Huang et al,\textsuperscript{[65]} mentioned earlier, found that those swaddled returned to their baseline HR and SO\textsubscript{2} values in shorter periods compared with those in containment and that PIPP scores were lower in the swaddled group. It is possible that there are different forms of swaddling, and some may be similar to FT. In their systemic review of swaddling, van
Sleuwen et al (92) caution that swaddling, especially if not used properly, can be a dangerous intervention that increases the risk of developmental hip dysplasia, respiratory infections, and sudden infant death. To date, there is not enough evidence for the practice of swaddling to decrease pain in premature infants because only 3 published studies with small samples have used this intervention with only one study being a RCT.

**Massage**

Massage therapy is a form of systematic tactile and kinesthetic stimulation that has been noted to enhance the infant's developmental outcomes, lower serum cortisol levels, shorten hospital stay, and enhance weight gain. (90-94) However, in terms of reducing painful experiences, only two studies are published. Gentle massages of the leg before heel prick in 23 preterm infants decreased behavioral pain responses on the NIPS and decreased HR, but there were no differences in RR or SO2 levels. (95) Another study randomly allocated infants to one of three groups: (1) moderate pressure massage, (2) light pressure massage, and (3) no massage therapy. (96) Preterm infants who received 15 minutes of moderate pressure massage therapy exhibited lower HRs than infants who did not receive massage therapy or who received light pressure massage therapy after removal of the surgical tape. (97) Currently, there is insufficient evidence to support the use of massage in reducing pain in preterm infants, mostly because the term is not clearly defined.

**Kangaroo Care**

Kangaroo care or skin-to-skin contact was first described in 1978 in Bogota, Columbia, as an alternative method of caring where incubators or radiant warmers were not available or available for infants born prematurely. The term is defined as laying the infant on the bare skin of the mother or father so that there is no loss of body temperature. The placement of the mother-infant dyad in skin-to-skin contact has been found to be beneficial for premature infants in terms of reducing nosocomial infections, respiratory infections, and hypothermia. (90)

Behavioral intervention with KC was found in 11 RCTs, all using the heel stick as the painful procedure (see Table 1). Kangaroo care was first assessed as an intervention to reduce pain in preterm infants in 2003. (98) Two more recent RCTs with a crossover design by the same author(s) assessed the benefits of KC on 61 and 62 preterm neonates at 28 to 36 weeks' GA. Infants were observed during a heel lance procedure while the infants were held in KC for 30 minutes. In one of the studies (99) where 62 infants were held by either the mother or the father, significantly lower scores on the PIPP were observed for infants held by mothers than those held by fathers. In the second single-blind, randomized, crossover design study where 61 preterm infants were either held in KC for 15 minutes before and throughout heel stick procedure or swaddled in a blanket in the incubator, it was found that the PIPP scores were lowest when infants were in KC. (100)

A series of small studies by Ludington-Hoe et al (77) assessed the effects of KC on physiologic as well as behavioral measures. A two-phase study with 10 and 18 infants showed lower PIPP scores for infants in KC, lower salivary cortisol, reduced HR variability (HRV), and decreased crying time during a heel stick procedure. (98) Fourteen preterm infants were assessed during a heel stick procedure either in KC or in the incubator. Infants in KC had less HRV and improved autonomic stability during heel stick. (101) Likewise, in a study with 24 premature infants who were randomized to 2 sequences of events, group A received a heel stick while in 3 hours of KC followed by a heel stick while in the warmer for three hours, and group B started off in the warmer. Results were that HR and length of crying in response to pain were significantly reduced during KC compared with when infants were in the warmer. (102) Two RCT crossover studies with 10 and 24 preterm infants randomly assigned to two sequences of heel stick in KC or 2 heel stick in the incubator also found that crying time was less during the heel stick while infants were in KC. (103,104)

Randomized, controlled trials with larger samples (N = 30–95) have likewise documented the benefits of KC in reducing pain during a heel stick procedure. Lower neonatal facial coding system (NFCS) scores, less HR increases, (105) lower PIPP scores, (106) improved neurobehavioral signs, (107) and significantly smaller variations in HR and SO2 have been reported. (108) A recent review of 14 studies on the efficacy of KC in reducing pain in preterm and full-term infants concluded that KC was one of the best strategies to decrease pain and pain reactivity in preterm infants. (109) Thus, there is conclusive evidence to recommend KC as an intervention for reducing pain reactivity and improving regulation of pain-related distress in preterm infants.

**Multisensory Stimulation or SS**

It involves using a combination of stimuli during a painful procedure: tactile (massaging the back and face), gustatory (placing a few drops of a pleasant smelling oil on the hands), auditory (talking gently), and olfactory (providing a cotton wool stick that is sprinkled with 10% glucose). (110) Four studies used SS in combination with other interventions. A randomized, prospective study with 17 infants divided into five different interventions, (a) control, (b) 10% oral glucose plus sucking, (c) SS, (d) oral water, and (e) 10% oral glucose, found that SS had the best analgesic effects as manifested by significantly reduced pain scores on the PIPP and less crying. (111) A larger RCT study with 150 preterm infants (GA, 27–32 weeks) divided infants into three groups (50 in each group): one group had FE (1–2 µg/kg); one group, FT; and one group, SS group. The authors report that the CRIES scores, which was used to evaluate procedural pain, was significantly lower in the SS and the FE groups. Levels of cytokines as markers of stress were highest in the FT group. (120) Ninety preterm neonates (n = 90) between 32 to 36 weeks' GA were randomized into one of two groups: one group received KC,
and one group was held in KC with the addition of rocking, singing, and sucking. The results indicate that the addition of sensory inputs from the mother did not affect the PIPP scores. \cite{104-106} In contrast, an RCT of 28 preterm newborns divided in two groups (14 subjects who received glucose solution and 14 subjects who received the SS) found that the group treated with SS had the lowest PIPP scores. \cite{84} To date, insufficient evidence remains as to the benefits of SS for reducing in preterm infants.

**Rocking**

The rocking of infants to soothe them and decrease crying has been practiced historically in many cultures. Rocking results in vestibular stimulation. \cite{109} Although rocking by the mother has been reported to decrease pain responses in full-term neonates in one study \cite{107} and rocking using waterbeds in preterm neonates has been found to promote quiet state and growth and to reduce apnea, \cite{118} it has not yet been found to have an analgesic effect. In fact, one study in 1997 by Johnston et al \cite{83} found that the rocking alone and the addition of rocking to the sucrose did not have a significant effect on pain scores. Thus, rocking as an intervention to decrease pain in preterm infants lacks evidence and is based on traditional practices.

**Nonnutritive Sucking**

Nonnutritive sucking refers to placing a pacifier in an infant's mouth to promote sucking behavior without providing breast milk or formula for nutrition. Nonnutritive sucking has been found to be effective in decreasing length of hospital stay in preterm infants, to facilitate the transition to bottle feeding, and to decrease pain during circumcision in newborns. \cite{104-106} However, the efficacy of NNS in reducing pain in preterm infants has not been sufficiently documented. Intervention using NNS with preterm infants has been assessed in five studies (all are RCTs) with some evidence that it has analgesic effects by stimulating orotactile and mechanoreceptors in the mouth, thus modulating transmission or processing of nociception by the endogenous nonopiod system. \cite{88,89,90} Although an earlier study suggested that NNS during a heel stick procedure may attenuate behavioral distress in neonates, \cite{91} newer studies found that NNS may have a potent analgesic. \cite{88,89,90} An RCT with 40 preterm infants undergoing a screening eye examinations and divided into 4 subgroups found that the highest PIPP scores were observed in those receiving water only, with the lowest scores in the intervention with either a pacifier or sucrose and a trend toward lower scores in the group receiving both sucrose and a pacifier. The authors conclude that the NNS was the most effective pain reliever. \cite{91} An RCT study with 104 preterm infants noted significantly lower PIPP scores for infants who received NNS compared with infants in the control group at all the phases of the heel stick procedures. \cite{88} A consequent study by the same authors \cite{89} compared a sequence of NNS, FT, and routine care in a convenient sample of 34 infants who acted as their own control during a heel stick procedure. Infants receiving NNS and FT had significantly lower mean pain scores on the PIPP during heel stick procedures. An RCT with 26 preterm infants found that crying and distress signals were significantly decreased during a heel stick procedure when a pacifier was provided to premature infants. \cite{90} It is possible that NNS with sucrose has an additive effect on pain relief during painful procedures. The evidence for NNS in reducing pain in preterm infants remains inconclusive.

**Sucrose**

Sucrose given to preterm infants during a painful procedure has been considered in over 45 publications from several countries and has been consistently proven to be safe and effective for reducing procedural pain from various painful events: heel lance, venipuncture, nasogastric tube insertion, and eye examination (eg, Elserafy et al, \cite{109} Holsti and Grunau, \cite{109} Cignacco et al, \cite{110} Milazzo et al \cite{111} and Simonse et al). \cite{88,89,91} Sucrose is the first nonpharmacologic intervention that has been established to have conclusive evidence based on a Cochrane review. \cite{113} What remains unclear are the required dose of sucrose needed for optimal efficacy (doses range between 0.012 and 0.12 g) and the safety in neonates who are of VLBW, unstable, and/or ventilated.

**Breastfeeding**

Although several studies have documented the efficacy of breastfeeding in reducing pain in full-term infants (eg, Shah et al \cite{114} and Carabajal et al), \cite{113,114} its efficacy in reducing pain in preterm infants has not been documented. On the contrary, breastfeeding during blood collection on 57 infants born at 30 to 36 weeks' GA who were randomized to be breastfed or to be given a pacifier during blood collection found that breastfeeding during blood collection did not reduce pain or interfere with the acquisition of breastfeeding skills. \cite{115} Likewise, a recent RCT with 71 preterm neonates randomly assigned to either breast milk or sucrose during a heel stick procedure found that there was no significant difference in mean PIPP score between neonates receiving breast milk and those receiving sucrose. \cite{115} Thus, the efficacy of breast feeding in reducing pain in premature infants based on current studies is inconclusive.

**Auditory Stimulation**

The sense of hearing is the most developed sensation in premature infants. By 29 weeks' gestation, the fetus can respond and remember auditory stimuli. Several studies over the last two decades have established the fact that newborns can recognize their mothers' voice \cite{116,119} and respond better to the mother's voice in her native tongue. \cite{120} Three descriptive studies with small samples reported a decrease in HR, better SO2 levels, faster weight gain, and better motor development
when premature infants listen to a recording of their mothers' voice compared with infants who listen to music or were in the control group. \cite{121,122} In contrast, and in a more recent experimental design study, Standley and Moore \cite{123} found that SO \(_2\) was significantly higher in premature infants who listened to music rather than their mother's voice. Thus, the benefits of auditory stimulation whether it is the mother's voice or music on the behavioral outcomes of preterm infants remain unclear. \cite{124} The efficacy of auditory intervention for reducing pain in preterm infants is inconclusive because of only three published studies with small samples. A study of 14 preterm infants found that music was effective in reducing pain during and after a heel stick procedure especially in older preterm infants (> 31 weeks). \cite{125} Another study with 27 neonates with GAs between 30 and 41 weeks found that music therapy had a better effect than NNS on HR, SO \(_2\), and pain responses. \cite{126} In contrast, a study by Johnston et al, \cite{127} which used a within-subject experimental design, found no significant differences in the PIPP scores and a significant decrease in SO \(_2\) levels after exposure to maternal voice compared with no exposure before the heel stick. The authors argued that the sound level for the maternal recording (70 dB) was greater than the recommended levels by the American Academy of Pediatrics and that it may have affected their negative results. Thus, the evidence for auditory stimulation to decrease pain responses in premature infants remains weak and inconclusive.

**Olfactory Intervention**

Newborns have been known to recognize the smell of their mother's milk. Recently, the role of olfaction as a soothing tool in full-term newborns was reported in a few studies. \cite{128-131} However, only one study assessed the effect of a familiar odor during a routine heel stick procedure or a venous puncture in premature infants. Fifty-one healthy preterm infants were randomly assigned to either a heel stick procedure or a venipuncture. The infants were then divided into three subgroups. One third of the infants were presented with an odor that they had been familiarized with before the procedure, one third of the infants were presented with an odor that they had not been previously exposed to, and one third was presented with no odor. Infants who were presented with a familiar odor during venipuncture showed no significant increase in crying and grimacing during the procedure compared with baseline levels. \cite{132} Because there is only one study using olfactory intervention for reducing pain in premature infants, the evidence remains weak and inconclusive.

**Conclusion and Implications for Practice**

Pain and its management are of crucial importance to all concerned with the care of preterm infants. Although much has been achieved in the past few decades, there remains much more to learn to achieve adequate pain control for premature infants. Most crucially is that sick premature infants who have been exposed to a multitude of stressful procedures may not manifest behavioral or physiologic signs of pain or may have damped responses to pain while, in fact, they may be experiencing pain and need to be treated appropriately. This raises even more serious concerns regarding the need to protect small premature infants who are at an increased risk for intraventricular hemorrhage (IVH) hemorrhage and its disconcerting long-term consequences. \cite{133} These concerns should be considered along with the fact that there remains inconclusive evidence for the negative long-term consequences of pain in preterm infants.

In terms of pain management, prevention is the key component. Thus, nurses should adopt strategies that limit the use of painful procedures including minimally invasive procedures such as weighing, bathing, and adjusting the continuous positive airway pressure (CPAP) prongs. If painful procedures are necessary, then adequate planning and preparation are required to provide appropriate analgesics. For procedures known to be severely painful such as mechanical ventilation and surgery, a low-dose morphine drip is recommended, although more studies are needed to determine efficacy and long-term outcomes. \cite{134,135} In addition, research on safer and more effective drugs is needed. \cite{136,137} For moderately painful procedures that are frequent in the NICU such as heel sticks, venipunctures, and eye examinations, nonpharmacologic interventions such as sucrose or KC should be the first choice. Blood should be obtained from central lines rather than peripheral blood sampling if available, and venipuncture should be used instead of heel lance. \cite{138,139,140} Nurses should follow written guidelines based on published recommendations and research and should apply principles of minimal handling and limited noxious stimuli (noise, light, bathing, handling, examination, etc). Not only should these guidelines be written, but also, there should be a system in place that ensures that all practitioners abide by these protocols. This requires nurse-physician collaboration, nurse-administration collaboration, and input from parents.

Despite the number of studies providing support to the benefits of nonpharmacologic interventions in reducing pain in preterm infants, only two interventions (sucrose and KC) provide conclusive evidence and should be implemented by all nurses working in the NICUs for moderate pain. The remaining interventions remain inconclusive, and more research is needed before there is sufficient evidence. Facilitated tucking and NNS seem to have some evidence for pain relief, but more RCTs with larger samples are needed. Massage, swaddling, breastfeeding, and rocking remain inconclusive, as very few studies have assessed the benefits of these interventions. Olfactory, auditory, and SS interventions are in the early stages of evidence and, to date, remain based on findings from older infants and newborns.
References


