REVIEWS

A systematic review of the effects of repeated painful procedures in infants: Is there a potential to mitigate future pain responsivity?

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Abstract

Background: Multiple lines of evidence suggest repeated painful procedures early in life may permanently disrupt the developing central nervous system. Painful diagnostic, medical, and minor surgical procedures performed in the neonatal intensive care unit such as venipunctures, heel lances, immunizations, and central venous catheter insertion are a significant portion of painful events experienced by infants. The objective of this systematic review is to synthesize findings from published clinical trials evaluating the effect of repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system and their influence on future pain responsivity.

Methodology/Principal Findings: A systematic review of peer-refereed clinical trials was conducted. Clinical trials examining the effect of repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system and their influence on future pain responsivity were identified from electronic databases PUBMED, MEDLINE and CINAHL. Application of inclusion/exclusion criteria and limitations identified five clinical trials for critical reviewed. Findings suggest that repetitive pain experienced during a critical window of neuro-development alters the structure and function of an infant's nervous system, influences subsequent pain responses through childhood and may contribute to the development of chronic pain.

Conclusions: Current research asserts that inadequate relief of infant pain and distress during tissue-damaging procedures may permanently decrease an individual's pain tolerance, and increase pain responses later in life.

Key words

Infant/newborn, Pain/neonatal pain, Neuro development, Nervous system, Chronic pain, Cortex, Review

1 Introduction

Experimental models assert that inadequate relief of pain and distress during infant tissue-damaging procedures may permanently decrease an individual's pain tolerance, increase pain responses later in life and contribute to the development of chronic pain. With approximately100 million American adults burdened with chronic pain [1], the hypothesis that the evolution from acute to chronic pain occurs after the initial exposure to undermanaged pain remodels nociceptive pathways [2], is especially significant for the developing nervous systems of neonates [3]. This review will examine clinical

trials conducted in the past 10 years that explore the effects of repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system and their influence on future pain responsivity.

1.1 Epidemiology of neonatal pain

In a recent multicenter study, infants in tertiary neonatal intensive care units (NICU) experienced 60,969 first-attempt procedures over a four month period; 42,413 procedures (69.6%) were identified as painful, 18,556 (30.4%) were considered stressful [4]. In addition to the first attempt procedures, there were an additional 11,546 supplemental attempts; 10,366 (89.8%) were painful procedures and 1180 (10.2%) were stressful procedures. The median number of all procedures during the study period for each neonate was 115 (range, 4-613), 16 procedures per day of hospitalization (range, 0-62). Each neonate was exposed to a median of 75 painful procedures during the study period (range, 3-364). They had at least 10 painful procedures per day of hospitalization (range, 0-51). Of the 42,413 painful procedures, 79.2% occurred without specific analgesia. If analgesic interventions were utilized, 2.1% of the interventions were pharmacological only; 18.2% of the interventions were behavioral or environmental only, 20.8% of the interventions were pharmacological, behavior and environmental, or both; 34.2% of the procedures were performed with concurrent analgesic or anesthetic infusions for other reasons.

This data supports earlier single center studies that reported the frequency of painful procedures in neonates. Barker and Rutter [5] reported a mean of 60 procedures for the 54 patients in their study. Porter and Anand [6] observed 144 patients and documented 7,672 procedures performed on that cohort. In a Dutch NICU, Simons [7] documented that 151 infants were exposed to 19,674 procedures, a mean of 14 (range 0 – 53) procedures per day. In all three studies the investigators report analgesic therapy was rarely applied before invasive procedures.

1.2 Physiology of infant pain, unique structures and processes

Independent of age, five processes are required for noxious stimuli to be perceived as pain. First, receptors specific to the noxious stimuli transduce the noxious stimuli into electrical activity at the peripheral terminals of first order thinly myelinated Aδ and unmyelinated C fiber neurons. Second, an action potential is generated. Third, the action potential is transmitted to the central nervous system (CNS). Fourth, second order neurons (found in the CNS) are activated by the inflammatory mediators released at the site of tissue damage and transmit the signal to the thalamus. Fifth, third order neurons within the cerebral cortex perceive the nociceptive signal as pain. Each step is mediated by a distinct set of receptor proteins [8].

The pain pathway, transduction, transmission and perception of noxious stimuli and the cortical, subcortical anatomic and endorphin substrates necessary for pain transmission are well developed as early as 23 weeks gestation [8, 9]. However, in contrast to adults, a preterm infant's afferent pain pathway has a higher density of high threshold Aδ and low threshold Aβ mechanoreceptors that respond with lower firing frequency [10] and the neurotransmitters in the inhibitory arm, found within the descending pathway, are immature and will not develop until 4 – 8 weeks later in postnatal life [11, 12]. Because the afferent excitatory pain neurotransmitters, which are plentiful at birth, are not balanced by descending inhibitory neurotransmitters, preterm infants are exposed to greater pain sensitivity and intensity than older infants and adults [13, 15].

1.3 Future pain responsivity: Evolution for acute to persistent pain

Encoded within the genome, the continuous interaction between prescribed genetic sequences and environmental interactions result in neuromaturation of the central nervous system (CNS). Successive gene regulation propels maturation forward and allows cells to react quickly to changes in their environment [16]. This environmental transcription influences cell division, differentiation, function, connection and migration [17]. It is hypothesized that these epigenetic interactions are the origins of chronic pain [2, 18].

The evolution from acute to persistent or chronic pain transpires through neuroplastic adaptations in the peripheral and central nervous system. The transition occurs in separate and distinct physiological and histological steps. Alterations are initiated by noxious stimuli such as damaged tissue, or dysfunctions of the peripheral and central nervous system [19]. Pain

inflammatory mediators that are released when tissue is damaged (e.g. substance P, prostaglandin and excitatory amino acids) activate primary afferent terminals in the periphery. Persistent acute pain transmits the noxious impulses through afferent pain pathways to the spinal cord. This continuous input of noxious stimuli eventually causes the death of descending inhibitory interneurons that are responsible for modulating the transmission of afferent nerves [20]. Sympathetic sprouting (growth) of dorsal root ganglion expands into the area vacated by the death of the descending inhibitory neurons. This expansion increases the receptive area and increases the sensitivity of nociceptive neuronal synapses. The sensitized afferent pain pathway is more excited, reacts more intensely to stimuli, and has more connections to second-order neurons within the dorsal horn of the spinal cord [2]. These activity dependent microscopic phenotypic changes seen in the dorsal horn neurons and other CNS structures offer a partial explanation why pain persists beyond the acute phase of the original injury.

The timing of the injury is significant. The unique anatomical structures and physiological processes of preterm and term infants predispose them to greater alterations in their nervous system. Beland and Fitzgerald [21] found carrageenan induced peripheral inflammation at birth alters the proportions and post-natal regulation of calcitonin gene related peptide (CGRP) and isolectin B4 +ve (IB4) cell profiles in neonatal dorsal root ganglia. In adult rats, carrageenan inflammation affected only CGRP cells. This data supports an earlier preclinical trial, where neonatal rats exposed to repetitive pain gained more weight and demonstrated decreased pain latencies. As adults, the neonatal rats exposed to the noxious stimuli displayed defensive withdrawal behavior and an increased preference for alcohol compared to age matched controls [22].

Earlier clinical studies and literature reviews emphasize the importance of managing pain and stress in infants. Findings from cohort and cross sectional studies explain how repeated painful procedures are associated with enhanced perceptual sensitization [23], blunting of the hypothalamic-pituitary-adrenal (HPA) axis response [24], greater distress during subsequent surgery requiring higher fentanyl dosing [25], lower thresholds for withdrawal responses that persist for at least the first year of life [26], and lower cognitive and motor development at 8 and 18 months [27]. Moreover, there is an association between greater neonatal procedural pain and supraspinal alterations. In preterm infants there are increased fluctuations in intracranial pressure leading to early intraventricular hemorrhage [12], heightened plasticity of the neonatal brain [12], significant activation of brain regions not activated by controls [28], and a reduced white and subcortical gray matter [29].

Evidence from systematic reviews on the long-term effects of undermanaged procedural pain in neonates recommends managing procedural pain from birth. One systematic review explored the development of nociceptive circuits and reported that early tissue injury may contribute to hyperalgesia, allodynia, and prolonged alterations in somatosensory function persisting into adulthood [14]. The data suggests that providing analgesia to neonates from the first week of life encourages positive long-term developmental effects [12, 30-32].

1.4 Purpose

If the origins of chronic pain lie in the nervous system itself, then preventing the subtle neural changes and increased pain sensitivity caused by undermanaged neonatal pain is a resolute goal for premature infants. The purpose of this systematic review is to synthesize findings from published clinical trials evaluating the effect of repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system and their influence on future pain responsivity. This review will answer the following research question: Among preterm and full term infants, does repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system influence future pain responsivity?

2 Methods

2.1 Ethics

This is a systematic review of clinical trials, ethical approval was not required.

2.2 Eligibility criteria

A systematic review was conducted to identify current peer refereed clinical trials exploring the long-term effects of repeated painful procedures in preterm and term infants and their influence on future pain responsivity. English language and articles published within the past 10 years restrictions were imposed.

Types of populations: Premature infants, full term infants, and children were included and considered for analysis. Preterm infants are defined as infants born before 37 completed weeks gestation. Full term infants are defined as infants born at or above 37 weeks to 42 completed weeks gestation [33].

Types of intervention: Clinical trials that explored the long-term effects of repeated painful procedures were eligible for inclusion in this review.

Types of outcome measures: Primary outcome measure: Anatomical and physiologic alterations to the peripheral and central nervous system such as altered response to pain, altered judgement concerning painful events, attention deficits, learning disorders, cognitive deficits, neurological deficits, cerebral palsy, poor motor performance, changes in behavioral and hormonal responses to stress, somatic complaints, and chronic pain.

Eligibility Criteria

- English Language
- Original research
- Peer refereed publication
- Clinical trial
- Study sample: preterm/full term human infants
- Setting: Neonatal intensive care units, term nurseries, Children's hospital,
- Intervention: Procedural pain
- Published within the past 10 years

Exclusion Criteria

- Journal articles without original data
- Unpublished data or manuscripts

2.3 Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles cited. The search was applied to peer refereed clinical trials published in PubMed, Medline, and Cumulative Index of Nursing and Allied Health (CINAHL) between January 1, 2002-Present. Although Medline is the largest component of PubMed, the two databases use different search engines to identify articles. Utilizing PubMed and Medline databases provides an opportunity to identify additional citations in PubMed that are not indexed in Medline [34]. The last search was conducted December 7, 2012.

2.4 Search strategy

We used the following key words and MESH headings to search keyword and title fields in the databases: infant/newborn, pain/neonatal pain, neuro*development, nervous system, chronic pain, cortex, review.

2.5 Study selection

Eligibility of studies was independently assessed in an unblinded manner by 3 reviewers. Disagreement between reviewers was resolved by consensus.

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2.6 Data collection process

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 Yale University Evidence-based Practice Pyramid and criteria [35]. Levels of evidence range from 1 (highest level of evidence) to 7 (lowest level of evidence), and are assigned based on study design and methodological quality. When evidence ratings differed, consensus was reached to assign a final score. Each reviewer independently extracted the data from the included studies. All authors reviewed the extracted data. Disagreements were resolved by discussion and consensus.

2.7 Data items

Information extracted from each included trial: (1) characteristics of trial participants, (2) type of painful intervention and (3) outcome.

2.8 Risk of bias individual studies

To assess the validity of eligible clinical trials, all reviewers worked independently to determine the adequacy of sample size, study design, and if the trial was a randomized controlled trial, randomization, allocation and concealment if the trial was a randomized controlled trial. To assess the variability of study outcomes, we hypothesized that primary outcomes may differ depending on the methodological design and quality of eligible studies.

2.9 Summary measures

Identification of alterations in behavior and the nervous system of preterm and term infants that persist into childhood was the primary measure of adverse long-term effects of repeated painful procedures.

2.10 Data analysis

Data were synthesized to indentify and describe the adverse long-term effects of repeated painful procedures.

3 Results

3.1 Study selection

The literature review recognized 888 articles. Articles judged not relevant: duplicate manuscripts (19), English language restriction (96), preclinical trials (268), articles over 10 years old (222), study design other than clinical trial (214), full text limitation (30), different study outcome (26), clinical practice guidelines (4), commentary (3) and editorials (2) were excluded from analysis. The remaining clinical trials examining the effects of repeated pain procedures in infants (n=4) were critically reviewed. An additional study that met the inclusion criteria was identified by checking the references of located relevant papers and searching for studies that cited the inclusion study. No unpublished data or relevant studies were obtained. Data from the 5 clinical trials were synthesized to provide an overall description of the effect of repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system and their influence on future pain responsivity. Figure 1 represents the study selection process and identifies the number of studies included in the analysis.

3.2 Study characteristics

All five studies selected for analysis were clinical trials published in English. Four studies recruited full term and preterm infants [27, 36-38]. One study recruited children 7 to 11 years of age [39]. The older children were recruited into the study to determine if the numerous painful interventions, experienced soon after birth, affected perceived pain and heart rate response later in life. The study was accepted for inclusion in this review because the inclusion criteria for study participants was their birth status and frequency of exposure to painful interventions in the neonatal intensive care unit

(i.e., term-born, born preterm and exposed to numerous painful interventions, or born preterm and exposed to minimal painful interventions) and the study's outcome corresponded with the outcome measures of this review.

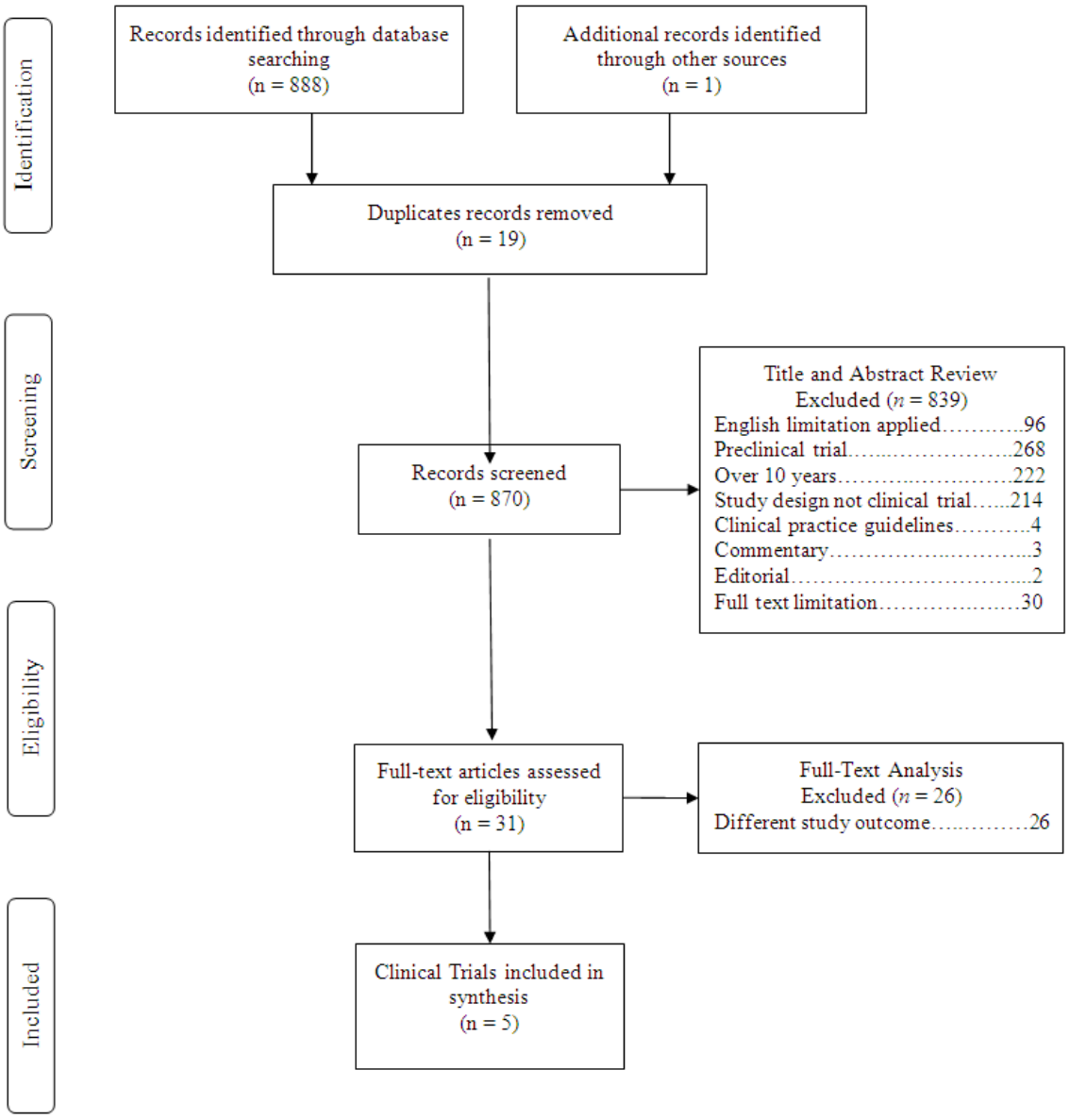

Figure 1. Flow Diagram: Selection Process for Systematic Review

Only two studies provided a rationale for sample size. One study preformed a power analysis [38], another study determined sample size based on requirements for multiple regression analysis [40]. Table 1 describes the sample characteristics for the included studies.

3.3 Intervention

3.3.1 Noxious stimuli

There was considerable heterogenicity in noxious stimuli. The majority of noxious stimuli were painful diagnostic and treatment procedures that infants are exposed to during standard care in the NICU. Standard procedures included newborn screening [36] (sample collection method not disclosed), blood sampling with 23 gauge standard needle [36],

AquaMEPHYTON injection [38], venipuncture [38] (needle gauge not documented), heel lance [37, 40], and a fixed series of nursing procedures (diaper change, measuring abdominal girth and mouth care) [40]. No infant study preformed painful interventions solely for the purpose of the study. For the older children, 7 to 11 years old, the noxious stimuli were thermal pain [39] and a cold pressor tank [39]. Thermal pain and cold pressor tank interventions were conducted for the purpose of the study.

Table 1. Summary of Sample Characteristics

Author (Year)	Setting	Number of Participants	Age Range	Inclusion Criteria
Ozawa, M. et al. (2011)	NICU	80	26 to 41 weeks gestational age	Full term infants: no painful skin breaking procedures Full term infants: exposure to painful skin breaking procedures Preterm infants: exposure to painful skin breaking procedures
Slater, R. et al. (2010)	NICU	15	24 to 40 weeks postmenstrual age	Term infants: < 7 postnatal days, no previous surgery, normal EEG Preterm infants: PMA = to term infants Diverse surgery, EEG, head ultrasound and brain MRI results
Taddio, A. et al. (2009)	NICU	240	≥ 36 weeks gestational age	Normal newborns and infants of diabetic mothers ≥ 36 weeks gestation
Goffaux, P. et al. (2008)	Not Reported	26	7 to 11 years	No neurological, cardiac or respiratory problems at time of testing. No surgery at birth. No chronic pain, or analgesia prior to testing
Grunau, R. et al. (2005)	NICU	87	22 to 32 weeks postconceptual age	Born ≤ 32 weeks completed gestational age

Note. Abbreviations: NICU, Neonatal Intensive Care Unit; EEG, Electroencephalography; PMA, Postmenstrual Age; MRI, Magnetic Resonance Imaging

3.3.2 Timing of intervention

To assess the long-term effects of undermanaged pain in infants, data for the included studies was collected at either 26 hours [38], 4 days [36], 7 days [40], 25 - 41 postnatal days [37] or 7 to 11 years [39] after initial insults. In those studies interested in cerebral alterations, the data were collected within 4-6 days of full term birth or when preterm infants reached their due date (range 25 – postnatal days) [36, 37]. Evidence that early CNS alterations persist into childhood and adulthood [42] may be the rationale for documenting cerebral data within days following the insult. Investigators interested in alterations in infant pain response (sensitivity, and physiological responses) collected data at either 26 hours [38] or 7 days [40] after the insult; whereas data exploring the long-term adverse effects of undermanaged pain that persist into childhood was collected 7 – 11 years after initial insult [39].

3.3 Primary outcome

Studies identifying the long-term effects of repeated painful procedures in neonates do not always provide clarity around the phenomenon of pain. Only one study defined pain conceptually in a broader context [40]. Three studies provided a scientific rationale for linking pain to stress, the primary outcome of interest [36, 38, 40]. From reported outcomes, one can deduce that investigators considered electroencephalic activity (EEG) [37], noninvasive near infrared spectroscopy (NIRS) [36], heart rate [39], heart rate variability [40], cortisol [40] and crying [38] to also be valid indicators of pain in infants. All studies but one [37] used self-report [39] or a multidimensional valid and reliable infant pain scale [36, 38, 40] which represents a more comprehensive conceptualization of pain. Although research on EEG, NIRS, heart rate, heart rate variability, cortisol, and crying may provide some indication of infant stress and distress, alone, they cannot confirm or deny the presence of infant pain [43]. It is appropriate that the studies correlated their findings with a multivariable composite pain score that included physiological [36, 38], behavioral [36, 38, 40], and contextual indices [36, 38]. Sex was not a significant risk factor for the development of persistent pain. Table 2 summarizes the relevant data from the clinical trials from 2002 to 2012 included in the analysis.

Table 2. Summary of Clinical Trials exploring the long-term effects of repeated painful procedures in preterm infants 2002-2012

Author (Year)	Purpose	Sample	Intervention	Outcomes	Quality of Evidence
Ozawa, M., Kanda, K., Hirata, M., Kusakawa, I., & Suzuki, C. (2011)	To determine the correlation between repeated skin puncture and prefrontal cortical pain responses	Exposure group 20 full-term and 30 pre-term infants Control group 30 full-term infants	Clinically required blood sampling (newborn screening test and blood sampling for clinical diagnosis)	Repeated painful events disrupt prefrontal cortical activity resulting in variability between somatosensory and prefrontal areas in infants. Preterm infants' responses to pain correlated with physiological responses that reflected stress rather than pain. Repeated painful procedures may alter cortical pain processing in preterm infants.	Level 4-
Slater, R. Fabrizi, L. Worley, A. Meek, J. Boyd, S. Fitzgerald, M., (2010)	To assess whether noxious and non-noxious stimulation is processed differently among infants: preterm infants who have reached their due date and healthy full term controls	15 infants; 8 term infants, born 37–40 weeks and 7 preterm infants born 24–32 weeks	Clinically-essential heel lance	Premature infants experiencing at least 40 days in the NICU have increased brain neuronal responses to noxious stimuli compared to healthy newborns at the same postmenstrual age. Evoked potentials generated by noxious heel lance stimulation are dependent on age at birth. Noxious-evoked potentials represent a functional change in the brain processing which is significantly larger in preterm infants.	Level 4
Taddio, A., Shah, V., Atenafu, E., & Katz, J. (2009)	To determine the effects of repeated painful needle procedures and sucrose analgesia on the development of remote hyperalgesia in newborn infants	120 healthy newborn and 120 infants of diabetic mothers randomized to sucrose analgesia or placebo prior to all needle procedures. Divided into two exposure groups according to number of needle procedures (high >5 or low <4)	All needle procedures in the first two days after birth	Infants in the high exposure group had a higher pain response during a subsequent venipuncture as assessed by Premature Infant Pain Profile and Visual Analog Scale. PIPP scores did not differ during diaper change, suggesting a nociceptive specific mechanism for remote hyperalgesia to venipuncture. Sucrose analgesia reduced PIPP, VAS, and cry duration scores during venipuncture, but did not prevent remote hyperalgesia in newborns.	Level 4+
Goffaux, P. Lafrenaye, S. Morin, M. Patural, H. Demers, G. Marchand, S., (2008)	To determine if numerous painful interventions, experienced soon after birth, affect counterirritation-induced analgesia later in life	26 children ages 7 to 11years Groups: (1) born at term, (2) born preterm numerous painful interventions, (3) born preterm few painful interventions	Thermal (heat) stimulations Cold pressor tank	Preterm children and term-born children had comparable pain thresholds. Exposure to conditioning cold stimulation significantly increased heart rate and significantly decreased the thermal pain sensitivity of term-born and preterm children who were only exposed to a few painful interventions at birth. No changes in heart rate and pain sensitivity in response to conditioning cold stimulation was observed in preterm children that had been exposed to numerous painful procedures during the neonatal period.	Level 4
Grunau, R. V. et al. (2005)	To examine relationships between prior neonatal pain exposure (number of skin breaking procedures), and subsequent stress and pain reactivity in preterm infants in the NICU	87 preterm infants (47 male and 40 female) born at 32 completed weeks gestational age	Fixed series of nursing procedures Blood collection	Infants born at <28 weeks gestational age: higher cumulative neonatal procedural pain exposure was related to lower cortisol response to stress and to lower facial reactivity to pain, at 32 weeks PCA, independent of early illness severity and morphine exposure since birth. Repeated neonatal procedural pain exposure among neurodevelopmentally immature preterm infants was associated with down-regulation of the hypothalamic–pituitary–adrenal axis, which was not counteracted with morphine.	Level 4 +

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3.4 Risk of bias within studies

All studies had at least one marker that put the study at potential risk for bias. Table 3 summarizes the potential risk of bias in the included studies.

Table 3. Potential risk bias of individual studies included in analysis

Author (Year)	Randomized Clinical Trial	Concealment of Randomization	Knowledge of allocation intervention prevented	Incomplete outcome data addressed	Problems that could put study at high risk of bias
Ozawa, M. et al. (2011)	No	No	No	Not addressed	Effects of acute prolonged pain were not assessed Inconsistent pain treatment in study institution Large preterm postnatal age range
Slater, R. et al. (2010)	No	No	No	Not addressed	Differences in evoked activity between premature and term infants may be associated with local sensitization of peripheral nociceptors in the heel
Taddio, A. et al. (2009)	Yes	Yes	Yes	Yes	Hyperalgesia may be due to underlying differences in infant prenatal environment
Goffaux, P. et al. (2008)	No	No	No	Not addressed	Variability in findings may be associated with undocumented analgesic use in the NICU
Grunau, R. et al. (2005)	Yes	No	No	Yes	Total skin breaking procedures are influenced by pain and cumulative exposure to stress since birth Did not control for different types of procedures – procedures may vary in intensity Did not separate biological immaturity from prior pain/stress exposure

3.5 Synthesis of results

Because the study designs, participants, interventions and reported outcomes varied significantly, we focused on describing the samples, the study results, and limitations rather than a quantitative analysis. Pain data were available for 4 trials reporting data for 433 patients [36, 38-40]. The data support earlier studies that report that infants exposed to cumulative early procedural pain demonstrate higher sensitivity and lower pain thresholds compared to healthy full term controls. These alterations persist into childhood and may place preterm infants at greater risk for developing chronic pain conditions. There were no significant adverse events or deaths reported.

There was heterogenicity in the studies. Retrospective exploration of the heterogenicity indentified one study that differed from the others [37]. The study examined only EEG recordings for 15 term and preterm infants. Pain data was not collected. However, findings suggest that the evoked potentials generated by noxious heel lance demonstrate infants can differentiate between noxious and innoxious stimuli. The investigators go on to propose their data support earlier studies that demonstrate (1) early exposure to noxious stimuli alters the infant's ability to attend to noxious input and (2) changes the infant perception of the stimulus as a result of excessive early activation of afferent nociceptive pathways.

4 Discussion

Repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system influence future pain responsivity in infants and children. Undermanaged procedural pain and distress has two detrimental effects on infants [44]. First, experiencing painful procedures without analgesia exposes infants to unnecessary pain and suffering. Second, newborns exposed to early repeated painful procedures may become sensitized to pain that can persist into childhood and possibly over a lifetime [12, 45]. This review demonstrates that the frequent undermanaged pain preterm infants experience during this critical window of neurodevelopment alters the structure and function of their nervous system [46], influences subsequent pain responses through childhood [37, 47, 48] and may contribute to the development of chronic pain [49].

Preclinical randomized controlled trials can provide valuable data for guiding clinical practice decisions for the management of infant pain. Recent studies provide evidence that repetitive painful events accentuate neuronal excitement and cell death in developmentally regulated cortical and subcortical areas [50], early life surgery predisposes individuals to hyperalgesic responses to suprathreshold painful stimuli [51], and neonatal peripheral inflammation influences subsequent CNS development [27]. While the data from these well designed randomized controlled trials contribute to our growing knowledge of pain, the extent to which these animal studies inform clinicians should be limited. Although the developmental trajectory of a neonatal rat closely resembles that of a human preterm infant, human behavior is far more complex.

Cohort studies involving human infants may be a useful consideration for the clinician. Two retrospective cohort studies found that both preterm and term children with NICU experience displayed greater sensitization to tonic heat [23, 28]. When exposed to tonic heat, preterm children exhibited significant activation in brain regions not activated in controls. Moreover, those preterm infants that received analgesia exhibited a markedly smaller loss of brain matter than controls [28]. While limited by a small sample size and highly selective criteria, the findings are consistent with animal studies. Findings from a cross-sectional follow-up study of 164 infants reported that within the first three months of life, even with adequate anesthesia and analgesia, infants who experienced earlier surgery will respond with greater distress during subsequent surgeries compared to infants undergoing surgery for the first time [25].

Emerging evidence on the neurological changes associated with persistent pain is not limited to infants. Research with adult post surgical patients found that even brief experiences of moderate-to-severe acute pain (such as a single surgical event) can lead to a reorganization of neurons [18]. In adults burdened with chronic back pain, research findings imply that chronic back pain is accompanied by specific anatomical and functional brain activity. The persistent afferent noxious impulse to specific areas of the brain results in atrophy of that area of the brain [52, 53].

Overall, the evidence identifying the long-term effects of untreated neonatal pain in the neonatal intensive care unit is effective in summarizing the increased sensitivity of pain experienced by neonates and describing the effects of stress on the brain structures that are associated with pain processing. However, the long-term behavioral and pain processing effects on neonates are inconsistent, making it difficult to make evidence-based clinical decisions to guide practice. Stronger evidence such as randomized controlled trials of preterm, ex-preterm, term and healthy controls are necessary to develop high quality systematic reviews and meta-analysis evaluating the effects repeated painful procedures on the developing peripheral and central nervous system of this vulnerable population.

5 Limitations

The review reported here combines data from clinical trials in order to evaluate the effect of repeated painful procedures experienced during the plasticity of the developing peripheral and central nervous system and their influence on future pain responsivity. Systematic reviews of strong, high level evidence such as peer-refereed clinical trials and randomized controlled trials are crucial to the development of evidence-based clinical practice guidelines in nursing [54]. Rigorous peer-review of manuscripts prior to publication prevents the dissemination of irrelevant findings, unwarranted claims, unacceptable interpretations, and personal views. To ensure high quality strong evidence, only clinical trials and randomized controlled clinical trials that had undergone a rigorous peer-review prior to publication were examined for this review. Publication bias may account for some of the positive results found in the published literature. In addition, there was significant heterogenicity of noxious stimuli utilized in the reviewed studies. Infant response and adaptability are influenced by the varying pain intensity of different procedures. The variable intensities of pain originating from the different procedures is an impediment to discriminating infant pain response from infant stress or infant distress [41] and makes it difficult to draw definitive conclusions.

We recommend the findings from this systematic review be considered cautiously because of the heterogenicity of noxious stimuli, the small number of published clinical trials, and even smaller number of randomized controlled trials conducted with preterm and term infants. Although the quality of clinical trials was generally satisfactory, all studies had at least one marker that put the study at potential risk for bias. Further randomized clinical trials with human infants are required to establish causality and identify the significant adverse outcomes of persistent undermanaged pain in this at risk population.

6 Implications for education, practice, research

It is incumbent for clinicians to search the literature for the best available evidence to educate and guide their clinical practice. However, before there can be strong evidence to guide practice there must be an understanding of the complex intricate relationships between the corticosteroids, infant neuromaturation and persistent pain [55]. This knowledge is crucial for moving clinical practice from symptom management to multimodal mechanism specific pharmacologic and behavioral therapy. When multimodal therapy is introduced, nociceptive pathways are utilized at the same time, analgesic effect can be reached at a lower dose, and side effect profiles are lower than that of an individual medication's therapy [56].

There are challenges associated with neonatal pain research. However, with the increasing evidence to support the association between undermanaged acute pain and the development of chronic pain, rigorous, well-designed randomized controlled trials will emerge to establish strong evidence to guide clinical practice. A research agenda to defining critical issues associated with sucrose analgesia is proposed in Table 4.

Table 4. Research Agenda for Evaluating Effects Repeated Painful Procedures in Neonates

Outcomes Measure
Genetic
Is there a genetic association guiding the evolution from acute to chronic pain?
Does neonatal pain response differ for male and female infants?
Behavioral
Are the observed differences across altered pain response studies due to the stress of preterm birth or to the multiple invasive and painful procedures that accompany it?
What is the association between prenatal and postnatal factors and the neurodevelopment of preterm infant pain responsivity?
Anatomical/Physiological
Is there a clear delineation between noxious stimuli and stress in the neonatal brain?
What is the distinction between long-term cerebral changes associated with untreated pain and structural abnormalities related to the status of ex-preterm?
Treatment Modalities
What is the safety, efficacy, dosage and appropriate timing of opioid analgesics in different situations?
What is the therapeutic and long-term benefit of multimodal therapy in neonates?

7 Conclusion

The public health and economic importance of preventing or ameliorating the subtle neural changes and increased pain sensitivity caused by undermanaged neonatal pain cannot be overestimated [12]. Inadequately treated pain occurring during a critical window of increased plasticity of the developing brain may affect neuronal and synaptic organization [57] and contribute to the development of chronic pain. Improvement of neurobehavioral and psychological outcomes is an important goal for infants receiving painful procedures [42].

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