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Review

Preterm newborn pain research review

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ABSTRACT

This narrative review is based on a literature search of PubMed and PsycINFO for research on preterm newborn pain published during the last ten years. The high prevalence of painful procedures being performed with preterm newborns without analgesia (79%), with a median of 75 painful procedures being received during hospitalization and as many as 51 painful procedures per day highlights the importance of this problem. This review covers the pain assessments that have been developed, the short-term effects of the painful procedures, the longer-term developmental outcomes and the pharmacological and alternative therapies that have been researched. The most immediate effects reported for repeated painful procedures include increased heart rate, oxidative stress and cortisol as well as decreased vagal activity. Lower body weight and head circumference have been noted at 32 weeks gestation. Blunted cortisol reactivity to stressors has been reported for three-month-olds and thinner gray matter in 21 of 66 cerebral regions and motor and cognitive developmental delays have been noted as early as eight months. Longer-term outcomes have been reported at school age including less cortical thickness, lower vagal activity, delayed visual– perceptual development, lower IQs and internalizing behavior. Pharmacological interventions and their side effects and non-pharmacological therapies are also reviewed including sucrose, milk and nonnutritive sucking which have been effective but thought to negatively affect breast-feeding. Full-body interventions have included tucking, swaddling, kangaroo care and massage therapy. Although these have been effective for alleviating immediate pain during invasive procedures, research is lacking on the routine use of these therapies for reducing long-term pain effects. Further, additional randomized controlled replication studies are needed.

1. Introduction

For this narrative research review, PubMed and PsychINFO were searched for the terms preterm newborn pain to identify publications from the last ten years. Inclusion criteria were randomized controlled trials, systematic reviews and meta-analyses that were peer-reviewed and published in English. Exclusion criteria included case studies and low-powered empirical studies. Of the 139 publications reviewed, 67 met criteria. This review covers the prevalence of painful procedures and their noted neurophysiology, the assessments that have been developed to evaluate pain responses, the immediate effects of the painful procedures, the longer-term developmental outcomes and the pharmacological and non-pharmacological therapies that have been researched.

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2. Prevalence of painful procedures and their noted neurophysiology

Reputedly 79% of painful procedures are experienced by preterm newborns without analgesia, with as many as 32–364 (median = 75) painful procedures being experienced during a neonatal intensive care unit (NICU) stay and an average of 10 (R = 0–51) painful procedures per hospital day (Hatfield, 2014). These numbers may have decreased over the past few years given the increasing recognition that preterm newborns experience pain. The lack of myelination (neuron insulation) led to the notion that preterm infants were incapable of experiencing pain. Although the ascending pathways are supposedly myelinated by 30 weeks gestation, the descending pathways are immature until approximately 48 weeks gestation, suggesting that preterm infants have a limited ability to modulate pain as compared to older infants and adults (Fitzgerald & Walker, 2009). In addition, although pain neurotransmitters are plentiful at birth, e.g. substance P and somatostatin, the pain modulators such as dopamine and serotonin are not as available to modulate pain before 40 weeks gestation (Fitzgerald, 2005). Mature functioning of the pain modulators is reputedly achieved by approximately two months of age (Vinall & Grunau, 2014). Data on the neonate's response to pain first occurred in a seminal paper by Anand et al. (1985). Most of the newborn pain studies since then have come from the Anand, the Fitzgerald and the Grunau research teams.

3. Pain assessments

Since behavioral responses to pain by preterm newborns were first observed, as many as 40 pain assessments have been developed (Maxwell, Malavolta, & Fraga, 2013). Because preterm newborns do not show behavioral and physiological signs of pain as reliably as full-term infants, only a few of those assessments have been frequently used with preterm newborns. These include the Neonatal Facial Affect Coding System (NFACS) (Grunau, Oberlander, Holsti, & Whitfield, 1998), the Premature Infant Pain Profile (PIPP) (Stevens, Johnston, Petryshen, & Taddio, 1996), The Neonatal Infant Pain Score (NIPS) (Lawrence et al., 1993), the Behavioral Indicators of Infant Pain (BIIP) (Holsti & Grunau, 2007) and the CRIES scale (Crying Requires (oxygen) Increased(vital signs) Expression, Sleepless) (Krechel & Bildner, 1995). These scales include both behavioral observations and recording of physiological measures taken from the neonate's monitor.

The most common behavioral indicators include changes in facial expressions, crying, general or specific body movements, muscle tone, color and sleep/wake states (Holsti, Grunau, & Shany, 2011). Examples of the facial expressions include brow bulge, eye squeeze, and a deepening of the nasolabial furrow (Hatfield, 2014). The BIIP also includes hand movements for younger preterm infants whose facial expressions are less salient (Holsti, Grunau, Oberlander, & Osiovich, 2008). The physiological measures included in these newborn pain assessments are those found on the NICU monitors including heart rate, respiratory rate, oxygen saturation and blood pressure (Holsti et al., 2011). One of the earliest empirical studies on preterm neonates' physiological responses was conducted by our group showing that heelsticks resulted in significant declines in transcutaneous oxygen tension (Morrow et al., 1990).

The behavioral observation scales are thought to be reliable, although a couple investigative teams have found that behavioral and physiological responses are sometimes divergent (Lucas-Thompson, Townsend, & Gunna, 2008; Morison, Grunau, Oberlander, & Whitfield, 2001). For example, a behavioral response to a pain stimulus may be noted at the same time that the physiological measure remains unchanged, highlighting the problem of combining the behavioral and physiological response scores and suggesting that they should be treated as individual scores. Another example of this is demonstrated by a study that showed high correlations between near-infrared spectroscopy and three separate facial expressions observed on the PIPP but a weaker correlation between the total multidimensional PIPP score and the spectroscopy (Slater, Cantarella, & Franck, 2008). Near-infrared spectroscopy uses near-infrared region of the electromagnetic spectrum to measure oxygen saturation. Some of the variability in behavioral and physiological responses to pain may be explained by personality/constitutional differences at birth. For example, some newborns respond behaviorally (about 20% being labeled externalizers) and some show their pain response physiologically (about 20% being called internalizers) and some manifest their pain response both behaviorally and physiologically (about 60% generalizers). These personality/constitutional differences are present at birth and were documented in a study showing greater concordance between monozygotic twins than dizygotic twins on this factor (Field, 1986).

Another type of pain assessment called near-infrared spectroscopy has revealed gestational age and gender differences in pain responses of preterm infants (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006). In this study, the response to hand venipuncture was inversely correlated with gestational age and positively correlated with postnatal age and more pronounced in male than female infants. These results were considered a demonstration that pain responses are processed at a cortical level and are not simply reflex responses. Gestational age differences have also been noted for behavioral responses which confound the relationship between invasive procedures and painful responses and suggest the need for controlling for gestational age. The PIPP, for example, adjusts for gestational age inasmuch as many facial responses become dampened after repeated painful procedures (Grunau et al., 2005) and interventions (Fitzgerald, 2009). Despite these confounds, the behavioral responses including facial grimacing, crying and changes in sleep–wake states account for most of the variance in the pain assessments of preterm newborns (Johnston, Stevens, Yang, & Horton, 1995).

Current practice requires pain assessments prior to, during and after invasive procedures, and these scales make the monitoring of preterm newborn pain convenient. However, significant training and inter-rater reliability testing are costly, as is the duplication of staff required for procedures and simultaneous assessments (Hall & Anand, 2014). This becomes even more complicated when interventions are also being simultaneously administered. Pain scales are further limited by their subjectivity and their questionable inter–rater reliability. In addition, they are subject to different interpretations. Further, when preterm newborns are experiencing persistent pain, they often appear to be in a passive state with limited body movements, difficult −to-read facial expressions and

reduced physiological reactivity (Hall & Anand, 2014). Despite these problems, the consistent use of pain assessment monitoring during all aspects of invasive procedures has been recommended by the American Neonatology Association. (Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine, 2016).

4. Immediate effects of painful procedures

Most of the studies on the effects of painful procedures have been conducted with preterm neonates. This relates not only to preterm neonates experiencing more painful procedures and a longer hospital stay but also because they have a lower pain threshold and less developed modulation of pain than full-term newborns as well as more pronounced responses to painful stimulation (Fitzgerald, 2005). As discussed below, the most immediate effects reported for repeated painful procedures in preterm neonates are the behavioral and physiological responses measured by the scales and monitors. Reduced body weight and head circumference have been noted later at 32 weeks gestation and reduced white matter and subcortical gray matter have been reported at term age.

In a study on behavioral responses to pain using the Neonatal Facial Affect Coding Scale and the Sleep-Wake States Scale as well as heart rate responses, similar behavioral responses were noted in male and female preterm neonates (N = 53) (Valeri, Gaspardo, Martinez, & Linhares, 2014). However, male newborns showed a greater increase in heart rate during the heelsticks in this study. The increased heart rate noted by these researchers as well as others suggests the possibility of increased risk for oxidative stress (a disturbance in the balance between the production of reactive oxygen (free radicals) and antioxidant defenses). Oxidative stress was measured by another research group during the painful removal of tape holding a catheter in preterm neonates (Slater et al., 2012). This tissue–damaging procedure increased pain scores on the Premature Infant Pain Profile in the group that experienced the tape removal. In addition, the measures of oxidative stress suggested that the tape removal newborns experienced more oxidative stress, and a significant correlation was noted between the behavior scores and the increased oxidative stress.

Newborn pain, as measured by the number of skin–breaking procedures, has led to lower body weight and head circumference percentiles at 32 weeks post-conceptional age (Vinall et al., 2012). This may relate to the release of stress hormones, e.g., cortisol, following repeated invasive procedures. More severe effects of repeated invasive procedures are the reduced white matter and subcortical gray matter that have been reported at term–equivalent age in preterm infants born at 24–32 weeks gestation (Brummelte et al., 2012). This may relate to the reduced cerebral blood flow that has been noted on near–infrared spectroscopy studies during invasive procedures, the non-specific neuronal bursts of EEG activity that are widespread in the brain (Grunau, 2013) and the altered microstructure resulting from pro-inflammatory cytokines following invasive procedures (Brummelte et al., 2012; Kalpakidou et al., 2012). Greater exposure to invasive procedures (e.g., heelstick and intubation) has been associated with reduced brain size mostly in the frontal and parietal regions in preterm newborns assessed at term age (Smith et al., 2011).

5. Longer term outcomes following repeated painful procedures

Longer-term outcomes related to repeated invasive procedures have been noted during the first few months of life and as late as adulthood. These have included increased cortisol levels and cortisol reactivity, less cortical thickness, smaller cerebellum, delayed motor, cognitive and visual-perceptual development, lower IQ scores and internalizing behaviors.

5.1. Elevated cortisol levels and cortisol reactivity

The data on cortisol and cortisol reactivity related to procedural pain have varied as a function of age. At three months post-conceptional age, for example, significantly lower saliva cortisol levels have been noted (Grunau et al., 2007) as well as a blunted salivary cortisol response to a stressor (the mother posing a still-face during face-to-face interactions) (Provenzi et al., 2016). But then later at eight months and 18 months, preterm infants exposed to more invasive procedures had higher cortisol levels (Grunau et al., 2007). Cortisol levels were related to toddler behavior at 8 months (Tu et al., 2007) and that relationship continued to school age. For example, in one longitudinal study, 7-year-old children who had received more invasive procedures as preterm newborns showed higher cortisol levels at bedtime than full-term infants, and they had more internalizing behaviors (anxiety/depressive symptoms) (Brummelte et al., 2011). In this study, boys were more affected by the early skin-breaking procedures while girls' cortisol levels were more affected by maternal depression and anxiety. In a more recent study, the brain-derived neurotrophic factor (BDNF) gene was noted to interact with preterm invasive procedures to predict elevated cortisol in seven-year-old children (Chau, Cepeda, Devlin, Weinberg, & Grunau, 2017). BDNF is notably reduced by stress so it is not surprising that children with the BDNF allele had higher salivary cortisol levels. In this longitudinal sample (N = 90 children born very preterm), the children with lower BDNF and higher salivary cortisol reactivity to a cognitive challenge had lower IQ scores and inferior visual − motor performance (Chau et al., 2017).

5.2. Lower vagal activity

Lower cardiac vagal activity might also contribute to elevated cortisol inasmuch as vagal activity has been associated with lower cortisol levels. Cardiac vagal activity or vagal tone is the activity of the vagus nerve of the parasympathetic branch of the autonomic nervous system that regulates the resting state of most of the body's internal organs including the heart, eyes, glands and digestive tract. In a French study 107 participants between seven and 25 years of age were asked to immerse their forearm in cold water for two minutes while their EKGs were recorded (Morin et al., 2014). Both the preterm and full term participants who had experienced invasive procedures during the newborn period showed a higher resting heart rate and lower cardiac vagal activity. The lower vagal

activity may not only contribute to elevated cortisol but to elevated pain responses inasmuch as lower vagal activity has been associated with heightened pain (Koenig, Falvay et al., 2016).

5.3. Heightened pain responses

At least two studies have suggested heightened responses to painful procedures by older children who had been born preterm. In a study on 56 seven-year-old children born very preterm (24–32 weeks gestation), the children experienced a blood sampling and reported their pain on an analog scale and on the Facial Affect Coding Scale. (Valeri et al., 2016). The number of invasive procedures they had experienced and other clinical factors were entered into a regression on the children's self − ratings of pain. A greater number of newborn invasive procedures was associated with higher pain intensity ratings during the blood sampling. In another study, 31 adolescents who had been born preterm and 28 adolescents who were born full-term were compared on their responses to a cold pressor task (hand in ice water) (Vederhus et al., 2012). Although the preterm group had reduced tolerance for this experimental pain (withdrew their hands from the cold water more rapidly), the preterm participants rated their pain responses as similar to those of the full-term group. In this study, the researchers noted that days of mechanical ventilation and morphine doses during the newborn period were also related to the early withdrawal responses. Surprisingly, the participants who had been born preterm and who had experienced the greatest number of painful invasive newborn procedures and the most morphine doses had pain responses that resembled those of the group who had been born full-term. These diminished pain responses may relate to a blunting/numbing effect of early repeated painful procedures. Although difficult to interpret, these data highlight the importance of including days of mechanical ventilation and number of morphine doses along with the number of invasive procedures in the data analyses.

5.4. Brain and developmental effects

Brain and developmental effects have been explored in a number of longitudinal studies. In a systematic review of this literature, 13 studies on children born preterm met inclusion criteria (Valeri, Holsti, & Linhares, 2015). The results of this systematic analysis suggested that those infants who had experienced greater numbers of painful procedures had delayed postnatal growth and neurodevelopment, greater cortical activation and altered brain development including less gray and white matter. At the toddler stage, greater pain reactivity was noted as well as a relationship between that reactivity and negative temperament. By one year of age, cognitive and motor development delays were reported. And at seven years, less cortical thickness as well as lower IQs and internalizing behaviors were noted in those who had experienced greater numbers of newborn invasive procedures. Many of these findings were based on the research of Grunau and her colleagues and were described by Grunau herself in an earlier narrative review (Grunau, 2013) and in a subsequent narrative review by Ranger and Grunau (2014).

One of the studies included in the earlier reviews assessed the cortical activity and visual − perceptual development of school-age children (Doesburg et al., 2013). In this longitudinal study, magnetoencephalography was used to assess cortical activity. The cortical activity was negatively correlated with visual perceptual development in these children and both, in turn, were related to cumulative newborn invasive procedures. In a related longitudinal study by Grunau and her colleagues, 42 children who were born preterm and had experienced a significant number of skin–breaking procedures as newborns were assessed by MRI neuroimaging for cortical thickness (Ranger et al., 2013). After correcting for many potential confounds including gestational age, illness severity, infection, mechanical ventilation, surgeries and morphine exposure, a greater number of invasive procedures was associated with a significantly thinner cortex in 21 of 66 cerebral regions, most predominantly in the parietal and frontal lobes. These results are based on sophisticated data analyses including constrained principal component analysis followed by generalized linear modeling. The results may also explain lower IQ scores noted in the same age children (seven-year-olds) (Vinall, Grunau et al., 2013).

In a more recent study by the same research group, 56 children born very preterm received neuroimaging at eight years of age (Ranger et al., 2015). This time, the focus was on cerebellum volumes adjusted for total brain volume and gender as well as neonatal clinical factors, and the same constrained principal component analysis was conducted. The findings suggested that the number of neonatal invasive procedures was associated with smaller volumes in the posterior lobules of the cerebellum. In turn, smaller volumes in those regions were related to inferior cognition and visual-motor performance. In this cohort, neonatal infection was also a contributing factor.

In still another study by Grunau and her research colleagues, 101 children were seen at eight years of age to determine the relationship between the number of skin-breaking procedures and internalizing behaviors (Ranger, Synnes, Vindall, & Grunau, 2014). The relationship between neonatal invasive procedures and internalizing behaviors had been noted in this sample at 18 months postnatal age. In addition, because morphine had been related to neonatal invasive procedures, it was also entered into these analyses. Finally, although ventilation does not typically involve skin-breaking, comparisons were made between the skin-breaking procedures of a group that had been ventilated at birth and a group who had not been ventilated. The results suggested that a greater number of skin-breaking procedures and parenting stress at the neonatal stage were related to more internalizing behaviors at the eight year follow-up assessment. Greater morphine exposure was associated with higher internalizing scores for those children in the ventilated group. The data from these studies highlight the importance of entering potentially confounding variables such as morphine and mechanical ventilation into the data analyses addressing the relationships between early invasive procedures and developmental outcomes.

In a smaller sample study (N = 19) by another group, morphine and neonatal invasive procedures were significantly associated with brain volume but not with neuropsychological functioning (Van den Bosch et al., 2015). In this study, gestational age, number of painful procedures and morphine exposure were correlated with brain volumes (Rs = 0.60–0.85), but no relations were noted

between these variables and neuropsychological function. The absence of these relationships in this study may relate to the study being underpowered (given the small sample size).

6. Interventions

Since painful responses to invasive procedures have been observed in preterm newborns, many pharmacological and non-pharmacological therapies have been researched. The most common pharmacological treatments applied during invasive procedures, e.g.heelsticks, injections, chest tube insertion and lumbar puncture, have been morphine and the stronger opioid, fentanyl, both of which have been questionably effective and have negative side effects. Non-pharmacological therapies have been noted to alleviate painful responses but have been used primarily to reduce immediate painful responses not to prevent long-term effects. These have included the orally administered therapies sucrose, glucose, milk, nonnutritive sucking and breastfeeding. Full-body therapies have included facilitated tucking, swaddling, kangaroo care and massage therapy.

6.1. Pharmacological interventions

In a comprehensive review of this literature, Anand and his colleague have addressed the positive and negative effects of the most common opioids that provide analgesia and sedation, those being morphine and fentanyl (Hall & Anand, 2014). The most frequent concerns expressed about the use of morphine are its potential for hypotension, the need for greater mechanical ventilation and the lesser tolerance for feedings. In a review of 13 randomized controlled trials, the preterm newborns experiencing morphine had less pain on the PIPP but required greater time to tolerate feedings (Bellu, de Waal, & Zanini, 2010). And, as compared to the group who did not receive morphine, there was a similar need for mechanical ventilation and similar neurodevelopmental outcomes at 5–6 years.

Studies on fentanyl, which is often used as an analgesic prior to the most invasive procedures, have yielded mixed results (Hall & Anand, 2014). In a study comparing fentanyl with facilitated tucking, lower pain scores and lower levels of cytokines were noted in the fentanyl group (Gitto et al., 2012). However, in a randomized controlled study, although fentanyl reduced acute pain based on the PIPP compared to a placebo group, no differences occurred between the fentanyl and placebo group on the prolonged pain (EDIN) scores (Ancora, Lago, Garetti et al., 2013). When fentanyl has been compared to morphine, the fentanyl group had greater opioid tolerance and withdrawal (Ancora et al., 2013). It also had less sedative or hypotensive effects and less effects on gastrointestinal motility than morphine. These authors as well as others have cautioned that these opioids may have deleterious effects and complications. Local anesthetics, sedatives and non–steroidal anti-inflammatory drugs have also been used with less concern about side effects, but they have not been as widely researched.

Others agree that the safety and side effects as well as long-term outcomes from these pharmacological agents are controversial (McPherson & Grunau, 2014). Many have not only suggested the need for further research on pharmacological therapies but also the need to identify alternative therapies. Ultimately, neonatal nurses' knowledge, perceptions and attitudes are critical factors in the practice of pharmacological and nonpharmacological therapies. In a survey on the perceptions of pain management by 237 American nurses and 106 Chinese nurses, knowledge deficits were related to the fact that preterm infants are more sensitive to pain and that they can experience long-term effects (Cong et al., 2014). Although most of the nurses reported regularly using pain assessments, fewer nurses thought that the scales they used were accurate or appropriate. Fewer Chinese nurses felt confident about using pain medications than American nurses (58% versus 83%) and more Chinese nurses than American nurses acknowledged the effectiveness of nonpharmacological interventions (78% versus 61%). Only half of the nurses in each country felt that pain was being well-managed on their units and less than half felt that the pain protocols they used were research-based. Nurses across this sample expressed concern that pain management was not effective because of lack of knowledge, lack of time, being fearful about side effects of pain medications and resistance to change.

6.2. Non-pharmacological therapies

As some have noted, non-pharmacological therapies for pain relief have been "under − appreciated, under–utilized and under–studied" (Ismail & Gandhi, 2011). Although some have suggested that complementary and alternative medicine studies have been methodologically flawed, others have viewed non-pharmacological therapies as "less dangerous and as effective as pharmacological therapy" (Hall, 2012). The non-pharmacological therapies that have been most frequently researched for pain relief during invasive procedures with preterm neonates include sucrose, glucose, milk, breastfeeding, tucking, swaddling, kangaroo care and massage therapy.

6.2.1. Sucrose and glucose

Sucrose has been one of the most effective pain relievers for preterm neonates for several procedures including heelsticks (Cignacco et al., 2012) and oral gastric tube insertions (Kristoffersen, Skogvoll, & Hafstrom, 2011). Research we conducted many years ago suggested that heart rate increased rapidly during heelsticks (Fernandez et al., 2003). However, after the heelsticks the heart rate of infants who received sucrose returned to baseline, whereas the heart rate remained elevated in infants who tasted water alone. During the heelsticks, the sucrose group cried and grimaced half as long as the infants in the water group. In addition, the EEG patterns of the infants who received water showed increased right frontal EEG (associated with withdrawal responses and negative emotions) whereas the EEG patterns in the sucrose group did not change. This randomized controlled trial was conducted in a

laboratory, making it easy to collect these measures unlike the collection of measures in neonatal intensive care units. Nonetheless, this research provided a model for the use of sucrose during invasive procedures experienced by preterm newborns.

In another double-blind, randomized controlled trial with preterm infants, the infants were randomly assigned to receive either sucrose or water for every painful procedure during the first week of life (Boyer, Johnston, Walker, Filion, & Sherrard, 2004). The authors hypothesized that the infants who received 24% sucrose for all painful procedures would be less stressed as measured by saliva cortisol and more physiologically stable based on heart rate variability. Saliva samples were collected before and 30 min after the painful procedures and heart rate was continuously monitored. Although there were no group differences on the cortisol response or the heart rate variability, the correlation between the heart rate variability and the number of sucrose doses was significant for the group who received the high doses of sucrose. This is one of the few repeated pain intervention protocols that unfortunately was not focused on cumulative effects of interventions for pain.

A *meta*-analysis on 38 studies has suggested that glucose has similar effects as sucrose in decreasing PIPP scores and crying times associated with the heelsticks (Bueno et al., 2013). In an even larger *meta*-analysis on 74 studies enrolling 7049 infants, there was moderate–quality evidence that sucrose in combination with non—nutritive sucking was more effective than sucrose alone (Stevens, Yamada, Ohlsson, Haliburton, & Shorkey 2016). However, these substances are controversial when used repeatedly as they are thought to interfere with breast-feeding (Holsti & Grunau, 2010). In addition, some null findings have been reported in the literature. For example, sucrose did not dampen the EEG response to pain in one study (Carbajal et al., 2008). And, cortisol levels and heart rate variability did not change following 24% sucrose for all painful procedures in the Boyer et al. (2004) study.

6.2.2. Non-nutritive sucking and breastfeeding

In a very early study we established the beneficial effects of nonnutritive sucking on both term and preterm neonates during heelsticks (Field & Goldson, 1984). In this study, behavioral state, heart rate and respiration were monitored during heelsticks in term and preterm neonates in intensive care units. The newborns who received pacifiers spent less time fussing and crying and their heart rate and respiration were more stable. Non-nutritive sucking may have attenuated crying and physiological arousal during invasive procedures because it is basically incompatible with crying. This became a model for many nonnutritive sucking studies showing the reduction in pain following invasive procedures.

The combined use of sucrose and nonnutritive sucking has become increasingly popular. A couple literature reviews suggest the synergistic effects of combining sucrose and nonnutritive sucking during painful procedures. In one of these reviews, studies on the combination of sucrose and nonnutritive sucking (the most commonly studied nonpharmacological therapies) were reviewed (Naughton, 2013). In another review, several non-pharmacological treatments were compared including swaddling, tucking, sweet solutions, nonnutritive sucking, breast-feeding, breast milk and music (Carbajal, Greteau, Arnaud, & Guedj, 2015). The results of this review suggested that the synergistic effect of sweet solutions and non-nutritive sucking had clear evidence to suggest its practice (Carbajal et al., 2015).

Human milk has been as effective as sucrose in relieving acute pain in preterm newborns (Ribeiro et al., 2013). However, this was a small pilot study (N = 14), suggesting that it may be underpowered. In addition, the infants were not randomly assigned to groups. In a breast-feeding study the breastfeeding was effective in reducing pain, although it was more effective when accompanied by skin − to − skin contact (Marin-Gabriel et al., 2013).

6.3. Facilitated tucking, swaddling and massage therapy

Facilitated tucking is the placing of a hand on the baby's hands or feet and positioning the infants to support them but to also let them control their own movements. For this technique the infant is placed in a flexed midline position while in a side-lying, supine or prone position. It has been successfully used for reducing pain during heelsticks (Hartley, Miller, & Gephart, 2015). In this recent review, facilitated tucking was noted to reduce painful expressions in preterm newborns. However, at least one study has shown that it is not as effective as oral sucrose for repeated painful procedures (Cignacco et al., 2012). In another study, 25 preterm newborns were randomly assigned to either oral sucrose, tucking, or a combination of the two interventions (Gerull et al., 2013). The preterm newborns received these interventions prior to five heelsticks within the first 14 days of life while heart rate, oxygenation and near infrared spectroscopy were monitored. The results revealed that the increase in heart rate was greater as was the oxygenation in the tucking group as compared to the other groups, suggesting that oral sucrose and oral sucrose plus tucking were more effective in reducing the reaction to pain than facilitated tucking alone. Once again this study focused on the immediate effects of the therapies rather than the cumulative effects.

A two-arm randomized controlled trial with repeated measures was conducted to assess the effects of swaddling on pain during heelsticks using the PIPP (Ho, Ho, Leung, So, & Chan, 2016). The mean changes in heart rate and oxygen saturation in the swaddled group were significantly less than those of the control group at several time points including immediately, two, four and six minutes after the heelsticks. In addition, the swaddled infants returned to baseline levels at two minutes whereas the control group did not reach that state until six minutes after the heelsticks.

Kangaroo care or the carrying the newborn under the parent's clothing for skin-to- skin contact has been notably effective in decreasing crying and pain scores during invasive procedures (Cong et al., 2012; Johnston et al., 2014). However, the data are mixed on whether kangaroo care provides sustained pain relief. In one randomized controlled trial, preterm newborns were randomly assigned to either an incubator group or a kangaroo care group and received four heelsticks (Gao et al., 2015). Group comparisons suggested that those infants who received kangaroo care had lower heart rate and shorter durations of crying and facial grimacing than the incubator group. In contrast, another group who randomly assigned preterm newborns to a kangaroo care group or a

standard care group showed no effects for sustained pain and stress relief (Mitchell et al., 2013). In this study, kangaroo care was provided for 5 to ten days with the expectation that there would be long-term effects on pain relief as measured by salivary cortisol levels. The pain scores and cortisol levels did not differ between the groups. These studies are not comparable in that the first study provided kangaroo care only during heelsticks (Gao et al., 2015), while the latter study provided two hours of kangaroo care per day but tested a more invasive suctioning procedure (Mitchell et al., 2013).

One of our earliest studies on massage therapy in the NICU established that massage therapy did not lower transcutaneous oxygen consumption levels whereas the heelstick procedure significantly lowered transcutaneous oxygen consumption, suggesting that massage was clinically safe as an intervention procedure (Morrow et al., 1990). Given that many massage therapy studies have been conducted in NICUs to enhance weight gain and shorten hospital stay, it is surprising that very few studies have been conducted on massage as an intervention for NICU painful procedures. In one study, 13 infants who received massage for 2-minutes prior to a heelstick showed decreased NIPS scores (Jain, Kumar, & McMillan, 2006). In a study by our group, moderate pressure massage (as opposed to light pressure massage) led to lower increases in heart rate, suggesting an attenuated pain response to surgical tape (Diego, Field, & Hernandez-Reif, 2009).

A potential underlying mechanism for the massage therapy lowering pain may be enhanced vagal activity and diminished cortisol. In a *meta*-analysis study chronic pain was associated with low vagal activity (Koenig, Falvay et al., 2016). In a large sample study (N = 647) chronic pain was negatively correlated with heart rate variability (a proxy measure for vagal activity) (Koenig, Loerbroks et al., 2016). The authors suggested that chronic pain and low vagal activity reflect dysfunction of the descendent inhibitory pathway, a pathway that is under developed in preterm neonates. We have argued elsewhere that stimulation of pressure receptors and the resulting increase in vagal activity and serotonin levels (the body's natural pain suppressor) is one potential underlying mechanism for pain relief (Field, 2016). A related mechanism we have discussed is based on substance P decreases (substance P causing pain) related to the decreased cortisol following massage therapy (Field et al., 2002).

6.4. Limitations of this literature

6.4.1. Limited replications

Although the data from these studies are compelling and have led to major advances in treating pain in intensive care preterm newborns, several methodological limitations limit the conclusiveness of the findings. First, most of the studies, both neonatal and longitudinal studies, have been conducted by two research groups led by Anand and Grunau. And, those investigators have many collaborators/students who have continued their research and publication of papers reviewing their own studies, often without critical commentary. To alleviate this potentially biasing problem, additional replications are needed by other research groups and in other countries. Replications by others are constrained, however, by limited pilot data, by being new to the field, by grant funding and by limited access to intensive care unit preterm newborns. As already mentioned, the assessment of pain interventions would involve several individuals simultaneously working with the newborn including the clinician, the intervention therapist and the assessor. And, the assessment training not only involves extensive practice in behavioral observations but also in physiological and biochemical measurement, as the assessments combine those measures.

6.4.2. Small samples

Some of the studies have small samples. This limits the ability to collect multi-variate data which are important as some individuals respond behaviorally and some show their pain response physiologically and some manifest their pain response both behaviorally and physiologically. Larger samples also need to be recruited so that the studies can be continued with longitudinal follow-ups which are critical for the assessment of outcomes. High attrition would be expected given early mortality/morbidity and the treatment of high risk births in regional medical centers that are often remotely located from parents' residence. Surprisingly, despite these concerns, sample size and attrition have not been major problems for most of the studies in this literature.

6.4.3. Randomization and blinding

The quality of the studies has sometimes been limited. Studies have been excluded from systematic reviews and meta-analyses because the methods haven't met randomization and blinding criteria or at least clarity of those methods Some repeated measures studies have lacked control groups or suitable control groups. Treatment as usual control group infants are not controlled for the attention factor and are usually known to parents and staff who might compensate for that lack of therapy attention, thus attenuating the expected treatment group effects. Waitlist control conditions are confounded by cohort effects with groups differing on the number of days in intensive care, the number of invasive procedures and developmental age. Attempts to provide an approximately equivalent control condition have sometimes resulted in negative change instead of no change in the control group. An example is our using light pressure massage as a control for moderate pressure massage (Diego et al., 2009).As already mentioned, the light pressure massage was aversive (elevated heart rate) much like a tickle stimulus. Once a treatment is notably effective, it cannot be denied to control groups for ethical reasons and would be denied by institutional review boards. Blinding in most of the nonpharmacological intervention studies was not possible in the way that pharmacological studies can effectively use placebo controls. Even to single blind interventions such as massage therapy would require some partitioning of the space to hide the intervention and then when it is provided by a parent or therapist, the intervention is known to them. For this reason, many systematic reviews and *meta*-analyses have excluded these non-blinded and single blind studies.

6.4.4. Variability on independent and dependent variables

No studies could be found on comparisons of invasive procedures on either behavioral and/or physiological measures. Yet they are typically combined as "number of invasive procedures" especially in longitudinal follow up studies. And, number of invasive procedures has often been the independent measure/predictor variable. This, of course, is highly variable not only on quantity but also on type of invasive procedure and its severity. Most of the studies have featured heelsticks as the invasive procedure which may be a more severe breaking of the skin than a tape removal procedure, but certainly less invasive than intubation. This qualitative difference in invasiveness has rarely been controlled or weighted especially in the longitudinal follow-up studies.

The dependent measures are most often pain assessments, one of the 50 pain assessments that have been developed, although most often the PIPP. These can be grouped for meta-analyses on total scores, but as has been mentioned, the behavioral scale is often inconsistent with the physiological measures and there has been inconsistency within the behavioral scale items and within the group of physiological measures. The variability on the physiological measure of choice has limited the numbers of studies included in meta-analyses and the conclusions that can be made. For example, in one recent meta-analysis, conclusions could not be reached on vagal activity associated with pain because only 5 vagal activity studies could be found in the literature on preterm newborn pain and each of those had derived vagal activity in different ways. Similarly, neurobehavioral data were only found in 7 studies, making any conclusions only tenuous. More often meta-analyses have included small numbers of studies simply because their authors haven't been able to retrieve standard deviations and attrition numbers from old databases.

Potentially confounding variables or covariates are rarely mentioned and not controlled in several studies. It would be expected that at least those variables that have been directly compared for pain responses, for example, gender would be entered as covariates in data analyses. Others would be age, days in intensive care, contagious illnesses, medications, number of research protocols (which are often considered interventions) and number of parent visits among others.

6.4.5. Focus on immediate intervention effects as opposed to preventive interventions

This is perhaps the most serious problem of the preterm newborn pain intervention literature. Almost all of the studies have focused on pharmacological and non-pharmacological interventions to reduce immediate pain during the invasive procedure. The relationships between numbers of invasive procedures and severe long-term outcomes such as cortical thinning and associated inferior IQ scores highlight the importance of assessing long-term interventions to prevent or at least reduce pain during repeated invasive procedures. Only a few studies have assessed repeated interventions but for immediate responses not for cumulative effects on lessening the pain and the negative outcomes for those preterm newborns who experienced repeated painful procedures.

6.4.6. Summary

The most immediate effects reported for repeated painful procedures in preterm newborns include increased heart rate, oxidative stress and cortisol as well as decreased vagal activity, lower body weight and head circumference, thinner gray matter and motor and cognitive developmental delays. School-age outcomes include less cortical thickness, lower vagal activity, delayed visual − perceptual development, lower IQs and internalizing behavior. Pharmacological interventions and their side effects and non-pharmacological therapies are reviewed including sucrose, milk and nonnutritive sucking. Full-body interventions have included tucking, swaddling, kangaroo care and massage therapy. Although these have been effective for alleviating immediate pain during invasive procedures, research is lacking on the routine use of these therapies for reducing long-term pain effects. Further, additional randomized controlled replication studies are needed.

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