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.

NAINR. 2012;12(3):141-153.

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. [10,15,16]

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, [a] meta-analysis, [b] or guidelines based on research results [c] 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*[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. [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. [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. [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. [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 [33,34] to mild analgesics such as acetominophen (paracetamol) [35] to the use of opiates such as morphine. [36] It is worth noting that although in some NICUs, 70% to 99% of infants are assessed and receive sedatives or analgesics before painful procedures, [36–39] in others, sedation is minimal or not used at all. [40,41] This is especially true for NICUs in developing counties where the fear of sedation and addiction prevails. [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. [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. [43] 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. [43,44] 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. [45]

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. [46] 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. [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. [31]

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 hypotension, 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. [36,47,48,49]

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. [36] 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 [48] 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. [31,53]

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)

Intervention	Design	Authors/Year/Reference	Subjects	Outcomes	Painful Procedure
FT	RCT/crossover	Axelin et al (2006) [61]	N = 20 GA, 25–33	NIPS HR/SO_2	Endotracheal suctioning
	RCT (random sequence)	Corff et al (1995) [62]	N = 30 GA, 25–35	HR/SO_2 Sleep states	Heel stick
	RCT three groups	Carbajal et al (2011) [63]	N = 150	CRIES	Heel stick

			GA, 27–32 N = 12 Level of cytokines	
	Convenient sample	Hill et al (2005) [64]	GA, 25–34 N = 32 PIPP	Routine nursing assessment
	RCT/crossover	Huang et al (2004) [65]	GA 25–36 HR/SO ^{2}	Heel stick
	RCT/crossover Three treatments	Liaw et al (2011) [66]	N = 34 PIPP GA, 29–37 HR, RR, SO ^{2}	Heel stick
	RCT/crossover	Ward-Larson et al. (2004) [67]	Behavioral responses N = 40 GA, 23–32 PIPP	Endotracheal suctioning
Swaddling	Case/control	Neu and Browne (1997) [68]	N = 14 Behavioral organization GA, 32 wk	Weighing infants
	Case/control	Fearon et al (1997) [69]	N = 15 NFCS GA, 27–36 Brazelton scale	Heel stick
			HR SO2 N = 23 NIPS	
Massage	RCT/crossover	Jain et al (2006) [70]	BW, 795–2507 g HR, RR, SO2 Serum cortisol	Heel stick
	RCT (three groups): a) moderate b) light c) control	Diego and Hernandez-Reif (2009) [71]	N = 56 GA, 22–35 wk HR	Monitoring lead removal
Kangaroo	RCT/crossover	Johnston et al (2003) [72]	N = 74 PIPP GA, 32–36 Spo $_2$	Heel stick
	RCT/crossover Three sites	Johnston et al (2008, 2011) [73], [74]	N = 61 GA, 32–37 PIPP, HR recovery N = 62 Parental preference	Heel stick
	RCT (two phases, pilot)	Cong et al (2011) [75]	GA, 28–36 N = 10 PIPP N = 18 Salivary and serum cortisol GA, 30–32	Heel stick
	RCT/crossover	Cong et al (2009) [76]	N = 14 Infant behavior	Heel stick

			GA, 30–32	HRV Crying time	
	RCT	Ludington-Hoe et al (2005) [77]	N = 24 GA, 27	Crying time Behavioral state HR	Heel stick
	RCT/crossover	Kostandy et al (2008) [78]	N = 10 GA, 30–32	Crying time	Heel stick
	RCT	Akcan et al (2009) [79]	N = 50 GA, 26–36 wk	PIPP NFCS crying	Heel stick
	RCT	Castral et al (2008) [80]	N = 59	HR Behavioral state	Heel stick
	RCT (three groups): a) sucrose b) KC c) control	Freire et al (2008) [81]	N = 95 GA, 28–36 wk	PIPP saturation HRV	Heel stick
	RCT	Ferber and Makhoul, (2008) [82]	N = 30 GA, 28–34	Neurobehavioral (NIDCAP)	Heel stick
Multisensorial stimulation	RCT/crossover	Johnston et al (2009) [83]	N = 90 GA, 32–36	PIPP, ECG, HR	Heel stick
	RCT	Bernardini et al (2011) [84]	N = 28 GA, 30–35	PIPP	Venipuncture
	RCT Five groups (85 heel stick procedures)	Bellieni et al (2001) [85]	N = 17 GA, 28–35	PIPP/DAN Crying	Heel stick
	RCT Three groups	Carbajal et al (2011) [63]	N = 150 GA, 27–32	Levels of cytokins CRIES	Heel stick
Rocking	RCT 4 groups:a) sucrose b) rocking c) rocking and sucrose d) control	Johnston et al (1997) [86]	N = 85 GA, 25–34	HR Behavioral states	Heel stick
NNS	RCT	Field and Godson (1984) [87]	N = 148 GA, 29–40	Behavioral and physiologic measures	Heel stick
	RCT	Liaw et al (2010) [88]	N = 104	PIPP, HR, RR, Spo $_2$	Heel stick

RCT (three sequences of interventions), NNS, FT, and routine care	Liaw et al (2011) [89]	GA, 28–38 N = 34 GA, 29–40 N = 26	PIPP Behavioral and physiologic HR, RR, Spo 2	Heel stick
RCT/crossover	Corbo et al (2000) [90]	GA, 26–39	Crying Behavioral state	Heel stick
RCT (four groups): a) sterile water b) sucrose c) sterile water + pacifier	Boyle et al (2006) [91]	N = 40 GA, 24–34	PIPP SO2	Eye examination

BW indicates birth weight; DAN, The Douleur Aigue Nouveau-ne; ECG, electrocardiogram; NIDCAP, neonatal individualized developmental care and assessment program

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. [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. [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_2) levels were reported in any of the studies, and only one study noted a lower mean heart rate (HR) in the intervention group. [62] The study by Liaw et al [66] noted less frequencies of abnormal SO_2 and HR, although there were no significant differences between groups. It is worth mentioning that with the exception of two studies, [62,65] the authors used validated assessment tools of pain.

The most recent studies by Gitto et al [63] and Liaw et al [66] reported conflicting results when using FT. Carbajal et al [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 [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_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. [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. [93] In fact, four studies from Thailand concluded that swaddled full-term infants manifested less pain during a heel stick procedure. [94] 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_2 during a heel stick procedure, whereas in infants 27 to 30 weeks' postconceptional age, recovery after heel stick was not influenced by swaddling. [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. [68] The study by Huang et al, [65] mentioned earlier, found that those swaddled returned to their baseline HR and SO_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. [95–98] 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 SO_2 levels. [70] Another study randomly allocated infants to one of three groups: (1) moderate pressure massage, (2) light pressure massage, and (3) no massage therapy. [71] 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. [71] 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 affordable 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. [99]

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. [72] 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 [73] 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. [74]

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. [75] 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. [76] 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. [76] 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. [77,78]

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, [80] lower PIPP scores, [78] improved neurobehavioral signs, [82] and significantly smaller variations in HR and SO_2 have been reported. [81] A recent review of 14 studies on the efficacy of KC in reducing pain in preterm and full-term infants concluded that KC care was one of the best strategies to decrease pain and pain reactivity in preterm infants. [100] 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 oflactory (providing a cotton wool stick that is sprinkled with 10% glucose). [84] 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. [85] 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. [63] 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. [83] 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. [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. [101] Although rocking by the mother has been reported to decrease pain responses in full-term neonates in one study [102] and rocking using waterbeds in preterm neonates has been found to promote quiet state and growth and to reduce apnea, [103] it has not yet been found to have an analgesic effect. In fact, one study in 1997 by Johnston et al [86] 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. [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 nonopioid system. [107] Although an earlier study suggested that NNS during a heel stick procedure may attenuate behavioral distress in neonates, [87] newer studies found that NNS may a potent analgesic. [88,89,91] 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. [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. [88] A consequent study by the same authors [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 sick procedure when a pacifier was provided to premature infants. [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, [108] Holsti and Grunau, [109] Cignacco et al, [110] Milazzo et al, [111] and Simonse et al). [112] Sucrose is the first nonpharmacologic intervention that has been established to have conclusive evidence based on a Cochrane review. [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 [114] and Carbajal et al), [115,116] 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. [117] 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. [112] 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 [118,119] and respond better to the mother's voice in her native tongue. [120] Three descriptive studies with small samples reported a decrease in HR, better SO_2 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. [121–123] In contrast, and in a more recent experimental design study, Standley and Moore [124] 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. [125] 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). [126] Another study with 27 neonates with GAs between 30 and 41weeks found that music therapy had a better effect than NNS on HR, SO_2, and pain responses. [127] In contrast, a study by Johnston et al, [128] 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. [129–131] 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. [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. [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 continuos 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. [134,135] In addition, research on safer and more effective drugs is needed. [36,136,137] 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. [30,134,137] 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

1. David L, Sackett DL, Rosenberg WM, Gray JA, Haynes RB. Evidence based medicine. London: Churchill Livingston; 1996.

2. Hunt J. Indicators for nursing practice: the use of research findings. *J Adv Nurs.* 1981;6:189–194.

3. Ciliska DK, Pinelli J, DiCenso A, Cullum N. Resources to enhance evidence-based nursing practice. *AACN Clin Issues.* 2001;12:520–528.

4. Guyatt G, Rennie D. Part 1. The basics: using the medical literature. Introduction: the philosophy of evidence-based medicine. *J Med Libr Assoc.* 2002;90:483.

5. Manchikanti L. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management, part I: introduction and general considerations. *Pain Physician.* 2008:161–186.

6. Hjørland B. Evidence-based practice: an analysis based on the philosophy of science. *J Am Soc Inf Sci Technol.* 2011;62:1301–1310.

7. Melnyk BM, Fineout-Overholt E. Making the case for evidence-based practice 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

8. Manchikanti L, Abdi S, Lucas LF. Evidence synthesis and development of guidelines in interventional pain management. *Pain Physician.* 2005;8:73–86.

9. French P. What is the evidence on evidence-based nursing? An epistemiological concern. *J Adv Nurs.* 2002;37: 250–257.

10. Pravikoff D, Tanner A, Pierce S. Readiness of U.S. nurses for evidence-based practice. *Am J Nurs.* 2005;105:40–50.

11. Paramonczyk A. Barriers to implementing research in clinical practice. *Can Nurse.* 2005;101:12–15.

12. Zahr LK, Balian S. Responses of premature infants to routine nursing interventions and noise in the NICU. *Nurs Res.* 1995;44:179–185.

13. Franck LS, Quinn D, Zahr L. Effect of less frequent bathing of preterm infants on skin flora and pathogen colonization. *J Obstet Gynecol Neonatal Nurs.* 2000;29: 584–589.

14. Alleyne JO, Jumaa MO. Building the capacity for evidence-based clinical nursing leadership: the role of executive co-coaching and group clinical supervision for quality patient services. *J Nurs Manag.* 2007;15:230–243.

15. McCaughan D, Thompson C, Cullum N, Sheldon T, Raynor P. Nurse practitioner and practice nurses' use of research information in clinical decision making: findings from an exploratory study. *Fam Pract.* 2005;22: 490–497.

16. Munroe D, Duffy P, Fisher C. Nurse knowledge, skills, and attitudes related to evidence-based practice: before and after organizational supports. *Medsurg Nurs.* 2008.

17. Cappelleri JC, Ioannidis JP, Schmid CH, et al. Large trials vs meta-analysis of smaller trials how do their results compare? *JAMA.* 1996;276:1332–1338.

18. Cesario S, Morin K, Santa-Donato A. Evaluating the level 666 of evidence of qualitative research. *J Obstet Gynecol Neonatal Nurs.* 2002;31:708–714.

19. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized controlled trials and recommendation of clinical experts. *J Am Med Assoc.* 1992;268:240–248.

20. Fernandes-Taylor S, Hyun JK, Reeder RN, Harris AHS. Common statistical and research design problems in manuscripts submitted to high-impact medical journals. *BMC Res Notes.* 2011;4:304.

21. Harris AHS, Reeder R, Hyun JK. Common statistical and research design problems in manuscripts submitted to highimpact psychiatry journals: what editors and reviewers want authors to know. *J Psychiatr Res.* 2009;43:1231–1234.

22. Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. *JAMA*. 1999;281:1110–1111.

23. Singer E. A question of accuracy: how journalists and scientists report research on hazards. *J Commun.* 1990;40:102–116.

24. Cignacco E, Hamers JP, Stoffel L, et al. Efficacy of non pharmacological interventions in the management of procedural pain in preterm and term neonates: a systematic review. *Eur J Pain*. 2007;11:139–152.

25. Fernandes A, Campbell-Yeo M, Johnston CC. Procedural Pain Management forNeonates Using Nonpharmacological Strategies Part 1: Sensorial Interventions. *Adv Neonatal Care.* 2011;11:235–241.

26. Campbell-Yeo M, Fernandes A, Johnston C. Procedural pain management for neonates using nonpharmacological strategies: part 2: mother-driven interventions. *Adv Neonatal Care.* 2011;11:312–318, http://dx.doi.org/10.1097/ANC.0b013e318229aa76.

27. Yamada J, Stinson J, Lamba J, Dickson A, McGrath PJ, Stevens B. A review of systematic reviews on pain interventions in hospitalized infants. *Pain Res Manag.* 2008;13:413–420.

28. Fitzgerald M, McIntosh N. Pain and analgesia in the newborn. *Arch Dis Child.* 1989;64:441–443.

29. Simons SH, van Dijk M, Anand KS, Roofthooft D, van Lingen RA, Tibboel D, et al. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med.* 2003;157:1058–1064.

30. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2008;300:60–70.

31. Anand KJS. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *J Perinatol.* 2007;27:S4-S11.

32. Fitzgerald M. When is an analgesic not an analgesic? *Pain.* 2009;144:9.

33. Taddio A, Ohlsson A, Ohlsson K. Lidocaine-prilocaine cream for analgesia during circumcision in newborn boys. *Cochrane Database Syst Rev.* 2000;2:CD000496.

34. 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.

35. Al-Mendalawi MD. Effects of high dose orally administered paracetamol for heel prick pain in premature infants. *Saudi Med J.* 2010;31:716.

36. Anand KJS, Hall RW, Desai N. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the neopain randomised trial. *Lancet.* 2004;363:1673.

37. Gradin M, Eriksson M. Neonatal pain assessment in Sweden—a fifteen-year follow up. *Acta Paediatr.* 2011; 100:204–208.

38. Walter-Nicolet E, Annequin D, Biran V, Mitanchez D, Tourniaire B. Pain management in newborns: from prevention to treatment. *Pediatr Drugs.* 2010;12:353–365.

39. Carbajal R, Eble B, Anand KJ. Premedication for tracheal intubation in neonates: confusion or controversy? *Semin Perinatol.* 2007;31:309–317.

40. Badr LK, Abdallah B, Hawari M, et al. Determinants of premature infant pain responses to heel sticks. *Pediatr Nurs.* 2010;36:129–136.

41. Prestes AC, Guinsburg R, Balda RC, et al. The frequency of pharmacological pain relief in university neonatal intensive care units. *J Pediatr.* 2005;81:405–410.

42. Larsson BA, Jylli L, Lagercrantz H, Olsson GL. Does a local anaesthetic cream (EMLA) alleviate pain from heel-lancing in neonates? *Acta Anaesthesiol Scand.* 1995 Nov;39:1028–1031.

43. Lehr VT, Taddio A. Topical anesthesia in neonates: clinical practices and practical considerations. *Semin Perinatol.* 2007;31:323–329.

44. Marcatto Jde O, Vasconcelos PC, Araújo CM, Tavares EC, Pereira e Silva Y. EMLA versus glucose for PICC insertion: a randomised triple-masked controlled study. *Arch Dis Child Fetal Neonatal Ed.* 2011;96:F467-F468.

45. Essink-Tebbes CM, Wuis EW, Liem KD, van Dongen RT, Hekster YA. Safety of lidocaine-prilocaine cream application four times a day in premature neonates: a pilot study. *Eur J Pediatr.* 1999;158:421–423.

46. van Ganzewinkel CJ, Mohns T, van Lingen RA, Derijks LJ, Andriessen P. Paracetamol serum concentrations in preterm infants treated with paracetamol intravenously: a case series. *J Med Case Reports.* 2012;6:1.

47. Bellù R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed.* 2010;95: F241-F251.

48. Simons SH, van Dijk M, van Lingen RA, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA.* 2003;290:2419–2427.

49. de Graaf J, van Lingen RA, Simons SH, 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.

50. Angeles DM,Wycliffe N, Michelson D, et al. Use of opioids in asphyxiated term neonates: effects on neuroimaging and clinical outcome. *Pediatr Res.* 2005;57:873–878.

51. Tadio A, Lee C, Yip A, Parvez B, McNamara PJ, Shah V. Intravenous morphine and topical tetracaine for treatment of pain in preterm neonates undergoing central line placement. *JAMA*. 2006;295:793–800.

52. Franck LS, Boyce WT, Gregory GA, Jemerin J, Levine J, Miaskowski C. Plasma norepinephrine levels, vagal tone index, and flexor reflex threshold in premature neonates receiving intravenous morphine during the postoperative period: a pilot study. *Clin J Pain.* 2000;16:95–104.

53. Saarenmaa E, Huttunen P, Leppaluoto J, Meretoja O, Fellman V. Advantage of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomized trial. *J Pediatr.* 1999;134.

54. Allegaert K, Peeters MY, Verbesselt R, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *Br J Anaesth.* 2007;99:864–870.

55. Gelber O, Gal M, Katz Y. Clonic convulsions in a neonate after propofol anaesthesia. *Paediatr Anaesth.* 1997;7:88.

56. Golden S. Combination propofol-ketamine anaesthesia in sick neonates. *Paediatr Anaesth.* 2001;11:119–122.

57. Shah PS, Shah VS. Propofol for procedural sedation/anaesthesia in neonates. *Cochrane Database Syst Rev.* 2011;16:CD007248.

58. Chana SK, Anand KJS. Can we use methadone for analgesia in neonates? *Arch Dis Child Fetal Neonatal Ed.* 2001;85:F79-F81.

59. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science.* 1965;150:971–979.

60. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med.* 1987;317:1321–1329.

61. Axelin A, Salanterä S, Lehtonen L. 'Facilitated tucking by parents' in pain management of preterm infants—a randomized crossover trial. *Early Hum Dev.* 2006;82: 241–247.

62. Corff KE, Seideman R, Venkataraman PS, Lutes L, Yates B. Facilitated tucking: a nonpharmacologic comfort measure for pain in preterm neonates. *Journal of Obstetric, Gynecologic, & Neonatal Nursing.* 1995;24(2):143–148 101.

63. Gitto E, Pellegrino S, Manfrida M, et al. Stress response and procedural pain in the preterm newborn: the role of pharmacological and non-pharmacological treatments. *Eur J Pediatr.* 2012;171:927–933.

64. Hill S, Engle S, Jorgensen J, Kralik A, Whitman K. Effects of facilitated tucking during routine care of infants born preterm. *Pediatr Phys Ther.* 2005;17:158–163.

65. Huang CM, Tung WS, Kuo LL, Ying-Ju C. Comparison of pain responses of premature infants to the heelstick between containment and swaddling. *J Nurs Res.* 2004;12:31–40.

66. Liaw JJ, Yang L, Katherine Wang KW, Chen CM, Chang YC, 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.* 2011.

67. Ward-Larson C, Horn RA, Gosnell F. The efficacy of facilitated tucking for relieving procedural pain of endotracheal suctioning in very low birthweight infants. *MCN Am J Matern Child Nurs.* 2004;29:151–156.

68. Neu M, Browne JV. Infant physiologic and behavioral organization during swaddled versus unswaddled weighing. *J Perinatol.* 1997;17:193–198.

69. Fearon I, Kisilevsky BS, Hains SM, Muir DW, Tranmer J. Swaddling after heel lance: age-specific effects on behavioral recovery in preterm infants. *J Dev Behav Pediatr.* 1997;18:222–232.

70. Jain S, Kumar P, McMillan DD. Prior leg massage decreases pain responses to heel stick in preterm babies. *J Paediatr Child Health.* 2006;42:505–508.

71. Field D, Hernandez-Reif. Procedural pain heart rate responses in massaged preterm infants. *Infant Behav Dev.* 2009;32:226–229.

72. 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.

73. Johnston CC, Campbell-Yeo M, Filion F. Paternal vs maternal kangaroo care for procedural pain in preterm neonates: a randomized crossover trial. *Arch Pediatr Adolesc Med.* 2011;165:792–796.

74. Johnston CC, Filion F, Campbell-Yeo M, et al. Kangaroo mother care diminishes pain fromheel lance in very preterm neonates: a crossover trial. *BMC Pediatr*. 2008;8:13–22.

75. Cong X, Ludington-Hoe SM, Walsh S. Randomized crossover trial of kangaroo care to reduce biobehavioral pain responses in preterm infants: a pilot study. *Biol Res Nurs.* 2001;13:204–216.

76. Cong X, LudingtonHoe SM, McCain G, et al. Kangaroo care modifies preterm infant heart rate variability in response to heel stick pain: Pilot study. *Early Hum Dev.* 2009;85:561–567.

77. Ludington-Hoe SM, Hosseini R, Torowicz DL. Skin-to-skin contact (kangaroo care) analgesia for preterm infant heel stick. *AACN Clin Issues.* 2005;16:373–387.

78. Kostandy RR, et al. Kangaroo care (skin contact) reduces crying response to pain in preterm neonates: pilot results. *Pain Manag Nurs.* 2008;9:55–65.

79. Akcan E, Yiğit R, Atici A. The effect of kangaroo care on pain in premature infants during invasive procedures. *Turk J Pediatr.* 2009;51:14–18.

80. Castral TC, Warnock F, Leite AM, Haas VJ, Scochi CG. The effects of skin-to-skin contact during acute pain in preterm newborns. *Eur J Pain.* 2008;12:464–471.

81. Freire NBS, Garcia JBS, Lamy ZC. Evaluation of analgesic effect of skin-to-skin contact compared to oral glucose in preterm neonates. *Pain.* 2008;139:28–33.

82. Castral TC, Warnock F, Leite AM, Haas VJ, Scochi CG. Neurobehavioural assessment of skin-to-skin effects on reaction to pain in preterm infants: a randomized, controlled within-subject trial. *Acta Paediatr.* 2008;97: 171–176.

83. Bernardini V, De Liso P, Santoro F, Allemand F, Allemand A. Procedural pain perception of preterm newborn in neonatal intensive care unit: assessment and non-pharmacological approaches. *Minerva Pediatr.* 2011;63: 247–255.

84. Johnston CC, Stremler RL, Stevens BJ, Horton LJ. Effectiveness of oral sucrose and simulated rocking on pain response in preterm neonates. *Pain.* 1997;72: 193–199.

85. Bellieni CV, Bagnoli F, Perrone S, et al. Sensorial saturation: an effective analgesic tool for heel-prick in preterm infants: a prospective randomized trial. *Biol Neonate.* 2001;80:15–18.

86. Johnston CC, Stremler RL, Stevens BJ, Horton LJ. Effectiveness of oral sucrose and simulated rocking on pain response in preterm neonates. *Pain.* 1997;72:193–199.

87. Field T, Goldson E. Pacifying effects of nonnutritive sucking on term and preterm neonates during heelstick procedures. *Pediatrics.* 1984;74:1012–1015.

88. Liaw JJ, Yang L, Ti Y, Blachburn ST, Chang YC, Sun LW. Non-nutritive sucking relieves pain for preterm infants during heel stick procedures in Taiwan. *J Clin Nurs.* 2010;19:2741–51149.

89. Liaw JJ, Yang L, Katherine Wang KW, Chen CM, Chang YC, Yin T. Non-nutritive sucking and facilitated tucking relieve preterm infant pain during heel-stick procedures: a prospective, randomized controlled crossover trial. *Int J Nurs Stud.* 2012;49:300–309.

90. Corbo MG, Mansi G, Stagni A, et al. Nonnutritive sucking during heelstick procedures decreases behavioral distress in the newborn infant. *Biol Neonate.* 2012;49:162–167.

91. Boyle EM, Freer Y, Khan-Orakzai Z, et al. Sucrose and non-nutritive sucking for the relief of pain in screening for retinopathy of prematurity: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2006;91:F166-F168.

92. Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, Kuis W, Schulpen TW, L'Hoir MP. Swaddling: a systematic review. *Pediatrics.* 2007;120:e1097-e1106.

93. Ohgi S, Akiyama T, Arisawa K, Shigemori K. Randomised controlled trial of swaddling versus massage in the management of excessive crying in infants with cerebral injuries. *Arch Dis Child.* 2004;89:212–216.

94. Prasopkittikun T, Tilokskulchai F. Management of pain from heel stick in neonates: an analysis of research conducted in Thailand. *J Perinat Neonatal Nurs.* 2003;17: 304–312.

95. Dieter JN, Field T, Hernandez-Reif M, Emory EK, Redzepi M. Stable preterm infants gain more weight and sleep less after five days of massage therapy. *J Pediatr Psychol.* 2003;28:403–411.

96. Ferber SG, Laudon M, Kuint J, Weller A, Zisapel N. Massage therapy by mothers enhances the adjustment of circadian rhythms to the nocturnal period in full-term infants. *J Dev Behav Pediatr.* 2002;23:410–415.

97. Field T, Diego M, Hernandez-Reif M. Preterm infant massage therapy research: a review. *Infant Behav Dev.* 2010;33:115–124.

98. Scafidi FA, Field T, Schanberg SM. Factors that predict which preterm infant benefits most from massage therapy. *J Dev Behav Pediatr.* 1993;14:176–180.

99. Conde-Agudelo A, Diaz-Rossello JL, Belizan JM. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev.* 2000: CD002771.

100. Pillai-Riddell RR, Racine NM, Turcotte K, et al. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev.* 2011;5: CD006275.

101. Ter Vrugt D, Pederson DR. The effects of vertical rocking frequencies on the arousal level of two-month-old infants. *Child Development.* 1973;44:205–209.

102. Mathai S, Natrajan N, Rajalakshmi NR. A comparative study of nonpharmacological methods to reduce pain in neonates. *Indian Pediatr.* 2006;43:1070–1075.

103. Tuck SJ, Monin P, Duvivier C, May T, Vert P. Effect of a rocking bed on apnoea of prematurity. *Arch Dis Child.* 1982;57:475–477.

104. Gunnar MR, Fisch RO, Malone S. The effects of a pacifying stimulus on behavioral and adrenocortical responses to circumcision in the newborn. *J Am Acad Child Psychiatry.* 1984;23:34–38.

105. Shiao SY, Chang YJ, Lannon H, Yarandi H. Meta-analysis of the effects of nonnutritive sucking on heart rate and peripheral oxygenation: research from the past 30 years. *Issues Compr Pediatr Nurs.* 1997;20:11–24.

106. Gunnar MR, Fisch RO, Malone S. The effects of a pacifying stimulus on behavioral and adrenocortical responses to circumcision in the newborn. *J Am Acad Child Psychiatry.* 1984;23:34–38.

107. Liu MF, Lin KC, Chou YH, Lee TY. Using non-nutritive sucking and oral glucose solution with neonates to relieve pain: a randomised controlled trial. *J Clin Nurs.* 2010;19: 1604–1611.

108. Elserafy FA, Alsaedi SA, Louwrens J, Bin Sadiq B, Mersal AY. Oral sucrose and a pacifier for pain relief during simple procedures in preterm infants: a randomized controlled trial. *Ann Saudi Med.* 2009;29:184–188.

109. Holsti L, Grunau RE. Considerations for using sucrose to reduce procedural pain in preterm infants. *Pediatrics.* 2010;125:1042–1047.

110. 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.

111. Milazzo W, Fielder J, Bittel A, et al. Oral sucrose to decrease pain associated with arterial puncture in infants 30 to 36 weeks' gestation: a randomized clinical trial. *Adv Neonatal Care.* 2011;11:406–411.

112. Simonse E, Mulder PG, van Beek RH. Analgesic effect of breast milk versus sucrose for analgesia during heel lance in late preterm infants. *Pediatrics.* 2012;129: 657–663.

113. Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev.* 2010;(1):CD001069.

114. Shah PS, Aliwalas L, Shah V. *Breastfeeding or breastmilk to alleviate procedural pain in neonates: a systematic review.. Breastfeed Med.* 2007;2:74–82.

115. Carbajal R, Veerapen S, Couderc S, Jugie M, Ville Y. *Analgesic effect of breast feeding in term neonates: randomized controlled trial Epidemiology and treatment of painful procedures in neonates in intensive care units. . BMJ.* 2003;326:13.

116. Efe E, Özer ZC. *The use of breast-feeding for pain relief during neonatal immunization injections.. Applied nursing research: ANR.* 2007;20:10–16

117. 117. Holsti L, Oberlander TF, Brant R. *Does breastfeeding reduce acute procedural pain in preterm infants in the neonatal intensive care unit? A randomized clinical trial. . Pain.* 2011;152:2575–2581.

118. Nakajima H. *Response of the newborn when gently accosted by the mother immediately after birth and subsequent growth and development.. Keio J Med.* 1994;43:167–170.

119. DeCasper AJ, Spence MJ. *Prenatal maternal speech influences newborn's perception of speech sounds.. Infant Behav Dev.* 1986;9:133–150.

120. Dehaene-Lambertz G, Montavont A, Jobert A, et al. *Language or music, mother or Mozart? Structural and environmental influences on infants' language networks.. Brain Lang.* 2010;114:53–65.

121. Chapman JS. *The relationship between auditory stimulation and gross motor activity of short-gestation infants.. Res Nurs Health.* 1978;1:29–36.

122. Malloy GB. *The relationship between maternal and musical auditory stimulation and the developmental behavior of premature infants.. Birth Defects.* 1979;15: 81–98.

123. Segall M. *Cardiac responsivity to auditory stimulation in premature infants.. Nurs Res.* 1972;21:15–19.

124. Standley JM, Moore RS. Therapeutic effects of music and mother's voice on premature infants. *Pediatr Nurs*. 1995;21:509–512.

125. Krueger C. *Exposure to maternal voice in preterm infants: a review.. Advances in Neonatal Care.* 2010;10:13–18 10.1097.

126. Butt ML, Kisilevsky BS. *Music modulates behaviour of premature infants following heel lance.. Can J Nurs Res.* 2000;31:17–39.

127. Bo LK, Callaghan P. *Soothing pain-elicited distress in Chinese neonates.. Pediatrics.* 2000;105:e49.

128. Johnston CC, Filion F, Nuyt AM. *Recorded maternal voice for preterm neonates undergoing heel lance.. Adv Neonatal Care.* 2007;7:258–266.

129. Sullivan R, Toubas P. *Clinical usefulness of maternal odor in newborns: soothing and feeding preparatory responses.. Biol Neonate.* 1998;74:402–408.

130. Rattaz C, Goubet N, Bullinger A. *The calming effect of a familiar odor on full-term newborns.. J Dev Behav Pediatr.* 2005;26:86–92.

131. Varendi H, Christensson K, Porter RH, Winberg J. Soothing effect of amniotic fluid smell in newborn infants. *Early Hum Dev. 1998;51:47–55.*

132. Goubet N, Rattaz C, Pierrat V, Bullinger A, Lequien P. *Olfactory experience mediates response to pain in preterm newborns.. Dev Psychobiol.* 2003 Mar;42: 171–180.

133. Myers E, Ment LR. *Long-term outcome of preterminfants and the role of neuroimaging.. Clin Perinatol.* 2009;36: 773–789.

134. Walden M, Gibbins S. Pain assessment and management: guideline for practice. Glenview, IL: National Association of Neonatal Nurses; 2001. Retrieved from www.NANN.org.

135. Yamada J, Stinson J, Lamba J, Dickson A, McGrath PJ, Stevens B. A review of systematic reviews on pain interventions in hospitalized infants. *Pain Res Manag.* 2008;13:413–420.

136. Durrmeyer X, Vutskits L, Anand KJ, Rimensberger PC. *Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data.. Pediatr Res.* 2010;67:117–127.

137. Cignacco E, Hamers J, van Lingen RA, et al. Neonatal procedural pain exposure and pain management in ventilated preterm infants during the first 14 days of life. *Swiss Medical Weekly.* 2009;139:15–16 226–32.