

Prevention and management of pain and stress in the neonate

Denise Harrison^{1,2}

Mariana Bueno³

Jessica Reszel²

¹School of Nursing, University of Ottawa, Ottawa, ON, Canada;

²Children's Hospital of Eastern Ontario and Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada; ³Department of Maternal Child and Psychiatric Nursing, School of Nursing, University of São Paulo, São Paulo, Brazil

Abstract: Neonates have blood work for newborn screening in their first days of life, and preterm and sick hospitalized infants often require repeated invasive needle-related procedures over the duration of their hospitalization. Reducing newborn infants' pain during such painful procedures is important and may reduce the risk of negative sequela of poorly treated procedural pain. High-quality synthesized evidence demonstrates analgesic effects of three pain management strategies: breastfeeding; skin-to-skin care, also referred to as kangaroo care; and small amounts of sweet solutions. These strategies are simple to use, easily accessible, and extremely cost-effective. Published neonatal and infant pain guidelines include recommendations to use these strategies prior to and during painful procedures. Yet, despite the robust evidence and pain management recommendations in guidelines and national and international organizations, knowledge has not been translated into consistent normalized care in diverse maternal newborn, neonatal, and pediatric settings where painful procedures for infants take place. There may be knowledge gaps or barriers impeding consistent use of effective pain management for newborn infants. This paper will present a brief review of methods used to assess neonatal pain, followed by a summary of the evidence supporting breastfeeding, skin-to-skin care, and sweet solutions for procedural pain reduction with a discussion about barriers and facilitators to using these strategies in the clinical setting. Finally, a review of recommendations included in current neonatal pain guidelines will be presented.

Keywords: infant, pain management, breastfeeding, skin-to-skin care, sucrose

Introduction

Almost all neonates have blood work for newborn screening in their first days of life, and preterm or sick hospitalized infants may require repeated invasive needle-related procedures for medical monitoring over the course of their hospitalization.¹⁻⁴ The publication of an increasing number of studies in recent years linking repeated neonatal pain exposure with poor neurological outcomes is concerning,⁵⁻⁹ and highlights the urgent need for health care professionals and parents of healthy, preterm, and sick neonates, to reduce pain exposure and to advocate for consistent use of effective pain management strategies.

The encouraging news is that health care providers (HCPs) now have well-validated means of assessing pain¹⁰ and simple, feasible, and effective ways to reduce pain during needle-related painful procedures. Breastfeeding (BF),¹¹ skin-to-skin care (SSC), also referred to as kangaroo mother care,¹² and sweet solutions; either sucrose¹³ or glucose,¹⁴ reduce pain during commonly performed painful procedures compared to no treatment, water, breast milk, or positioning, swaddling, holding, or cuddling.

Correspondence: Denise Harrison
Children's Hospital of Eastern Ontario,
401 Smyth Road, Ottawa, ON, Canada,
K1H 8L1
Tel +1 613 737 7600 ext 4140
Fax +1 613 737 6504
Email dharrison@cheo.on.ca

HCPs and parents now have effective pain-reducing strategies available to use for neonatal pain – the next step is to ensure that these strategies are consistently used during necessary painful procedures.

This paper will present an overview of indicators used to assess pain in the neonate, a review of the evidence supporting BF, SSC, and sweet solutions for procedural pain reduction, and recommendations included in neonatal pain management guidelines.

Pain indicators

Extensive research by multiple professions including nursing, psychology, basic science, and medicine, focusing on neonatal pain measurement has been conducted over the past 20 years.¹⁰ The most frequently used indicators of neonatal pain for clinical care and research purposes are behavioral indicators – most commonly, facial expressions and crying. Nearly all composite pain assessment tools developed include one or both of these behavioral indicators. The first identified systematic descriptions of infants' facial expressions during periods of crying were by Charles Darwin, using a series of photographs accompanying written explanations of the facial muscles involved in the formation of expressions of distress.¹⁵ Over a century later, authors of the neonatal facial coding system categorized ten facial expressions in response to heel lancing, with the four most frequently occurring facial expressions of brow bulge, eye squeeze, nasolabial furrow, and open lips described as the most specific behavioral indicators of acute procedural pain in infants regardless of gestational age or severity of illness.^{16–18} These four facial expressions form the basis of the majority of the more than 40 composite uni- or multidimensional published pain assessment tools used to quantify the existence and intensity of pain in neonates.^{19,20}

Crying incidence and duration, although unable to be assessed in neonates with endotracheal or tracheostomy tubes, are also frequently used as behavioral indicators of pain. For example, in the systematic review of sucrose for neonatal procedural pain, crying duration was used as an outcome measure in 35 (61%) of the 58 included studies.¹³ The acoustic characteristics of a newborn's cry such as pitch and amplitude have been studied in the past;^{21–23} however, they are rarely used in clinical care or clinical research due to the need for specialized equipment as well as the lack of specificity to pain, especially in preterm and sick infants with altered crying characteristics. Physiological responses to painful procedures are less sensitive and specific to procedural pain than behavioral indicators, and are highly influenced by health

status. However, they are also frequently used in studies evaluating interventions for reducing pain in neonates and are included in many composite and multidimensional pain assessment tools. The most commonly included parameters are heart rate, oxygen saturation levels, and respiratory rate and pattern. In the search for reliable objective specific indicators of pain, numerous other indicators of neonatal pain have also been explored. These include: heart rate variability;²⁴ skin conductance, a measure of sympathetic nervous system activation due to the release of sweat in response to stress;^{25–28} stress hormone levels, such as serum, salivary, urinary, or hair cortisol;^{29–31} and neural activity such as electroencephalography (EEG)^{32,33} or cerebral near-infrared spectroscopy (NIRS).³⁴ Despite the multitude of indicators of pain in newborns that have been identified and explored to various degrees, questions remain about the validity, reliability, and specificity of these different pain indicators. A lack of convergence of behavioral, physical, hormonal, and cortical responses³⁵ further highlight the complex nature of pain assessment and ongoing research questions to address. While further research is being planned and conducted to continue to evaluate neonatal pain assessment methods and indicators to use in research and clinical care over the spectrum of neonatal care, in the meantime, clinicians are faced with decisions about the best pain assessment method to use. The best answer currently is – use a pain assessment method that is:

- already developed and tested in the clinical area
- suitable for the specific unit/setting/population
- feasible to use
- acceptable to staff
- used consistently
- used in ward rounds, handovers, and in clinical care to make decisions about pain management.

When planning to introduce a new pain assessment method or composite measurement tool, it is important that the bedside clinicians are involved in the decision-making process about which tools are the most suitable for their patient population. Once the decision has been made, providing initial and ongoing education to ensure all HCPs are familiar with the use of the pain assessment tools is vital for integrating pain assessment into normalized practice.

In addition to the need for further exploration of issues surrounding the measurement of pain, clinically important challenges are also to: i) reduce pain exposure, and ii) consistently utilize effective pain reduction strategies in diverse settings where painful procedures take place. Recommendations aimed at reducing neonatal procedural pain need to start

with minimizing pain exposure. Worryingly, despite the often quoted study by Barker et al nearly two decades ago in 1995, which showed that for a cohort of 54 infants in a neonatal intensive care unit (NICU), over 3,000 procedures were performed, the large majority being heel lances,³⁶ more recently published studies continue to report large numbers of painful procedures with suboptimal use of effective pain management strategies.^{1–4,37–47} Such large numbers of painful procedures continue to occur despite the trend in the last decade toward use of less invasive respiratory support.⁴⁸ Although respiratory support-related procedures such as endotracheal intubations and airway suctioning have decreased, Axelin et al reported that the number of heel lances actually increased.⁴⁸ This situation highlights the need for HCPs to balance the need for close monitoring of preterm and sick neonates' pathology with efforts to minimize exposure to painful procedures.

When painful procedures are necessary, however, evidence-based pain reduction strategies are available. High-quality synthesized evidence shows that BF, SSC, and sweet solutions – either sucrose or glucose, effectively reduce pain during commonly performed needle-related painful procedures.^{11–14,49} These three strategies are effective, feasible, simple to use, and cost-effective. If the mother is able to participate, BF and SSC during blood collection are free, and sucrose is inexpensive. Sucrose made by hospital pharmacies costs approximately 45 cents/dose (R Vaillancourt, personal communication, 2013) and manufactured sucrose (TootSweet 24%) costs \$1/unit (currency in Canadian dollars).

The following section will review the evidence for these three strategies, facilitators and barriers to using each strategy in clinical care, and recommendations for practice.

Breastfeeding

A Cochrane systematic review of BF or breast milk for procedural pain management demonstrated analgesic effects of BF for medically stable newborn infants during heel lance and venipuncture.¹¹ Twenty trials were included; ten of which evaluated BF and ten studied analgesic effects of small volumes of breast milk. Comparators included no treatment, placebo, sweet solutions, non-nutritive sucking, holding, and positioning. Overall, findings were that BF effectively reduced behavioral and physiological responses and composite pain scores during or following painful procedures. However, small volumes of breast milk were ineffective in reducing pain. The mechanism of action of BF is considered to be multifactorial, combining maternal SSC,⁵⁰ sucking and slightly sweet taste,⁵¹ as well as the presence of endorphins

in the breast milk.^{52–54} However, lactose, the sugar in breast milk, is the least sweet of the four sugars,⁵⁵ and therefore has minimal sweet taste-mediated analgesic effects when used in isolation. The conclusions of the systematic review were that if the mother is available, BF should be used during painful procedures where feasible.

Facilitators and barriers to implementation

BF is a simple and cost-effective method of pain reduction for neonates during non-urgent procedures such as newborn screening or routine bloodwork performed by heel lance and venipuncture. As long as the mother is available, BF requires no additional resources (ie, cost or equipment) and can thus be implemented in diverse settings (such as hospitals, clinics, and in the home). Yet, despite the evidence, BF has not been consistently implemented in clinical practice.^{38,42} In a Canadian-wide study of pain management practices in NICUs, Johnston et al³ showed that of the 582 neonates in their study, almost half received no pain management during skin-breaking procedures, and only 0.03% of infants were breastfed during bloodwork. Barriers to using BF for pain management, especially in preterm and/or sick neonates in NICUs may include delayed or impaired sucking reflex,⁵⁶ separation from the mother,⁴² as well as the need for further evidence of effectiveness and feasibility in this population.¹¹ Other barriers include lack of awareness of the benefits, parents not being aware of the possibility of participating in pain management, and HCPs' lack of knowledge of the evidence and beliefs surrounding BF during painful procedures, such as: the baby will associate feeding with pain and BF during painful procedures will cause the baby to choke.⁵⁷ Organizational factors such as the need to schedule non-urgent blood work around the availability of the mother and ergonomic factors such as having the nursing or laboratory staff change positions to accommodate drawing blood during BF, have also been identified as barriers to implementing this strategy.³⁸

Skin-to-skin care

Johnston et al recently published a Cochrane systematic review of the effectiveness of SSC for pain management during painful procedures.¹² The systematic review included 19 studies and a total of 1,594 infants. The majority of the included studies examined heel lance (n=15, 744 infants), and the remaining studied SSC during venipuncture and heel lance combined, and intramuscular injection. Fifteen studies included preterm infants and four included full-term

infants. Eleven of the studies compared SSC with the mother to a no treatment control group, while the other studies' comparators included SSC with other family members; sucrose or other sweet solutions; BF; or enhanced SSC (rocking, singing, talking, non-nutritive sucking). There was significant heterogeneity across the studies, including wide variations in the dose of SSC prior to the procedures, outcome measures used, and timing of measurement of outcomes. These factors limited pooling of the results across the studies. Overall, SSC with the mother had variable effects but in most studies, was more effective than no treatment. The authors concluded that SSC is safe, and a potentially beneficial method of reducing physiological and behavioral responses in neonates during heel lance, venipuncture, and intramuscular injections.

Facilitators and barriers to implementation

Similar to BF, SSC is a cost-effective method for pain management, requiring only the mother or another caregiver to hold the infant against their skin, facilitating implementation in diverse settings. Factors influencing implementation of SSC during painful procedures have been examined and include a positive effect of HCPs' perception of the physiologic stability of the infant^{58–60} and the level of experience of the nurse, with more experienced nurses more likely to implement SSC during painful procedures.⁵⁸ However, use of SSC in practice may be hindered by several factors. SSC requires that the mother or other caregiver be present for the painful procedure; therefore, non-urgent procedures need to be scheduled accordingly.³⁸ In addition, there may be the perception that implementing SSC is not feasible as it takes additional time to prepare the infant and parent for SSC.^{38,60} Environmental factors such as dim lighting and lack of privacy for caregivers, as well as ergonomic factors such as challenges to drawing blood while the infant is in SSC have also been identified.^{38,56,60}

Sweet solutions

Sweet solutions are the most frequently investigated strategy for neonatal pain relief. There are now more than 200 published studies reporting calming and analgesic effects of sweet-tasting solutions in infants, the large majority of which are placebo-controlled trials.^{49,61,62} Although the exact mechanism remains uncertain, effects are considered to be orally mediated through endogenous opioid mechanisms, with reversal of effects by administration of opioid receptor antagonists.^{54,63–65} Analgesic effects of sweet solutions

are considered to be taste-dependent, with the sweetest solutions providing more effective pain relief.⁵⁵ Sucrose, a disaccharide (glucose and fructose) is the sweetest of the sugars (sucrose > fructose > glucose > lactose)⁵⁵ and the most effective when compared to less sweet solutions.⁴⁹ However, glucose, if administered in sufficient concentrations, eg, 20%–30%, is also considered as an effective alternative.¹⁴

Two large systematic reviews, including 57 studies of sucrose¹³ and 39 studies of glucose,¹⁴ highlight the extensive and rigorous evidence of sweet taste-induced analgesia for neonatal pain reduction. The results of both systematic reviews demonstrated consistent reduction of behavioral parameters and composite pain scores compared to no treatment groups, water, small volumes of breast milk or formula milk, and non-nutritive sucking during heel lancing and venipuncture, as well as less frequently studied painful procedures such as gastric tube insertions or arterial punctures. However heterogeneity in outcome measures across studies included in both systematic reviews precluded broad pooling of results.^{13,14} Furthermore, although sucrose or glucose consistently reduce behavioral responses during painful procedures compared to no treatment, placebo, or less sweet solutions, physiological indicators and stress hormone responses are inconsistently affected by sweet solutions. In addition, two studies examining the effects of sweet solutions on cortical responses showed no effects compared to placebo.^{32,33,66} Norman et al³³ concluded that EEG was not a useful measure of cortical brain activity in newborn infants, yet Slater et al concluded that further analgesic studies using cortical measures of pain as outcomes measures were warranted.³² Weak correlations between indicators of pain, direction, and degree of responses have long been reported,⁶⁷ highlighting challenges in interpreting and making decisions about the implementation of research findings. However, the extensive research conducted over the past 25 years provides indisputable evidence that small volumes of sweet solutions significantly reduce behavioral responses and composite pain scores to painful procedures in newborn and young infants.³⁵ It can therefore be argued that a condition of clinical equipoise, a requirement for conducting ethical placebo-controlled trials, has not been in existence since the publication of the international consensus statement of neonatal pain management in 2001.^{49,68} In response to this statement, calls have been made to cease further conduct of placebo-controlled trials of sweet solutions for single episodes of painful procedures for neonatal pain.^{49,61,62,69,70}

However, uncertainties and important research questions still remain:

- What are the exact mechanisms of analgesic effects of sweet solutions?
- Does consistent use of sweet solutions as required, during repeated painful procedures, ameliorate negative sequela of procedural pain exposure?
- Are sweet solutions efficacious when used in the context of exogenous opioids?
- What is the minimal effective volume required for analgesic effects?

Addressing these remaining key knowledge gaps need to be prioritized in future research on sweet solutions for analgesia.

Facilitators and barriers to implementation

Sucrose or glucose solutions are simple to use and cost-effective, and maximum analgesic effects are rapidly achieved after delivering the solution onto the tongue (1–2 minutes),^{35,71} facilitating its use before scheduled and non-scheduled painful procedures. Ensuring availability and easy accessibility in diverse postnatal and neonatal settings where bloodwork, immunizations, and other painful procedures take place is vital for facilitating consistent use during painful procedures. Many hospital pharmacies now produce their own sucrose solutions, and commercially manufactured sucrose solutions are available for purchase. Glucose is commonly available in clinical settings for intravenous use and can be orally administered prior to and during painful procedures.

Remaining knowledge gaps, however, may be acting as barriers to adoption of sweet solutions into normalized care. In addition, despite the prolific research conducted to date, repeated doses of sweet solutions over prolonged periods have only been investigated in a small number of studies.^{72–75} Although these studies showed ongoing effectiveness of sucrose over weeks to months of use, further research in this area, especially with the aim of exploring if consistently reducing procedural pain over prolonged hospitalizations ameliorates negative sequela of untreated pain for preterm and high-risk neonates, will add valuable information to the science of neonatal pain management.

Recommendations for practice and clinical practice guidelines

Over the past decade, increasing numbers of clinical practice guidelines (CPG) focusing on, or including neonatal and infant pain management, have been developed at the level

of individual organizations,^{40,42,43} as well as at a national and international level.^{76–80} In a recent systematic review of CPGs focusing on pain reduction in neonates, infants, and children, 18 published CPGs were identified, and seven specifically related to neonates or infants.⁸⁰ Recommendations for this age group included minimizing the number of painful procedures, reducing environmental noise and light, using SSC or BF during painful procedures, and using sucrose with or without non-nutritive sucking.

A consistent and coordinated approach to improving neonatal pain management and implementing pain management recommendations included in nationally and internationally endorsed guidelines is called for. Such a coordinated effort requires commitment and engagement from all involved parties, including parents, HCPs from the level of frontline carers, through to organizational and professional association leadership, as well as administrators and consumer groups.⁸⁰ To optimize effectiveness, knowledge translation (KT) efforts need to target HCPs as well as the parents of healthy, preterm, and hospitalized term infants. Strategies planned to support parents to advocate for their infants and participate in their infants' pain management during painful procedures need to include the parents of infants, particularly the mothers, if BF during routine non-urgent blood draws is to be promoted. To date, however, very little research has targeted parents of hospitalized infants as partners in pain management improvement initiatives, despite care being viewed as a partnership between HCPs and the family,^{81,82} and parents expressing the need to be more involved in comforting their infants during painful procedures.^{83,84} In addition, in a Canada-wide study, infants in the NICU whose mothers were present during painful procedures were more likely to receive effective pain management strategies than those infants whose mothers were not present,³ highlighting a positive influence of parents. There is therefore a clear need for developing and testing acceptable parent-targeted interventions, alongside HCP-targeted KT interventions, to support parents to be involved in comforting their infants and to increase use of BF, SSC, and sucrose during painful procedures. An example of such an intervention is a publicly accessible YouTube video, targeted at parents of infants, showing three scenarios; a mother BF, a mother holding her infant in SSC during heel lance, and an infant being given sucrose with non-nutritive sucking during a venipuncture procedure (<http://tinyurl.com/BSweet2newborns>). The effectiveness of this YouTube video and other interventions disseminated via social media are potentially promising methods to widely disseminate knowledge. Research is warranted on the reach, impact, and

effectiveness of using social media avenues such as YouTube in changing practices.

Conclusion

In conclusion, extensive high-quality synthesized evidence demonstrates the analgesic effects of BF,¹¹ SSC,¹² and sweet-tasting solutions during short-lasting acute painful procedures.^{13,14,49} The growing and concerning evidence of adverse effects of untreated neonatal pain^{5-9,85} behooves HCPs in partnership with parents of infants, to strongly advocate for consistently using suitable effective pain reduction strategies during necessary painful procedures. Focusing on KT of existing evidence, while conducting further research to address remaining key knowledge gaps, will help to ensure that no infant suffers unnecessary pain during painful procedures.

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Author contributions

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Disclosure

The authors report no conflicts of interest in this work.

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