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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