



Breast-Feeding Analgesia in Infants

An Update on the Current State of Evidence

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ABSTRACT

To provide an updated synthesis of the current state of the evidence for the effectiveness of breast-feeding and expressed breast milk feeding in reducing procedural pain in preterm and full-term born infants. A systematic search of key electronic databases (PubMed, CINAHL, EMBASE) was completed. Of the 1032 abstracts screened, 21 were found eligible for inclusion. Fifteen studies reported on the use of breast-feeding or expressed breast milk in full-term

infants and 6 reported on preterm infants. Direct breast-feeding was more effective than maternal holding, maternal skin-to-skin contact, topical anesthetics, and music therapy, and was as or more effective than sweet tasting solutions in full-term infants. Expressed breast milk was not consistently found to reduce pain response in full-term or preterm infants. Studies generally had moderate to high risk of bias. There is sufficient evidence to recommend direct breast-feeding for procedural pain management in full-term infants. Based on current evidence, expressed breast milk alone should not be considered an adequate intervention.

Key Words: breast-feeding, expressed breast milk, infants, procedural pain, systematic review

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All infants undergo routine diagnostic and therapeutic painful procedures as part of universal medical care. While this exposure is highest in preterm and critically ill infants in the neonatal intensive care unit (averaging 12 painful procedures per day^{1,2}), healthy full-term infants are also routinely exposed to painful procedures. For example, many infants will undergo a routine intramuscular injection of vitamin K to prevent bleeding³ and at least 1 heel lance to collect blood for metabolic testing⁴ and routine total serum bilirubin screening⁵ within the first days of age. Full-term infants who are at risk of hypoglycemia will further undergo repeated heel lancing for blood glucose testing on the basis of guidelines for infants at risk for low blood glucose.⁶ Furthermore, children undergo upward of 20 intramuscular injections for immunizations, with the majority occurring from 2 to 18 months of age.⁷

OUTCOMES OF UNTREATED PAIN IN INFANTS

In addition to causing unnecessary suffering to the smallest and most vulnerable of our population,

unmanaged early pain exposure is associated with adverse neurological consequences. In research conducted with largely preterm infant samples, repeated pain exposure is associated with changes in somatosensory processing that continues into childhood, including changes in sensitivity and response to later pain.^{8–11} Pain exposure in preterm infants has additionally been associated with structural changes in the brain, including reduced maturation of white and subcortical gray matter at term equivalent age¹² and reduced cortical thickness¹³ and cerebellum volume¹⁴ at school age in children born very preterm. The influence of untreated pain on the developing brain is further evidenced by research suggesting long-term motor, cognitive, and behavioral deficits. For example, exposure to pain in the neonatal period has been shown to be associated with poor body and head growth,¹⁵ reduced visual perceptual abilities at school age,¹⁶ poorer language outcomes at 18 months corrected age,¹⁷ greater internalizing behaviors throughout childhood,^{18,19} and altered development of the hypothalamic-pituitary-adrenal axis.^{20–23}

While the majority of research examining the influence of untreated pain in infants has been conducted with those born preterm, the available evidence suggests that such exposure also produces adverse outcomes in full-term born infants. Studies examining the influence of early full-term infant exposure to major surgery,^{24–27} circumcision,^{28,29} burns,³⁰ and repeated acute pain^{31–34} predominantly suggest that this exposure is associated with heightened pain responses to later painful stimuli.

BREASTFEEDING FOR THE TREATMENT OF INFANT ACUTE PAIN

In recognizing the adverse consequences of untreated pain in infants, national guidelines for evidence informed pain assessment and management practices have been developed.^{35,36} An intervention recommended in such guidelines for procedural pain management is breast-feeding. The most recent synthesis of the evidence of the use of breast-feeding or expressed breast milk as an analgesic intervention in infants was published in a Cochrane review in 2012. In this review, Shah and colleagues³⁷ reported on 20 studies for a total sample of 2071 neonates who directly breastfed (10 studies, $n = 1075$) or received expressed breast milk (10 studies, $n = 996$) during acute needle-related painful procedures such as venipuncture, heel lance, and intramuscular injections. Of the 10 studies included in this systematic review examining direct breast-feeding,^{38–47} those examining its influence on physiological (eg, heart rate) and unidimensional behavioral (eg, cry time) measures of infant pain demonstrated

consistent findings. Specifically, breastfed neonates demonstrated significantly lower heart rates,^{38,41,46} proportion crying time,^{38,41,44} duration of first cry,^{38,40,46–48} and total crying time⁴⁴ than infants who were swaddled, held by their mothers, or received oral sucrose, a pacifier, placebo, or no intervention during the procedure.³⁷

With respect to validated behavioral and biobehavioral infant pain measurement tools, Premature Infant Pain Profile (PIPP)⁴⁹ scores were significantly lower in neonates who were breast-feeding during heel lance or venipuncture than in those who were positioned in their mothers' arms or received oral sucrose or a placebo.^{39,40,44} Similarly, Douleur Aiguë du Nouveau-né (DAN)⁵⁰ scores were significantly lower in those neonates who were breast-feeding during painful procedures than in those neonates who were held in their mothers' arms or received a placebo.³⁹ However, there was no significant difference in DAN scores between breast-feeding neonates and those receiving oral glucose.³⁹ Similarly, while Neonatal Infant Pain Scale (NIPS)⁵¹ scores were lower for breast-feeding neonates than for those with no intervention, there was no significant statistical difference in NIPS scores between breast-feeding neonates and those who received oral sucrose.⁴⁸ Finally, while Neonatal Facial Coding System⁵² scores were lower in the breast-feeding group than those in oral glucose, pacifier use, maternal holding, or no intervention, breast-feeding was not statistically significantly more effective than provision of formula.^{45,46} A moderate level of evidence quality based on the GRADE (ie, Grading of Recommendations Assessment, Development, and Evaluation)⁵³ criteria was reported for all of the studies examining the influence of direct breast-feeding.³⁷

In comparison to direct breast-feeding, there was considerable variability across the 10 studies examining provision of expressed breast milk for pain relief.³⁷ Expressed breast milk reduced duration of crying when compared to placebo,^{54–60} and behavioral pain response measured using the NFCS when compared to placebo in one⁶¹ of three studies reporting on this outcome. However, oral sucrose in 12.5%, 20%, and 25% concentrations; oral glucose in 25% and 30% concentrations; and pacifier use, rocking, and no intervention were more effective than breast milk in reducing duration of crying^{55,59,60,62} and heart rate.^{54,55,57,63} Furthermore, expressed breast milk was not effective in reducing NIPS⁶² and DAN scores.⁵⁹ Taken together, the authors of this review reported that direct breast-feeding is clearly superior when compared with the provision of expressed breast milk for procedural pain relief.

Despite this evidence, the routine use of breast-feeding to reduce needle-related pain in healthy infants remains underutilized in practice.⁶⁴ The limited reported

use of breast-feeding to reduce acute pain in newborns may be related to outstanding clinical research questions. However, since the publication of the most recent Cochrane review and meta-analysis of the breast-feeding literature, there has been substantial research activity on this topic. Specifically, the majority of studies included in this Cochrane review reported on only healthy full-term born infants, with only 1 of the 20 studies including stable late preterm infants in addition to full-term infants in their sample.⁵⁴ There are now several studies reporting on the influence of expressed breast milk and direct breast-feeding for pain reduction in strictly preterm infant samples. Furthermore, there are additional available studies including samples of full-term infants. A synthesis of this evidence makes a valuable contribution to the literature to inform timely updates to clinical practice guidelines and future research in this area.

AIMS

The purpose of this systematic review of the literature is to provide an updated synthesis of the current state of the evidence for the influence of breast-feeding and expressed breast milk feeding on acute procedural pain in preterm and full-term born infants.

METHODS

To address the aims of this article, a systematic review methodology was utilized. Standards for the conduct of systematic reviews have been outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) group⁶⁵ and include standards for clearly reporting the rationale of the paper, eligibility criteria, sources of information, search terms and delimiting, and synthesis of the evidence. These guidelines were followed in the completion of this systematic review.⁶⁵

Literature search

Key electronic databases (PubMed, CINAHL, EMBASE) were searched from 2011 (as this was the date to which the most recent Cochrane review search strategy was completed) through to December 22, 2016. The systematic search strategy, which was developed in collaboration with a health sciences librarian specializing in systematic searches, included key terms for infants, pain exposure, and breast-feeding. Medical Subject Headings (MeSH) terms and other key terms were included where possible in each database.

Eligibility criteria

Eligibility criteria required that included studies (1) be an empirical investigation (ie, an experimental or quasi-

experimental quantitative study) examining the use of breastfeeding or expressed breast milk as a pain relieving intervention, (2) include a sample of full-term or preterm born infants, and (3) be published in English in a peer-reviewed journal. Pain exposure was defined as acute procedural pain (eg, heel lancing, intramuscular injections, venipuncture). Studies that quantified physiological (eg, heart rate, oxygen saturation), behavioral (eg, facial actions, cry duration), brain-based (eg, pain-specific response using neurophysiological measures), and hormonal (eg, changes in cortisol patterns) pain responses were all considered eligible for inclusion.

Study selection and data extraction

The titles and abstracts of all of the articles generated by the systematic search were reviewed by the first author (B.B.), and full texts of articles deemed to be relevant were reviewed by the first author (B.B.) and study coinvestigator (M.C.Y.) to verify eligibility for inclusion. Of those studies meeting inclusion criteria, full texts of the articles were reviewed and data on study purpose, sample characteristics, and all outcomes were extracted. Figure 1 outlines the PRISMA flow diagram for identification and screening of studies in this review. Risk of bias for each included study was rated by the first author (B.B.) using the Cochrane Risk of Bias Assessment Tool for Randomized Studies of Interventions⁶⁶ or the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tools⁶⁷ as appropriate. Specifically, the first author scored each study as low, high, or unclear risk of bias across each of the 7 domains included in the Cochrane risk of bias tools and drew conclusions regarding the overall risk of bias score for each study by judiciously considering the rating and contribution of each domain.⁶⁸

RESULTS

The number of studies reporting on the use of direct breast-feeding for acute pain management in full-term infants has more than doubled, with an additional 15 studies ($n = 1908$ infants) being published (see Table 1). Furthermore, 6 studies ($n = 428$) have been published examining the use of breast-feeding and expressed breast milk feeding for procedural pain management in preterm infants, which have not been previously synthesized in the literature.

Evidence for breast-feeding and expressed breast milk in full-term infants

All of the additional studies comparing direct breast-feeding to alternate interventions in full-term infants report consistent and positive analgesic effects. Two

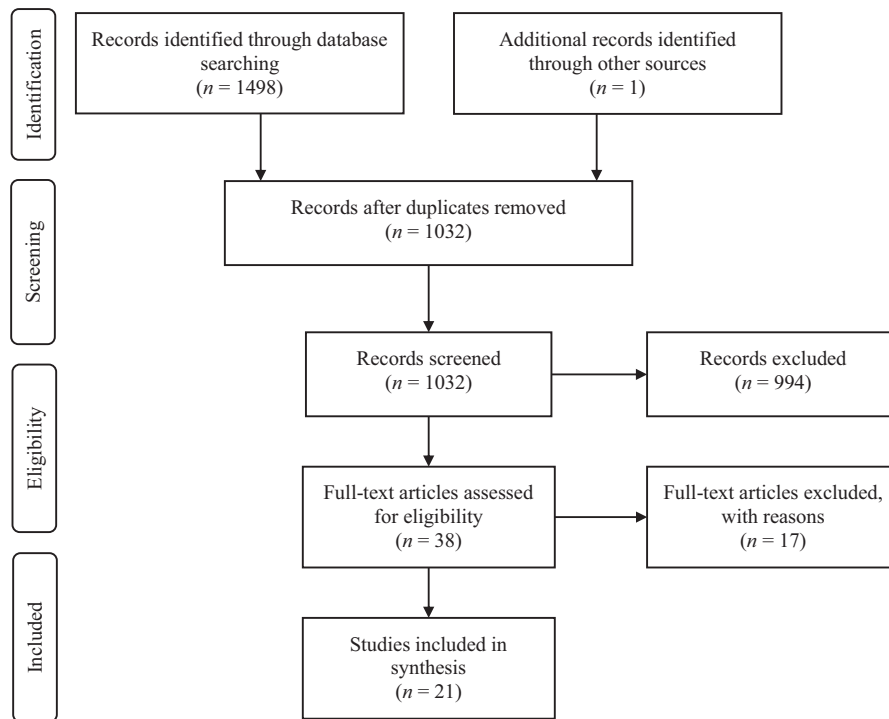


Figure 1. PRISMA flow diagram for the process of identification and screening of articles for inclusion in a systematic review and meta-analysis. From Moher et al.¹¹⁷

additional studies compare direct breast-feeding with topical anesthetics,^{69,70} 3 compare breast-feeding with sweet taste interventions (oral sweet solutions such as glucose or sucrose placed on to the anterior tip of the infant's tongue),^{71,72,73} and 2 compare breast-feeding with skin-to-skin contact (SSC).^{74,75} Three new studies compare breast-feeding with simple holding,^{76–78} 1 with music therapy,⁷⁹ and 1 with nonnutritive sucking.⁸⁰ Finally, 3 studies have reported on the use of expressed breast milk compared with sweet taste interventions.^{81–83} These studies generally had moderate to high risk of bias (see Table 1). As the findings of these studies have not previously been synthesized, the following section of this review will report on their results.

Breast-feeding versus music therapy

A single randomized controlled trial of 288 healthy full-term neonates compared the influence of music therapy, breast-feeding, or the combination of these interventions on NIPS scores, cry duration, and latency to cry, following a heel lance.⁷⁹ The authors reported that infants who were breast-feeding, both with or without music, demonstrated significantly lower NIPS scores than those who received music therapy alone.⁷⁹ Furthermore, infants who were breast-feeding had significantly longer latency to first cry and shorter duration of first cry

than those receiving music therapy. Thus, the findings of this study suggest that when compared with breast-feeding, music therapy is an ineffective intervention for the reduction of procedural pain in full-term neonates.

Breast-feeding versus topical anesthetics and cooling sprays

One study reported on the comparison of breast-feeding with topical anesthetics and 1 reported on the use of a cooling spray. In a sample of full-term born infants undergoing intramuscular injection for immunization, those who were breast-feeding during the procedure demonstrated a significantly higher frequency of painless injections as measured using the NIPS than those infants who received a vapocoolant spray at the site of injection or no intervention.⁶⁹ A similar finding was demonstrated by Gupta and colleagues,⁷⁰ who assigned healthy full-term infants to receive (1) EMLA (*Eutectic Mixture of Local Anesthetics*) plus breast-feeding, (2) EMLA plus water, or (3) placebo cream plus water before immunization. Those infants who received the combined intervention of EMLA and breast-feeding demonstrated significantly lower Modified Facial Coding System scores and shorter duration of cry than those infants receiving EMLA alone or placebo, suggesting synergistic effects of breast-feeding and topical anesthetics during immunization.⁷⁰

Table 1. Summary and risk of bias of included studies reporting on the use of breast-feeding or expressed breast milk as an analgesic intervention in full-term newborns undergoing acute procedures

Author (year), country	Study objective	Study design	Study setting	Painful procedure	Participants	Intervention group	Comparison group	Risk of bias
<i>Direct breast-feeding studies</i>								
Breast-Feeding versus music therapy Zhu et al ⁷⁹ (2015) China	To test the effect of breast-feeding, music therapy, and combined breast-feeding and music therapy on pain	RCT	Hospital	Heel lance	288 full-term neonates <4 d PNA	(a) Breast-Feeding initiated 5 min prior to procedure + classical music 5 min prior to procedure (b) Breast-Feeding initiated 5 min prior to procedure	Classical music playing 5 min prior to procedure	Mod
<i>Breast-Feeding versus topical anesthetics and cooling sprays</i>								
Boroumandfar et al ⁶⁹ (2013) Iran	To compare vaccine pain between infants who receive vapocoolant spray or breast-feeding	RCT	Hospital	IM injection	144 full-term born infants at 2, 4, and 6 mo of life	Breast-Feeding during procedure	(a) Vapocoolant sprayed 10 s preprocedure (b) No treatment	High
Gupta et al ⁷⁰ (2013) India	To evaluate the analgesic effect of EMLA and breast-feeding	RCT	Clinic	IM injection	90 full-term infants <3 mo PNA	1 g EMLA 60 min prior to procedure + breast-feeding 2 min prior to procedure	(a) EMLA + 2-mL bolus distilled water 2 min prior to procedure (b) Vaseline + 2-mL bolus distilled water 2 min prior to procedure	Low
<i>Breast-Feeding versus sweet taste interventions</i>								
Bembich et al ⁶⁴ (2013) Italy	To evaluate cortical and behavioral responses to a painful procedure during either breast-feeding or glucose	RCT	Hospital	Heel lance	30 full-term neonates <3 d PNA	Breast-Feeding initiated 2 min prior to procedure	2-mL bolus of 20% oral glucose 2 min prior to procedure	High
Chiabi et al ⁷³ (2016) Cameroon	To compare the effect of breast-feeding and 30% glucose on pain	RCT	Hospital	Heel lance	100 full-term born infants at least 24 h of age	Breast-Feeding initiated 2 min prior to procedure	(a) 30% oral glucose (1-2-mL dose based on weight)	High
Goswami et al ⁷² (2013) India	To compare the analgesic effect of breast-feeding, 25% dextrose, and placebo	RCT	Clinic	IM injection	120 full-term infants <3 mo PNA	Breast-Feeding initiated 2 min prior to procedure	(a) 2-mL bolus of 25% dextrose 2 min prior to procedure (b) 2-mL bolus distilled water 2 min prior to procedure	Low
<i>Breast-Feeding versus simple holding</i>								
Modarres et al ⁷⁶ (2013) Iran	To examine the effect of breast-feeding on pain	RCT	Hospital	IM injection	130 full-term neonates <24 h PNA	Breast-Feeding initiated 2 min prior to procedure	Held by mother with no breast-feeding	Mod
Obeidat et al ⁷⁷ (2015) Jordan	To determine the efficacy of breast-feeding with maternal holding to holding alone	RCT	Hospital	Heel lance	128 full-term neonates <6 d PNA	Breast-Feeding while held in mother's lap	Held in mother's lap with no breast-feeding	Mod
Thomas et al ⁷⁸ (2011) India	To compare pain response between infants who are breast-feeding and not breast-feeding	Quasi-experimental	Not stated	IM injection	40 full-term infants <15 wk PNA	Breast-Feeding initiated 2 min prior to painful procedure	No breast-feeding	High

(continues)

Table 1. Summary and risk of bias of included studies reporting on the use of breast-feeding or expressed breast milk as an analgesic intervention in full-term newborns undergoing acute procedures (Continued)

Author (year), country	Study objective	Study design	Study setting	Painful procedure	Participants	Intervention group	Comparison group	Risk of bias
Breast-Feeding versus skin-to-skin contact Fallah et al ⁷⁴ (2016) Iran	To compare the analgesic effect of SSC, breast-feeding, and swaddling	RCT	Hospital	IM injection	120 full-term neonates <24 h PNA	Breast-Feeding initiated 2 min prior to procedure	(a) SSC 10 min before, during procedure (b) Swaddled 10 min before, during procedure	Mod
Marin Gabriel et al ⁷⁵ (2013) Spain	To evaluate the analgesic effect of breast-feeding combined with SSC vs other nonpharmacologic analgesics	RCT	Hospital	Heel lance	136 full-term neonates in first days of life	Breast-Feeding initiated 5 min prior to procedure + SSC	(a) 2-mL bolus 24% sucrose 2 min prior to procedure + SSC 5 min prior to procedure (b) SSC contact 5 min prior to procedure (c) 2-mL bolus 24% sucrose 2 min prior to procedure	High
Breast-Feeding versus nonnutritive sucking Lima et al ⁸⁰ (2015) Brazil	To verify the analgesic efficacy of nutritive and nonnutritive sucking during venipuncture	RCT	Hospital	venipuncture	64 full-term newborns	Breast-Feeding initiated 2 min prior to procedure	(a) Nonnutritive sucking (b) No treatment	High
EBM studies Cordero et al ⁸¹ (2014) Spain	To evaluate the effectiveness of 24% oral glucose and breast milk	RCT	Hospital	Heel lance	93 healthy newborns	EBM	(a) 24% oral glucose solution (b) No treatment	High
Sabety et al ⁸³ (2013) Iran	To compare the analgesic effects of 50% oral glucose, topical lidocaine, EBM, and no intervention	RCT	Hospital	venipuncture	121 full-term neonates (average PNA = 6.49 d)	2-mL EBM administered orally 2 min prior to procedure	(a) 2-mL 50% glucose administered orally 2 min prior to procedure (b) 1-g 2% lidocaine applied topically (c) No treatment	Mod
Sahoo et al ⁸¹ (2012) India	To compare EBM, 25% dextrose, and sterile water on procedural pain	RCT	Hospital	venipuncture	160 full-term infants (PNA ranging from 54 to 102 h)	2-mL EBM administered orally 2 min prior to procedure	(a) 2-mL 25% dextrose administered orally 2 min prior to procedure (b) 2-mL sterile water administered orally 2 min prior to procedure	Mod

Abbreviations: EBM, expressed breast milk; EMLA, Eutectic Mixture of Local Anesthetics; IM, intramuscular; Mod, moderate; PNA, postnatal age; RCT, randomized controlled trial; SSC, skin-to-skin contact.

Breast-feeding versus sweet taste interventions

Three studies compared the analgesic efficacy of breast-feeding and sweet taste interventions and demonstrated findings consistent with those previously synthesized in the literature. For example, duration of cry, latency of cry, and Modified Facial Coding System scores were consistent between those infants who were breastfed during intramuscular injection and those who received 25% dextrose solution.⁷² However, both of these interventions (ie, breast-feeding or receiving 25% dextrose 2 minutes prior to injection) were found to significantly reduce duration of cry and latency of onset of cry compared with placebo.⁷² In a trial of 100 full-term newborns randomly assigned to receive 30% glucose or breastfeed during heel lance, NIPS was significantly lower in the breastfed group.⁷³ Furthermore, a randomized controlled trial including 30 healthy full-term neonates demonstrated that NIPS was significantly reduced in those infants who were breastfed before heel lance compared with those receiving 20% oral glucose prior to procedure.⁸⁴ In this trial, brain-based response measured using near infrared spectroscopy was reported in addition to the NIPS score. Infants who were breast-feeding during the procedure demonstrated significant increases in oxygenated hemoglobin over the left superior sensorimotor cortex, left somatosensory cortex, right superior sensorimotor cortex, right posterior-superior frontal cortex, and the right posterior parietal cortex.⁸⁴ Increases in oxygenated hemoglobin measured using near infrared spectroscopy may reflect an increase in neuronal activation secondary to the painful stimulus.⁸⁵ However, as activation of these brain regions would be anticipated during breast-feeding due to the sensory and motor stimulation associated with close maternal contact and oral movements, the influence of breast-feeding on pain-specific activity isolated from the confounding activity in this intervention group is difficult to discern. Thus, consistent with the finding synthesized by Shah and colleagues,³⁷ the current evidence would suggest that the analgesic effect of breast-feeding is equally as effective, if not more effective, than sweet taste interventions for full-term infants undergoing acute procedures.

Breast-feeding versus simple holding and direct skin-to-skin contact

Three studies comparing breast-feeding with being held without SSC during painful procedures all demonstrated that breast-feeding is significantly more analgesic.⁷⁶⁻⁷⁸ Pain associated with intramuscular injection measured using the DAN⁷⁶ and the NIPS⁷⁸ was found to be significantly lower when infants were actively breast-feeding 2 minutes prior to and during immunization when compared with simply being held in their mothers' lap dur-

ing the procedure. Furthermore, in a sample of 128 healthy full-term neonates undergoing a heel lance for routine metabolic screening, breast-feeding was found to significantly reduce PIPP scores compared with maternal holding.⁷⁷

In the 2 studies that compared breast-feeding with direct maternal-infant SSC, breast-feeding continues to appear superior for pain management in full-term neonates. Marin Gabriel and colleagues⁷⁵ first compared these interventions in a randomized controlled trial of 136 healthy full-term neonates who were randomly assigned to 1 of 4 intervention conditions: (1) maternal SSC and breast-feeding, (2) maternal SSC and 24% oral sucrose, (3) 24% oral sucrose alone, or (4) maternal SSC alone. Median NIPS scores and the percentage of time that the neonates were scored as having moderate to severe pain were significantly lower in the maternal SSC and breast-feeding group than in the other groups. Furthermore, both the maternal SSC and breast-feeding and maternal SSC and sucrose groups demonstrated a significantly lower percentage of crying than the SSC alone group,⁷⁵ suggesting a potential additive effect of combining these interventions. Breast-Feeding was further demonstrated to be significantly more effective in reducing pain response measured using NIPS and cry duration than maternal SSC or swaddling prior to immunization in healthy full-term infants.⁷⁴ While it is unclear whether infants were held in SSC during breast-feeding in this study,⁷⁴ it is likely that the combination of maternal SSC and breast-feeding provides the greatest analgesic benefit.

Breast-feeding versus nonnutritive sucking

Only 1 study was identified that compared direct breast-feeding with nonnutritive sucking in full-term healthy newborns.⁸⁰ This study, which was described as a case-control study but reported randomized controlled trial methodology, found that those infants who were breast-feeding during the procedure and those who received nonnutritive sucking both had lower NIPS scores than those infants who did not receive any analgesia during venipuncture. However, there was no statistically significant difference in NIPS scores between the breast-feeding and nonnutritive sucking groups.⁸⁰

Expressed breast milk versus sweet taste interventions

Three studies were included that reported on the comparative analgesic efficacy of expressed breast milk and sweet taste interventions in full-term infants. Expressed breast milk has been found to be more effective than no intervention in reducing DAN score and crying time during venipuncture.⁸³ One study comparing expressed breast milk and 24% oral glucose

demonstrated that those infants who received breast milk had significantly lower heart rates and higher oxygen saturation following heel lance.⁸¹ In contrast, Sahoo and colleagues⁸² compared expressed breast milk, 25% dextrose, and sterile water for pain relief during venipuncture and found that while expressed breast milk was more effective in reducing PIPP scores, heart rate, and cry duration than sterile water, it was not more effective than 25% dextrose.⁸²

Evidence for breast-feeding and expressed breast milk in preterm infants

Of the 6 studies ($n = 428$; see Table 2) identified by this systematic review reporting on direct breast-feeding and expressed breast milk feeding for pain management in preterm infants, there is limited evidence for its analgesic efficacy. Provision of expressed breast milk was not as effective as sweet taste in premature neonates ranging from 32 to 36 completed weeks' gestational age at birth,^{54,86-88} and no difference was found between expressed breast milk and maternal-infant SSC during tape removal in very low-birth-weight neonates with an average gestational age at enrollment of approximately 32 weeks.⁸⁹ One study examining direct breast-feeding in preterm infants, which randomly assigned 57 infants born between 30 and 36 weeks' gestational age to receive either direct breast-feeding or nonnutritive sucking during heel lance (performed, on average, at day 9 of age), reported no significant difference in Behavioral Indicators of Infant Pain score or heart rate between the 2 groups.⁹⁰ However, although no overall group effect of breast-feeding was found, preterm breast-feeding infants in this study who had more mature breast-feeding behaviors as assessed using the Premature Infant Breast-Feeding Behaviors Scale demonstrated lower pain responses during the heel lance, heel squeeze, and recovery phases of data collection.⁹⁰ One study examining the analgesic effect of expressed breast milk combined with standard care (topical anesthetic drops applied to the eye, swaddling, and nesting) for retinopathy of prematurity examinations in neonates born at less than 35 weeks' gestational age found that the addition of breast milk significantly reduced pain scores when compared with standard care alone.⁹¹ These studies generally had low risk of bias (see Table 2).

DISCUSSION

As is evidenced from this systematic review of the literature, the number of studies reporting on the use of direct breast-feeding and the provision of expressed breast milk as an analgesic intervention in infants has more than doubled in the last 4 years. While the majority of these studies have reported on the use of this

intervention in full-term infants, there is an emerging body of evidence using breast-feeding and expressed breast milk for pain in preterm infants.

The findings of this review are consistent with the previously synthesized literature in that direct breast-feeding appears to be superior in comparison to the use of expressed breast milk. The additional studies included in this review utilizing expressed breast milk compared with sweet taste in preterm infants found that the provision of expressed breast milk was no more effective than sweet taste (ie, 25% glucose or 24% sucrose) in reducing pain from heel lancing as measured by composite biobehavioral pain score (ie, PIPP) or cry indicators such as duration of cry after procedure.^{54,86-88} Of the 3 additional published records reporting on the use of expressed breast milk in full-term newborns, only 1 reported a significant effect of expressed breast milk compared with sweet taste on select physiologic pain indicators.⁸¹ This limited effect of expressed breast milk is not surprising given current hypotheses regarding the mechanisms of effectiveness of expressed breast milk and sweet-tasting interventions. While the exact mechanisms of these interventions are not yet fully elucidated, research demonstrating that the effects of sucrose occurred rapidly, are short lasting, and are blocked by systemic opioid receptor antagonists suggest that the effects are mediated by endogenous opioid release.⁹²⁻⁹⁵ Sweeter and more concentrated solutions (eg, 24% oral sucrose; 20%-30% glucose⁹⁶) have demonstrated more robust pain-reducing effects than solutions with lower concentrations of sweet taste.^{97,98} Given that breast milk contains only 7% lactose, provision of breast milk alone does not appear to be an effective pain-relieving intervention and thus, direct breast-feeding is likely necessary to gain optimal analgesic efficacy.

Direct breast-feeding is a multisensorial intervention that encompasses a combination of individually pain-reducing interventions such as maternal closeness and SSC,⁹⁹ olfactory,^{100,101} and oral¹⁰² stimulation. Thus, it is not surprising that in contrast to studies examining the provision of expressed breast milk, the newly synthesized studies examining direct breast-feeding consistently found it to be an effective analgesic intervention in full-term infants. Consistent with the studies reported in the most recent Cochrane review,³⁷ breast-feeding demonstrated superior analgesic efficacy in all studies comparing it with simple maternal holding.⁷⁶⁻⁷⁸ Interestingly, the use of breast-feeding in combination with alternate interventions, such as EMLA⁷⁰ and SSC,⁷⁵ appears to be more effective in reducing behavioral responses to pain than using these interventions alone in full-term infants. This suggests the potential benefit of using breast-feeding in combination with adjuvant therapies to provide optimal pain relief.

Table 2. Summary and risk of bias of included studies reporting on the use of breast-feeding as an analgesic intervention in preterm newborns undergoing acute procedures

Author (year), country	Study objective	Study design	Study setting	Painful procedure	Participants	Intervention group	Comparison group	Risk of bias
Direct breast-feeding studies								
Holsti et al ⁶⁰ (2011) Canada	To evaluate the efficacy of breast-feeding for reducing pain	RCT	Hospital	Heel lance	57 preterm neonates (30-36-wk GA; mean PNA at procedure = 9 d)	Breast-Feeding initiated 2 min prior to procedure	Nonnutritive sucking initiated 2 min prior to procedure	Low
EBM studies								
Bueno et al ⁶⁶ (2012) Brazil	To compare the efficacy of EBM vs 25% glucose on pain response	RCT	Hospital	Heel lance	88 late preterm neonates (34-36-wk GA)	2-mL EBM applied to the anterior portion of the tongue	2-mL 25% glucose applied to the anterior portion of the tongue	Low
Nanavati et al ⁶⁹ (2013) India	To compare the effect of KMC and EBM on pain	RCT	Hospital	Tape removal	50 VLBW neonates (mean GA in weeks = 32.56; mean PNA at procedure = 6.26 d)	Swab soaked in EBM kept in babies' mouth for 2 min prior to procedure	Baby kept in KMC for 15 min prior to procedure	Mod
Ou Yang ⁶⁸ (2013) Taiwan	To determine whether EBM reduces pain response	RCT	Hospital	Heel lance	123 preterm neonates (<37 wk GA; <7 d PNA at procedure)	5-mL EBM into the oral cavity	(a) 5-mL 25% glucose into the oral cavity (b) 5-mL sterile water into the oral cavity	Low
Rosali et al ⁹¹ (2015) India	To assess the effectiveness of EBM on neonatal pain	RCT	Hospital	Retinopathy of prematurity examination	40 preterm neonates (<35-wk GA; mean PNA at procedure = 25.6 d)	2-mL EBM into the oral cavity 2 min prior to procedure + standard care	Standard care (nesting, swaddling, and topical propraracaine)	Low
Direct breast-feeding and EBM studies								
Simonse et al ⁶⁷ (2012) Netherlands	To investigate whether breast milk has a better analgesic effect than sucrose	RCT	Hospital	Heel lance	70 preterm neonates (32-37-wk GA; mean PMA at procedure = 36.6 wk)	(a) Direct breast-feeding until continuous sucking observed (b) EBM via syringe while held by nurse	1-2-mL 24% sucrose 2 min prior to heel lance + nonnutritive sucking	Mod

Abbreviations: EBM, expressed breast milk; GA, gestational age; KMC, kangaroo mother care; Mod, moderate; PMA, postmenstrual age; PNA, postnatal age; RCT, randomized controlled trial; VLBW, very low birth weight.

While the available evidence suggests that breast-feeding is more effective in reducing pain than simple holding, topical anesthetics, and SSC alone during acute procedures, the additional studies included in this systematic review continue to report inconsistent outcomes when comparing direct breast-feeding and sweet tasting interventions. For example, while breast-feeding infants were found to have significantly lower NIPS scores than those receiving 20% glucose⁸⁴ in 1 study, pain response measured as facial actions and cry indicators were statistically similar between breast-feeding infants and those receiving 25% dextrose in another.⁷² While it could be hypothesized that these findings are related to the concentration of sweet solutions utilized in these studies, future research is needed to examine the relationship between these interventions. However, unlike the administration of sucrose during pain, which has reported potential adverse effects following repeated dosing such as poorer attention and motor development in preterm infants born less than 31 weeks,^{103,104} no studies to date have reported on adverse effects associated with breast-feeding during painful procedures.^{37,75} While additional research examining the potential for adverse outcomes associated with sweet-tasting solutions for pain in full-term infants is needed, there is no evidence for adverse infant outcomes associated with breast-feeding. With the exception of the rare risk of transmitting microorganisms from mother to infant,³⁷ breast-feeding has been associated only with optimizing infant and maternal outcomes, including improved immunological function,¹⁰⁵ improved developmental outcomes,¹⁰⁶ reduction in obesity risk^{107,108} and reduced risk of diabetes,^{107,109,110} celiac disease,¹¹¹ and inflammatory bowel disease¹¹² in infants, as well as reduced risk of breast and ovarian cancers¹¹³ in mothers.

Recommendations for clinical practice

Given that direct breast-feeding has demonstrated efficacy that is equal to, or greater than, sweet taste interventions in reducing behavioral and physiological responses to pain in full-term infants undergoing heel lance, intramuscular injection, and venipuncture (in addition to numerous additional health outcomes in a nonpain context and no demonstrated adverse outcomes), direct breast-feeding should be considered the preferred first-line analgesic intervention for painful procedures performed on full-term infants. Therefore, targeted education and supports should be directed toward both clinicians and parents to facilitate the utilization of direct breast-feeding as an analgesic intervention for full-term infants during painful procedures.

In contrast, there is limited evidence to support that expressed breast milk should be used as a sole analgesic intervention in full-term infants undergoing painful pro-

cedures. For preterm infants who do not have demonstrated maturity to feed directly at the breast, provision of expressed breast milk for pain reduction should not be utilized as the sole pain-relieving intervention, given the limited evidence for its efficacy. Rather, use of maternal infant skin-to-skin⁹⁹ contact and/or 24% oral sucrose⁹⁵ that have demonstrated efficacy in the preterm population should be utilized.

Recommendations for future research

While the majority of studies comparing these interventions reported that breast-feeding was significantly more analgesic than sweet taste,^{73,84,114} these studies predominantly had high risk of bias. In one study with a low risk of bias, breast-feeding and higher concentrations of sweet-tasting solutions (eg, 25% dextrose⁷²) demonstrated similar efficacy in reducing behavioral responses to pain. Furthermore, studies reporting on the ability of these interventions to reduce pain response in the infant brain—and thus act as true analgesic interventions—are limited. One study reporting on the use of 24% sucrose to reduce pain-specific event-related potentials in the neonate brain demonstrated that while sucrose significantly reduced biobehavioral pain response measured using the PIPP, its effects in the brain did not differ from placebo.¹¹⁵ This would suggest that the effects of sucrose may be sedative in nature, rather than analgesic—a hypothesis that is supported by the limited ability of sucrose to prevent hyperalgesia from developing in infants who are exposed to repeated acute procedures in early life in one study.³³ Given the multimodal nature of breast-feeding analgesia, it is reasonable to hypothesize that breast-feeding may demonstrate superior effects to sweet taste in reducing pain response in the infant brain. However, while one study has examined the influence of breast-feeding on a brain-based measure (i.e., near infrared spectroscopy) during a painful procedure,⁷¹ the activation demonstrated could not be isolated as pain specific. Therefore, rigorous randomized controlled trials examining the influence of breast-feeding on sensitive and specific brain-based indicators of pain, in addition to behavioral pain indicators, are needed.

Only 1 study in this review reported on the use of direct breast-feeding for pain relief in preterm infants and found no effect.⁹⁰ However, the findings of this study suggested that breast-feeding maturity (such as longer sucking bursts and more active rooting reflexes) may contribute to the analgesic efficacy of breast-feeding and should be considered when determining whether direct breast-feeding is an appropriate intervention for preterm infants undergoing painful procedures. Future research aimed at identifying at what point breast-feeding maturity is sufficient to offer analgesia

to preterm infants is thus warranted. Furthermore, while studies reporting on the use of expressed breast milk demonstrate limited efficacy, future research to determine whether there is a dose-dependent effect of expressed breast milk as well as the potential benefit of using expressed breast milk as an adjuvant intervention (eg, combined with SSC) in preterm infants is needed to inform its use in research and clinical practice.

Strengths and limitations

A strength of the present systematic review is that it followed the acceptable standards for the completion and reporting of a systematic review of the literature.⁶⁵ A limitation of this work is that, because of resource constraints, only 1 reviewer (B.B.) completed risk of bias scoring and level 1 and 2 screening for eligible studies, with the final sample of included studies being verified by a study coinvestigator (M.C.Y.). Although unlikely given the explicit inclusion criteria, not employing 2 independent reviewers in the screening process may have reduced the number of eligible studies that were identified for inclusion.¹¹⁶

CONCLUSION

The use of breast-feeding and expressed breast milk for pain relief in infants undergoing acute procedures is increasingly being examined in the literature. While there is limited evidence to support the use of these interventions in preterm infants, the available literature supports that breast-feeding is as or more effective than sweet-tasting solutions such as 24% oral sucrose. Future research examining the influence of breast-feeding on brain-based indicators of pain, as well as the influence of breast-feeding maturity and expressed breast milk dose on pain-reducing effects in preterm infants, is needed to support understanding of the mechanisms of efficacy and recommendations regarding utilization in clinical care. However, based on the evidence supporting the benefits of direct breast-feeding in both pain and nonpain contexts, it should currently be supported as a first-line intervention in full-term infants undergoing heel lance, venipuncture, and intramuscular injections.

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