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A Systematic Review of Behavioral and Environmental Interventions for Procedural Pain Management in Preterm Infants☆

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ABSTRACT

Problem: Current research suggests behavioral and environmental interventions to prevent neonatal pain prior to an invasive procedure are rarely administered and seldom documented. The aim of this study was to systematically review findings from published randomized controlled trials that tested the effects of behavioral and environmental procedural pain management interventions on behavioral pain response in preterm infants.
Eligibility Criteria: Randomized controlled trials examining the effects of behavioral and environmental pain management interventions on behavioral pain response in preterm infants were identified. Articles accepted for inclusion met the following criteria: English language, original, peer refereed, randomized controlled clinical trials published within the past 5 years, study sample: preterm infants, setting: neonatal intensive care units, study intervention behavioral and environmental, outcome pain measurement score from valid and reliable pain scale.
Sample: Fourteen randomized controlled trials from a literature search of PubMed and Medline databases were included in this review.
Results: Across all age groups, facilitated tucking, oral sucrose, and kangaroo care decreased behavioral and physiologic pain response alone and in combination with other behavioral and environmental interventions.
Conclusion: Among preterm infants, facilitated tucking, oral sucrose, and kangaroo care significantly mitigates biobehavioral pain response associated with acutely painful procedures.
Implications: Evidence suggests that behavioral and environmental interventions can decrease biobehavioral pain response associated with acutely painful procedures in preterm infants. This review highlights the need for rigorous studies to help healthcare providers to build a tailored pain treatment plan for preterm infants.

Introduction

It is rarely appreciated that all chronic pain was once undermanaged acute pain (Katz & Seltzer, 2009). Undermanaged acute pain early in life is the greatest risk factor for the alteration of subsequent pain processing and long-term neurological development (Grunau, 2013), increased pain sensitivity (Low & Schweinhardt, 2012), and the transition from acute to chronic pain (Buchheit, Van de Ven, & Shaw, 2012; Hatfield, Meyers, & Messing, 2013; Shipton, 2011). Current research suggests that pharmacological interventions to prevent neonatal pain prior to the invasive procedure are rarely administered and behavioral and environmental interventions are seldom documented (Cruz, Fernandes, & Oliveira, 2016). Our systematic review synthesized findings from published randomized controlled trials (RCTs) conducted in the past 5 years to assess the efficacy of behavioral and environmental procedural pain management interventions on behavioral pain response in preterm infants.

Background

Epidemiology of Neonatal Pain

In a recent systematic review examining the epidemiology of painful procedures performed in neonates, investigators found that the first 14 days of life, neonates experienced 6832 to 42,413 invasive procedures, an average of 7.5–17.3 painful procedures per neonate per day.

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This number of painful procedures is most likely low because some procedures were not successful and multiple attempts for the same procedure were not recorded (Cruz et al., 2016). These findings were similar to a previous multicenter study of 13 tertiary NICUs in France (Carbajal et al., 2008). Over four months, 60,969 first-attempt procedures were performed on neonates. Among the first attempt procedures, 42,413 (69.6%) were identified as painful procedures. The remaining 18,556 procedures, (30.4%), were considered stressful procedures. There were 11,546 supplemental attempts performed during procedures; 10,366 (89.8%) painful procedures and 1180 (10.2%) stressful procedures. Each infant had a median of 115 (range, 4–613) painful and stressful procedures, 16 (range, 0–62) painful and stressful procedures for each hospital day. Among the 42,413 painful procedures, 79.2% were conducted without analgesia being administered to the neonates.

Physiology of Infant Pain

Across all ages, four processes are requisite for a noxious stimulus to be perceived as pain. Each process is regulated by specific receptor proteins. In the first process, transduction, tissue damage releases chemical mediators, such as prostaglandins, bradykinin, serotonin, substance P, and histamine. At the peripheral ends of thinly myelinated Aδ and unmyelinated C fiber first order neurons, these substances activate specific noxious stimuli receptors that convert the noxious stimuli into an action potential that will relay the noxious impulse to the central nervous system (CNS). In transmission, the second process, the action potential moves along afferent nerve fibers from the site of injury to nociceptors at the spinal cord. Within the CNS, second order neurons transmit the noxious signal to the thalamus through the activation of inflammatory mediators released at the site of tissue damage. During the third process-perception, third order neurons located in the cerebral cortex perceive the nociceptive signal as pain. Finally, during the fourth process-modulation, the activation of the periaqueductal gray (PAG) of the midbrain stimulate the neurotransmitters endorphins, enkephalins, serotonin (5-HT), and dynorphin, that descend the central nervous system. These neurotransmitters activate additional neurotransmitters that inhibit transmission of the pain impulse at the dorsal horn through the release of endogenous opioids and (Garland, 2012; Scholz & Woolf, 2002).

Multiple lines of seminal research provided evidence to support fetal transduction, transmission and perception of a noxious stimulus. Anand and Hickey (1987) state as early as 20 weeks gestation, the fetal cortex has a greater number of neurons than an adult, a full contingent of 10^9 neurons. Transduction, cortical and endorphin substrates essential for transmission, and the perception of noxious stimuli are well developed by 23 weeks' gestation (Anand et al., 1985; Anand & Hickey, 1987). The preterm infant's afferent pain pathway, has a higher density of Aδ (high threshold) and Aβ (low threshold) mechanoreceptors that react with lower firing frequency compared to adults (Gliess & Stuttgen, 1970). Neurotransmitters of the descending pathway (the inhibitory arm), are immature and do not develop until postnatal life (Anand & Scalzo, 2000; Fitzgerald & Beggs, 2001). Because there is an imbalance of plentiful afferent excitatory pain neurotransmitters and scarce descending inhibitory neurotransmitters, when exposed to a noxious stimuli preterm infants exhibit greater pain sensitivity and intensity than older infants and adults (Anand, 1998; Fitzgerald & Walker, 2009; Grunau, 2013).

Preterm Infant Pain Assessment and Measurement

Valid and reliable pain scales are the foundation to assess and measure pain in preterm infants (American Academy of Pediatrics, Committee on Fetus and Newborn and Section on Surgery, Canadian Paediatric Society, & Fetus and Newborn Committee, 2006; Anand & The International Evidenced-Based Group for Neonatal Pain, 2001). The challenge is finding the correct tool. Health care providers should consider the gestational age of the infant, the context of the pain (procedural, surgical, etc.), the variables within the tool, and finally the limitations of the tool. A complete discussion of each challenge is beyond the scope of this paper however, each variable will be briefly addressed.

Gestational Age of the Infant

A neonate's gestational age is a factor in the selection of an infant pain scale because a neonate's gestational age influences their behavioral state (Foreman, Thomas, & Blackburn, 2008) and the maturity of the HPA axis (Grunau et al., 2005). Preclinical trials demonstrate that neonatal stressors (e.g. maternal separation and environmental manipulations) can have a permanent effect of increasing or decreasing the development of hypothalamic–pituitary–adrenal axis (HPA) responsiveness to subsequent stressors (Ladd et al., 2000; Pryce & Feldon, 2003). Very premature infants, commonly the sickest, often demonstrate low basal cortisol and adrenal insufficiency (Grunau et al., 2005).

Context of the Pain

The context of the noxious event is significant. The type of pain and the infant's response to that pain is significantly different if the pain originates from acute or surgical origin compared to persistent pain. The vast majority of scales were designed and validated for acute pain, either procedural and/or postoperative. Prolonged pain in neonates is much more difficult to assess, as neonates may adapt to the presence of prolonged pain from the standpoint of both physiologic and behavioral measures (Debillon, Zupan, Ravault, Magny, & Dehan, 2001).

Variables in the Scale

Preterm infants are preverbal, therefore neonatal pain scales reflect surrogate markers for the physiologic and behavioral responses to noxious stimuli. For clinicians, the identification of evidence-based variables within a pain scale is a complex task. The two strongest evidence-based physiological variables correlated to infant pain are heart rate or heart rate variability and oxygen saturation. The behavioral variables with strong evidence for infant pain response are facial expression and body movements (Hatfield & Ely, 2015).

Limitations of Preterm Measurement

Finally, it is important to consider the constraints in the measurement of pain in preterm infants, specifically the contribution of each variable to the total score. Does each variable have an equal contribution when being scored? When assessing preterm infant pain most infant pain scales assume each variable, physical, behavioral and contextual, is equally represented and scored. In clinical practice, it is accepted that the total infant pain score represents the intensity of pain experienced by the infant. An infant scoring a 0 in some variables may achieve a total pain score representing a moderate amount of pain if the other variables in the pain scale are scored at the highest level. Assigning equal contribution to each variable prevents the comprehensive understanding of the individual or collective influence of behavioral and physiological indicators as contextual factors (Stevens et al., 2007).

Multiple pain scales are available to healthcare providers to assess and measure an infant's response to noxious stimuli. However; only 5 scales have utilized meticulous psychometric testing with the study of neonates serving as their own controls and measuring infant physiologic and behavioral pain responses with the scale being assessed (Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine, 2016). The five scales: the Neonatal Facial Coding System (Grunau, Oberlander, Holsti, & Whitfield, 1998; Peters et al., 2003), the Premature Infant Pain Profile (Ballantyne, Stevens, McAllister, Dionne, & Jack, 1999; Gibbins et al., 2014; Stevens, Johnston, Petryshen, & Taddio, 1996; Stevens, Johnston, Taddio, Gibbins, & Yamada, 2010), the Neonatal Pain And Sedation Scale (Hummel, Lawlor-Klean, & Weiss, 2010; Hummel, Puchalski, Creech, & Weiss, 2008), the Behavioral Infant Pain Profile (Holsti & Grunau, 2007) and the Douleur Aigue du Nouveau-ne

(Carbajal, Paupe, Hoenn, Lenclen, & Olivier-Martin, 1997) are described in Table 1.

Behavioral and Environmental Pain Management

Rationale

If undermanaged pain in preterm infants is associated with adverse neurological and developmental outcomes, then use of a multimodal approach to neonatal pain management that includes behavioral and environmental interventions is a resolute goal for the care of premature infants experiencing painful procedures. Opiates, specifically morphine, are the gold standard for acute procedural pain management in critically ill newborns despite the lack of documented efficacy in preterm neonates (Carbajal et al., 2005). Moreover, opioid analgesic therapy has been shown to influence neuronal apoptosis in preterm neonates (Attarian et al., 2014), increase demands of the neonate to metabolize opiate based drug therapy (Kesavan, 2015) and induce the development of opioid induced hyperalgesia (Anand et al., 2010).

The mechanisms of action for behavioral and environmental pain management interventions are poorly understood and their influence on growth and development outcomes continues to be elusive. Evidence within the past 5 years demonstrates that benefits of pain reduction behavioral and environmental pain management strategies for pain with preterm infants. These include: skin to skin contact (Cong et al., 2012), sucrose and non-nutritive sucking (Liaw et al., 2013), dextrose (Kataria, Narang, Chawla, Sood, & Gupta, 2015), acupressure (Abbasoglu et al., 2015), music (Cavaiuolo, Casani, Di Manso, & Orfeo, 2015), breast milk (Sahoo et al., 2013), kangaroo care (Mitchell, Yates, Williams, Chang, & Hall, 2013), and facilitative tucking - holding the infant's arms and legs in flexed positions close to the midline of the torso (Alinejad-Naeini, Mohagheghi, Peyrovi, & Mehran, 2014). Both in adults and infants many of these nondrug measures are associated with reductions in the dose and duration of pharmacologic therapy (Demir, 2012; Wuhrman & Cooney, 2011) and mitigate the short and long-term adverse risks of pharmacological interventions (Galloway, Buckenmaier, Gallagher, & Polomano, 2011). Importantly, nondrug approaches for pain effectively decrease the acute behavioral pain responses in premature neonates (Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine, 2016; Lago et al., 2014; Pillai Riddell et al., 2015).

Purpose

The purpose of our systematic review was to synthesize findings from published RCTs evaluating the efficacy of pain management interventions for procedural pain management in preterm infants. This systematic review will answer the following research question: In preterm infants, what effect do behavioral and environmental pain management interventions have on acute procedural behavioral pain response? Pain management interventions from herein pertain to those that are behavioral and environmental in nature, and when necessary specific interventions will be mentioned.

Methods

To ensure the transparent and complete reporting of systematic reviews, the Preferred Reporting of Items of Systematic reviews Meta

Table 1
Neonatal pain scales with rigorous psychometric testing.

Pain assessment and measurement scale	Infant age scale validated	Indicators	Type of pain	Pain intervention used in study	Validity and reliability
Premature Infant Pain Profile Revised (2014)	26 ≥ 37 weeks GA	Maximum HR % Decrease in O_2 sat Brow bulge Eye squeeze Nasolabial furrow GA and behavioral state assessed if with response to pain	Acute procedural pain	Retrospective comparison of PIPP and PIPP-R scores	Construct validity
Neonatal Pain Agitation and Sedation scale (2010)	23–40 weeks GA	Crying Behavioral state Facial Expression Extremities tone Vital signs (HR, BP, RR, O_2 sat)	Acute Procedural Pain	Heel lance	Construct and convergent validity IR: 0.86–0.93 IC; 0.84–0.89 Test-retest reliability: 0.87
Behavioral Indicators of Infant Pain (2007)	24–32 Weeks GA	Behavioral state Facial expression Hand movements	Acute procedural pain	Heel lance	Construct and concurrent validity IR: 0.80–0.92 IC: 0.82
Neonatal Facial Coding System (1998, 1999)	24–32 weeks GA	Brow bulge Eye squeeze Nasolabial furrowing Lip opening Vertical mouth stretch Horizontal mouth stretch Taut Tongue Chin quiver Lip pursing	Acute procedural pain Surgical pain	Heel lance Abdominal and Thoracic surgery	Construct validity IR: 0.88
Douleur Aigue du Nouveau-ne (1997)	24–41 weeks GA	Facial movement Limb movement Vocal expression	Acute procedural pain	Heel lance venipuncture	IC: 0.88 IR: (Krippendorf) 91.2
Premature Infant Pain Profile (1996, 1999, 2010)	28–48 weeks GA	GA Behavioral State Maximum HR % Decrease in O_2 saturation Brow bulge Eye squeeze Nasolabial furrow	Acute procedural pain	Heel lance	Construct validity IR: 0.94–0.98 IC: 0.71

Abbreviations: GA – gestational age; HR – heart rate; BP – blood pressure; RR – respiratory rate; O_2, — oxygen; IR – interrater reliability; IC – Internal consistency.

Analyses (PRISMA) was used to report the findings from this review (Liberati et al., 2009).

Eligibility Criteria

Types of Studies

This review included RCTs that explored the efficacy of pain management interventions on behavioral pain response in preterm infants. Eligible criteria imposed included: English language; publication dates within a 6-year period, and publication in peer-refereed journals.

Population and Setting

Studies involving premature or preterm infants hospitalized in neonatal intensive care units were targeted with preterm infants defined as infants born before 37 completed weeks gestation (Landry, 1993).

Intervention and Outcome Measure

Eligible RCTs tested pain management interventions on behavioral pain responses in preterm infants. The primary outcome measure for RCTs included behavioral pain response scores using a valid and reliable neonatal pain scale.

Articles Excluded

Journal articles without original data and unpublished data or manuscripts were not considered for inclusion.

Information Sources

RCTs for this systematic review were retrieved from PubMed and Medline between January 1, 2013–September 2, 2017. Although Medline is a large subset of PubMed, the databases identify articles using different search strategies. Individually searching both PubMed and Medline can uncover citations indexed in PubMed that do not appear in Medline (U.S. National Library of Medicine, 2010). The last search of databases occurred September 2, 2017.

Search Strategy and Study Selection

The following key words and MESH headings for the search of databases were neonatal, preterm infant, pain, randomized controlled trial (RCT) behavioral, and nonpharmacological. Study eligibility was independently assessed in an unblinded manner by 3 reviewers. Disagreement between reviewers was resolved by consensus.

Data Collection Process and Data Items

All studies included in the analysis were rated independently by all authors and compared for consistency. The quality of evidence (level of evidence) was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence in systematic reviews or clinical guidelines. Levels of evidence range from high to very low and are assigned based on type of evidence, quality of evidence, consistency, directness and effect size (Grade Working Group, 2004; Guyatt et al., 2008). All authors independently reviewed extracted data from studies targeted from the search. In the event of disagreement of evidence ratings, a final score was determined by discussion and consensus. Data extracted from each clinical trial focused on: (1) the pain scale used in RCT, (2) study participant characteristics, (3) type of noxious stimulation, and (4) primary outcome.

Summary Measures and Data Analysis

Behavioral pain response utilizing a valid and reliable neonatal pain scale for preterm infants was the primary measure of treatment effect. Data were analyzed and synthesized to behavioral pain response obtained from a valid and reliable neonatal pain scale for preterm infants. Measures of central tendency assessed participant characteristics, study methodology and, preterm infant biobehavioral pain response scores.

Results

Study Selection

The literature review recognized 379 articles. Articles that were judged not relevant and therefore excluded from the analysis were: duplicate manuscripts (9), English language restriction (32), preclinical trials (29), infants over 37 weeks gestation (53), articles over 5 years old (167), study design other than clinical trial (68), pharmacological studies (5) and full text limitation (2). The remaining RCTs examining the efficacy of pain management interventions in decreasing behavioral pain response in preterm infants ($n = 14$) were critically evaluated. A manual search identified one additional study that met the inclusion criteria. This review did not utilize unpublished data or relevant studies. Synthesis of data from the 14 clinical trials assessed the efficacy of procedural pain management interventions in decreasing behavioral pain response in preterm infants. Study selection and identification of studies included in the analysis are represented in Fig. 1.

Pain Scales Used in the RCTs

Seven of the 14 studies used the Premature Infant Pain Scale, one of the neonatal scales recognized for rigorous psychometric testing utilizing participating neonates as their own controls and measuring their behavioral and physiologic pain responses using the scale in question (Abbasoglu et al., 2015; Alinejad-Naeini et al., 2014; Cavaiuolo et al., 2015; Ho, Ho, Leung, So, & Chan, 2016; Kataria et al., 2015; Mitchell et al., 2013; Sahoo et al., 2013). Two studies used the Neonatal Infant Pain Scale (Costa et al., 2013; Peyrovi, Alinejad-Naeini, Mohagheghi, & Mehran, 2014) and one study used the Bernese Pain scale for Neonates (Gerull, Cignacco, Stoffel, Sellam, & Nelle, 2013). Four studies did not measure preterm infant pain with a valid and reliable pain scale. Of the four studies, two studies used autonomic pain responses to assess the efficacy of pain management interventions. One study evaluated the efficacy of kangaroo care (Cong et al., 2012). The other examined oral sucrose (Yin et al., 2015). The third study assessed behavioral indices such as cry, grimace, limb extension, and self-soothing measures (Gao et al., 2015). The remaining study assessed infant pain response by assessing infant behavioral state (Liaw et al., 2013).

Characteristics of Study Participants

All 14 studies selected for analysis were RCTs published in English. Nine studies recruited preterm infants (Abbasoglu et al., 2015; Cavaiuolo et al., 2015; Cong et al., 2012; Costa et al., 2013; Gao et al., 2015; Gerull et al., 2013; Ho et al., 2016; Kataria et al., 2015; Mitchell et al., 2013). Five studies recruited preterm and term infants (infants up to term, 37 weeks gestation) (Alinejad-Naeini et al., 2014; Liaw et al., 2013; Peyrovi et al., 2014; Sahoo et al., 2013; Yin et al., 2015). Five of the studies that recruited only preterm infants disregarded infants after 30 weeks (Mitchell et al., 2013), ≤32 weeks (Costa et al., 2013), 32.2 weeks (Kataria et al., 2015), 32 6/7 weeks (Cong et al., 2012), and 36 weeks (Abbasoglu et al., 2015; Cavaiuolo et al., 2015).

Other than inclusion and exclusion criteria, seven studies (Cong et al., 2012; Ho et al., 2016; Kataria et al., 2015; Liaw et al., 2013; Mitchell et al., 2013; Sahoo et al., 2013; Yin et al., 2015) provided a power analysis. Two studies (Ho et al., 2016; Sahoo et al., 2013) provided a rationale for sample size based on a previous study. Mitchell et al. (2013) stopped recruitment and randomization of participants before full recruitment because the culture of the NICU changed. Kangaroo care was becoming routine and widely accepted transforming the standard of care within the NICU. Table 2 describes the sample characteristics for the included studies.

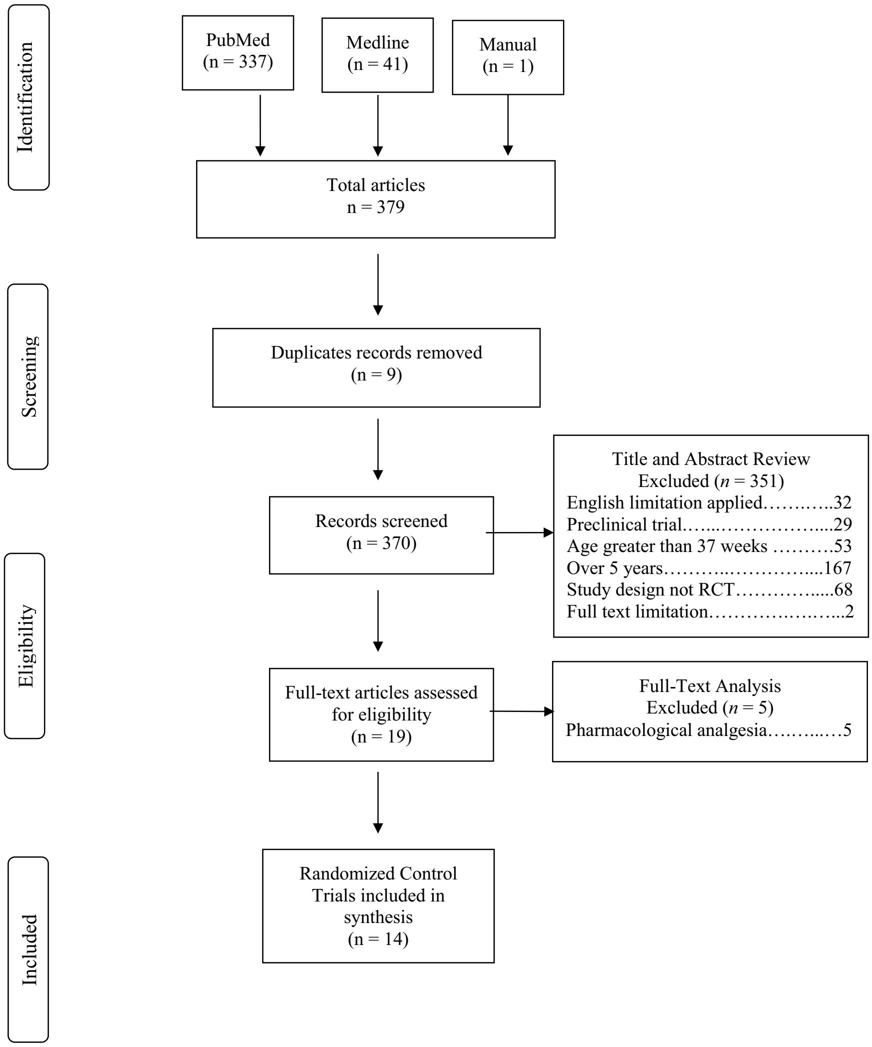

Fig. 1. Flow diagram: selection process for systematic review.

Type of Noxious Stimulation

Across RCTs analyzed in this review, there was significant heterogenicity in the type of exposure to noxious stimuli eliciting infant pain. RCTs evaluated pain from painful diagnostic and treatment procedures infants experienced during standard care in the NICU. Standard procedures included heel lance (Abbasoglu et al., 2015; Cavaiuolo et al., 2015; Cong et al., 2012; Gao et al., 2015; Gerull et al., 2013; Ho et al., 2016; Liaw et al., 2013; Yin et al., 2015) venipuncture with 23-gauge needle (Sahoo et al., 2013), endotracheal suctioning (Alinejad-Naeini et al., 2014; Mitchell et al., 2013; Peyrovi et al., 2014) and laser treatment of retinopathy of prematurity. (Costa et al., 2013; Kataria et al., 2015). No RCT performed a painful intervention that did not have therapeutic benefit. Variability in procedures and pain intensity influenced the neonate's response to noxious stimuli and adaptability. Differentiating between infant behavioral pain response, infant stress, or infant distress is impeded by the variable intensities of pain response from neonates (Hatfield & Polomano, 2012) making it difficult to draw definitive conclusions.

Primary Outcome

Studies assessing the efficacy of pain management interventions in decreasing behavioral pain response in preterm infants do not always provide clarity around the concept of pain. Only one study defined pain conceptually in a broader context (Cong et al., 2012). Nine studies provided a scientific rationale for linking the variable of interest to pain, the primary outcomes of interest (Abbasoglu et al., 2015; Alinejad-Naeini et al., 2014; Cong et al., 2012; Gao et al., 2015; Ho et al., 2016; Kataria et al., 2015; Liaw et al., 2013; Peyrovi et al., 2014; Yin et al., 2015). From reported outcomes, one can deduce that investigators considered duration of procedure (Abbasoglu et al., 2015), quiet sleep occurrences (Liaw et al., 2013), limb and trunk extension (Yin et al., 2015), self-soothing behaviors (Yin et al., 2015), heart rate (Cavaiuolo et al., 2015; Cong et al., 2012; Gao et al., 2015; Gerull et al., 2013; Sahoo et al., 2013), heart rate variability (Cong et al., 2012), the low frequency (LF) area of the heart rate which reflects sympathetic activity (Cong et al., 2012), the high frequency (HF) area of the heart rate which reflects respiratory frequency (Cong et al., 2012), LF/HF ratio (Cong et al., 2012), infrared spectroscopy (Gerull et al., 2013), oxygen saturation (Cavaiuolo et al., 2015; Sahoo et al., 2013), cortisol (Mitchell et al., 2013), grimacing (Gao et al., 2015; Yin et al., 2015) and crying (Abbasoglu et al., 2015; Gao et al., 2015; Liaw et al., 2013; Sahoo et al., 2013) to also be the valid indicators of pain in infants. Research on these outcomes do not verify or refute infant pain (Stevens, Taddio, Ohlsson, & Einarson, 1997). RCTs must correlate their findings with valid and reliable physiological, behavioral, and contextual pain scale indices (Hatfield & Ely, 2015). Table 3 summarizes the relevant

Table 2
Summary of sample characteristics.

Author(s) (Year)	Setting	Number of participants	Age range	Inclusion criteria
Ho et al. (2016)	ICU Hong Kong	54	30–36 weeks GA	Preterm infants in the incubators and requiring a blood sample using heelstick procedure were recruited Preterm infants who had major congenital abnormalities, severe cardiovascular disease, neurological impairment, and those who required ventilation support, sedatives and analgesics were excluded
Abbasoglu et al. (2015)	ICU Turkey	32	28–36 weeks GA	All infants were in incubators All infants in stable condition Infants with major malformation, congenital abnormalities or previous treatment with analgesics and sedatives were excluded
Cavaiuolo et al. (2015)	NICU Italy	42	27–36 weeks GA	No hearing loss, significant cerebral lesions on cranial ultrasound, previous analgesia or sedation, invasive respiratory support or sepsis
Gao et al. (2015)	NICU China	75	<37-week GA	Singleton infants with gestational age <37 weeks, cared for in an incubator, anticipated to have at least four routine capillary blood draws within 2 weeks after birth, and not scheduled to receive paralytic, analgesic, or sedative medications 48 h prior to a study session Infants with congenital or neurological anomalies, grade III or IV intraventricular hemorrhage, surgery, signs of heel tissue breakdown or inflammation/necrosis, medically unstable, required oxygen or respiratory support, or mother had a history of drug abuse during pregnancy were excluded
Kataria et al. (2015)	NICU India	24	27.2–32.2 GA at birth	Type 1 ROP as per Early treatment of ROP classification Infants with concurrent analgesia, mechanical ventilation, major congenital malformation were excluded
Yin et al. (2015)	NICU Taiwan	110	27–37 weeks GA	Gestational age (GA) 27–37 weeks and PMA 27.4–38 weeks, post birth age 3–28 days, and disease condition acceptable for observation (illness severity indicated by the Neonatal Therapeutic Intervention Scoring System [NTISS] score ≤ 20) Infants with a condition that might influence their behavioral responses, e.g. congenital anomalies, surgery, or severe illnesses requiring treatment with sedatives, muscle relaxants, antiepileptic, or analgesic drugs were excluded
Alinejad-Naeini et al. (2014)	NICU Iran	34	29–37 weeks GA	Endobrachial tube present No congenital anomalies, seizures, chest tubes, IVH higher than II, analgesia or sedatives for 4-h prior, painful procedure 30 min before intervention
Peyrovi et al. (2014)	NICU Iran	34	29–37 weeks GA	Gestational age between 29 and 37 weeks of gestational age, birth weight 1200 g or more, having an endotracheal tube, Infants with congenital anomalies, seizures diagnosis, chest tubes, intracranial hemorrhage higher than Grade II, receiving opiates and sedatives within four hours before intervention and receiving any painful procedure at least half an hour before the intervention were excluded
Costa et al. (2013)	NICU Brazil	124	≤32 weeks GA	Birth weight ≤ 1500 g No exclusion criteria
Gerull et al. (2013)	NICUs Switzerland	25	24–32 weeks GA	Between 24 0/7 and 32 0/7 weeks of gestation, if hospitalized in the neonatal intensive care unit and if it was anticipated that they would need five capillary blood samples within the first 14 days of life Infants with intraventricular hemorrhage grade III or IV, presence of severe malformations, umbilical artery pH < 7.00, surgery for any reason, conditions associated with partial or total loss of sensitivity and congenital malformations affecting the brain circulation or the cardiovascular system were excluded
Liaw et al. (2013)	NICU Taiwan	110	26.4 to 37 weeks GA	DOL 2–28 days, Neonatal Therapeutic Intervention Scoring System ≤22 No congenital anomalies, convulsion, IVH > II, PVL, sepsis, surgery, growth restriction, substance abusing mother, sedative, muscle relaxants, antiepileptic, or analgesia drugs
Mitchell et al. (2013)	NICU USA	38	27–30 weeks GA	DOL <5 days, receiving mechanical ventilation, CPAP, NC No maternal opioid use, clinical instability, congenital defect, major surgery, APGAR at 5 min <3, cord blood pH < 7.0 or base deficit below −15
Sahoo et al. (2013)	NICU India	160	>34 weeks GA	Required venipuncture and were on oral feeds No illness, APGAR score at 5 min <5, congenital malformations, opioid analgesics, sedatives, or phenobarbi-tone
Cong et al. (2012)	NICU USA	26	28–32 weeks GA	DOL <14 days, in incubator, NPO or bolus feeds No congenital anomalies, IVH > III, major or minor surgery, sedation vasopressors or analgesia, mother positive drug history, tissue damage or inflammation in either heel

Abbreviations: GA – Gestational age; NICU – Neonatal Intensive Care Unit; ROP – Retinopathy of Prematurity; DOL – Day of Life; IVH – intraventricular hemorrhage; PVL – periventricular leukomalacia; CPAP – Continuous Positive Airway Pressure; NC – Nasal Canula; NPO – nothing by mouth.

data from RCTs from January 1, 2013–September 2, 2017 included in the analysis.

Study Characteristics

Types of Study

All 14 studies selected for review were RCTs published in English. Study duration ranged from 3 to 20 months.

Participants

The included studies involved 889 participants. The main inclusion criteria entailed preterm infants (GA 21 to 37 weeks) in stable condition.

Intervention

The interventions received among the participants were swaddling, acupuncture, kangaroo care, oral dextrose, oral glucose, oral sucrose, non-nutritive sucking, facilitative tucking and breast milk.

Outcomes

In all studies the primary outcome was a biobehavioral pain score obtained utilizing a valid and reliable pain scale for preterm infants.

Risk of Bias Within Studies

Appropriate sample size, study design, randomization and allocation concealment were independently reviewed to evaluate the validity of eligible RCTs. Authors hypothesized that the variability in the effectiveness of pain management interventions and study outcomes were influenced by the study setting, study design and quality of eligible studies. All studies had at least one marker that put the study at potential risk for bias. No study concealed randomization or addressed incomplete data, four studies prevented knowledge of allocation (Cavaiuolo et al., 2015; Costa et al., 2013; Kataria et al., 2015; Mitchell et al., 2013), and only seven studies conducted a power analysis (Cong et al., 2012; Ho et al., 2016; Kataria et al., 2015; Liaw et al., 2013; Mitchell et al., 2013;

Sahoo et al., 2013; Yin et al., 2015). Table 4 summarizes the potential risk of bias in the included studies.

Discussion

This systematic review synthesized findings from published RCTs conducted in the past 5 years to assess the efficacy of pain management interventions in decreasing behavioral pain response in preterm infants. Although, the 14 studies were strengthened by using a RCT design, there was wide variation in participants, interventions and reported outcomes. Thus, the focus of our descriptive review of these studies summarizes their sample populations, results and limitations. Findings suggest there is evidence to support that different pain management interventions can be used with preterm infants to significantly manage pain behaviors associated with acutely painful procedures.

Synthesis of Results

Although based on very low-quality evidence, across age groups facilitated tucking was the most frequent intervention and demonstrated decreases in behavioral and physiologic pain response alone and in combination with other pain management interventions (Alinejad-Naeini et al., 2014; Gerull et al., 2013; Liaw et al., 2013; Peyrovi et al., 2014; Yin et al., 2015). Oral sucrose (Gerull et al., 2013;Liaw et al., 2013; Yin et al., 2015) and kangaroo care (Cong et al., 2012; Gao et al., 2015; Mitchell et al., 2013) are also promising interventions although each study had at least one marker that puts the study at potential risk for bias.

There was heterogenicity in the studies which limited our confidence in the findings. Moreover, the variability in the primary outcome and the preponderance of low quality evidence made it difficult to draw definitive conclusions. Retrospective exploration of the heterogenicity identified three studies whose outcome variables significantly differed from the others (Cong et al., 2012; Gao et al., 2015; Yin et al., 2015). These studies did not use a valid and reliable neonatal pain scale to assess and measure pain. The studies examined autonomic pain responses of preterm infants as surrogate markers for infant pain exposing the study to potential bias. Our findings suggest that the autonomic response generated by noxious stimuli were decreased during sucrose, facilitative tucking and kangaroo care compared to standard care.

These data support systematic reviews (Pillai Riddell et al., 2015) and evidence-based clinical guidelines (Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine, 2016) that suggest pain management interventions can be used with preterm infants to mitigate biobehavioral responses to procedural pain. All analyses reflect the need for more research to bolster confidence toward positive outcomes. There were no reports of significant adverse events or deaths associated with interventions studied in this review.

Risk of Bias Across Studies

Limiting the inclusion criteria to peer-refereed RCTs introduced a publication bias because non-publication of small trials with negative results were excluded from our review. Trial quality was generally low to very low and study heterogeneity in biobehavioral interventions, cultural context, and outcomes contributed to bias across studies.

Summary of Evidence

Findings from this systematic review must be cautiously interpreted because of the small number of published RCTs with preterm infants within the last five years. Although all studies demonstrated the potential risk for bias, the appraisal of quality for the RCT using GRADE was generally acceptable. More RCTs with preterm infants are required to establish the efficacy of pain management interventions for the management of acute procedural pain in this vulnerable population.

Limitations

Systematic reviews of well-designed, peer-refereed RCTs are crucial to the development of evidence-based clinical practice guidelines in nursing (Jackson & Sackett, 1996). To ensure a rigorous, trustworthy systematic review of evidence, only peer-reviewed RCTs were examined for this review. The authors recognize that limiting the inclusion to published peer-refereed RCTs may generate a publication bias of positive results.

Completeness and Applicability of Evidence

There is a steep developmental neurobiology trajectory that occurs during infancy and young childhood (Hatfield, 2014). Because of progressive changes in the ability of the nervous system to process and modulate pain over time, infants' responses to pain procedural pain vary considerably as they mature. Therefore, the evaluation of the efficacy of pain management interventions was confined to preterm infants gestational age 24 to <37 weeks. Findings may only be applicable for the gestational age for which they are reported.

Quality of Evidence

The strength of the evidence for the RCT included in this review was very low. The quality of the evidence in this systematic review was challenged by the lack of sufficient evidence for the intervention strategies. All studies had issues with blinding of allocation to interventions, sparse data (small sample sizes), and generalizability. Although no study reported odds ratios, relative risk or hazard ratios for study comparison, two studies (Liaw et al., 2013; Yin et al., 2015) reported rate ratios. Some interventions (such as facilitated tucking) did not yield consistent results because of high risk for bias and imprecision, a decreased number of studies examining the intervention, and inadequate sample sizes that may have affected the ability to detect treatment differences. The best available evidence, however, was used despite limitations in study quality. This observation should encourage investigators conducting RCTs to improve the rigor of their studies.

Implications for Practice

There is evidence to demonstrate that pain management interventions can be used with preterm infants and neonates to significantly manage acute pain associated with painful procedures (Pillai Riddell et al., 2015). In clinical practice, an evidence-based, multidisciplinary, multimodal approach to acute pain management in preterm infants should be adopted. The approach involves identifying, removing or mitigating potential stress, pain triggers (such as environmental noise, frequent handling, undermanaged pain during repeated painful procedures, absence of soothing touch, or frequent drastic weaning) or noxious stimuli. Pain management interventions are often successful at alleviating noxious environmental stimuli and mild procedure-related pain. Pain management interventions in concert with pharmacological interventions (e.g. opioids and/or benzodiazepines) are appropriate for procedures that are more painful. This multimodal approach may be helpful in reducing opioid use and mitigating the transition from acute to chronic pain.

Implications for Research

This review identifies significant gaps in the existing literature on pain management interventions for in decreasing behavioral pain response in preterm infants. The greatest gaps are for well-designed RCTs that examine behavioral interventions such as sucking, rocking, holding, tucking, swaddling, massage, odor, visual distraction and structured-care giver interventions. These interventions have some evidence to support their efficacy, but confidence is lacking due to low quality evidence and lack of replication (Pillai Riddell et al., 2015). While the findings of this systematic review contribute to the existing literature related to infant pain, the inability to quantify the results through a comparative analysis points to the need for standardization in future research studies to better understand findings and their relationship to the existing evidence.

Conclusion

In summary, evidence suggests that behavioral and environmental interventions can be used with preterm infants to significantly mitigate biobehavioral pain response associated with painful procedures. However, significant gaps in the literature exist in testing the efficacy of pain management interventions in decreasing behavioral pain responses in preterm infants. Among the highest priority to address these gaps is the need for well-designed RCTs that study sucking, swaddling, rocking, holding, tactile, olfactory, gustatory, auditory interventions and parent or caregiver interactions. Studies evaluating these interventions have been potentially effective, but confidence is limited because of poor study methodology and lack of replication. Finally, sample size in treatment groups in RCTs examining behavioral and environmental interventions to mitigate pain in preterm infants must increase.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedn.2018.10.004.

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