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# Breastfeeding or Breastmilk to Alleviate Procedural Pain in Neonates: A Systematic Review

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## ABSTRACT

*Objectives*: **To (1) compare breastfeeding with control (placebo, no treatment, sucrose, glucose, pacifiers, or positioning) and (2) compare breastmilk with control for procedural pain in neonates.**

*Methods*: **Systematic review and meta-analyses of randomized and quasi-randomized trials of breastfeeding or supplemental breastmilk for procedural pain in neonates was carried out on studies identified from electronic databases and hand searches without language restrictions. The methodological quality of the trials was assessed according to the Neonatal Review Group of Cochrane Collaboration.**

*Results*: **Eleven eligible studies were identified. Marked heterogeneity in control intervention and pain assessment measures was noted. The breastfeeding group had significantly less increase in the heart rate, reduced proportion of crying time and reduced duration of crying compared to the swaddled or pacifier group. Premature Infant Pain Profile scores were lower in the breastfeeding group when compared to the placebo and the group positioned in mother's arms, but were not different compared to the no-treatment and the glucose groups. Neonates in the supplemental breastmilk group had a significantly less increase in the heart rate and Neonatal Facial Coding Score but no significant difference in the duration of crying time and oxygen saturation change compared to the placebo.**

*Conclusions*: **If available, breastfeeding or breastmilk should be used to alleviate pain in neonates undergoing painful procedure compared to placebo, positioning, or no intervention. Administration of glucose/sucrose had a similar effectiveness as breastfeeding for reducing pain. The effectiveness of breastmilk for repeated painful procedures is not established, and further research is needed.**

## INTRODUCTION

EVALUATION AND TREATMENT OF pain in neonates is difficult due to the subjective nature of pain and the inability of neonates to verbally express pain. Surrogate measures used to describe pain in neonates include motor responses,[1] facial expressions,[2,3] cry[2,4] and changes in physiologic parameters. These measures have been compiled to create various scores.[5] Validated scores for the assessment of pain include the Neonatal Facial Coding System (NFCS),[1] the Neonatal Infant Pain Scale (NIPS),[6] or the Premature Infant Pain Profile (PIPP).[7] Pain may contribute to the development of hypoxia, hypercarbia, acidosis, venti-

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lator asynchrony, pneumothoraces, reperfusion injury and venous congestion, and subsequent late intraventricular hemorrhage or late extension of early intraventricular hemorrhage and periventricular leukomalacia.[8,9] Pain may also disrupt adaptation, bonding, and feeding.

Clinical studies have shown beneficial effects of preemptive analgesic administration.[10] Pharmacological interventions include acetaminophen, sucrose, and opioid analgesics. Nonpharmacological interventions include reduction of noxious stimuli,[11] neurobehaviorally supportive relationship-based care,[12,13] limitation of the number of painful procedures,[14] and breastfeeding during the procedure.

Sucrose was found to be effective in alleviating procedural pain in neonates.[15] However, concerns regarding hyperosmolality, effects on neurodevelopment, and feeding remains. On the contrary, natural, easily available, potentially nontoxic alternative of breastfeeding needs consideration. Breastmilk contains only 7% lactose and may not be as effective, and it may interfere with the regular breastfeeding schedule.

## MATERIALS AND METHODS

### *Objectives*

Our primary objectives were to (1) compare breastfeeding with control (placebo, no treatment, sucrose, glucose, pacifiers or positioning) and (2) compare breastmilk with control (placebo, no treatment, sucrose, glucose, pacifiers, or positioning) for analgesia in neonates. Our secondary objective was to conduct subgroup analyses within each comparison according to (1) types of control intervention: placebo, no treatment, sucrose, glucose, pacifiers, and positioning, (2) type of painful procedure: heel lance and venepuncture, and (3) gestational age: preterm (<37 weeks) and full term (≥37 weeks).

### *Data sources*

MEDLINE (1966–August 2006); EMBASE (1980–August 2006); CINAHL (1982–August 2006); The Cochrane Library (Issue 3, 2006); abstracts of the annual meetings of the Pediatric Academic Societies and the European Society of Pediatric Research (2001–2006); and bibliographies of identified articles were searched (August 2006). When information was not available the primary authors were contacted to obtain additional information or for clarification. No language restrictions were applied (see Appendix).

### *Study selection*

We included randomized or quasi-randomized controlled trials of breastfeeding or supplemental breastmilk to alleviate procedural pain in both term (≥37 completed weeks postmenstrual age) and preterm neonates (<37 completed weeks postmenstrual age) up to maximum of 44 weeks postmenstrual age undergoing heel lance or venepuncture for diagnostic and/or therapeutic procedures. Both breastfeeding and supplemental breastmilk were compared with either placebo or no treatment or sucrose or glucose or pacifiers or positioning.

### *Data extraction*

Identified studies were reviewed, and data from eligible studies were abstracted independently by two reviewers (P.S. and L.A.) and compared. Discrepancies were resolved by consensus and involvement of the third author (V.S.). The methodological quality was assessed using the available information. Quality was assessed regarding allocation concealment, method of randomization, and masking of outcome assessment. The intervention could not be masked. A typical effect size was calculated and reported as relative risk (RR), risk difference (RD), and mean difference (MD) as appropriate with a 95% confidence interval (CI). All analyses (fixed effects model) were performed using Revman 4.3.8 software (Cochrane Collaboration). The $I^2$ test of between-study heterogeneity was applied to assess the appropriateness of combining study results.[16] As is traditional with systematic reviews, no statistical corrections were employed to adjust for multiple analyses.

### *Outcomes*

Outcome of interest was pain as assessed by (at least one of the following): (1) physiological parameters (changes in the heart rate, respiratory rate, oxygen saturation, or blood pres-

sure), (2) cry variables (percentage time crying, duration of crying), or (3) pain measures (NIPS[6] or PIPP[7] or NFCS[1] or other pain scores as reported). We were also interested in knowing the effect on subsequent breastfeeding following use of this intervention.

## RESULTS

### *Study description*

Out of the 74 potentially eligible titles, 18 papers were read in detail, 12 were selected as potentially eligible. A total of 11 studies eligible for inclusion were identified (Tables 1 and 2). Five studies evaluated breastfeeding[17–21] and six studies[22–27] evaluated supplemental breastmilk. One report[28] was excluded from the review because it was a duplicate publication.[24] Clinical details regarding the participants, interventions, outcomes, and methodological qualities of the studies are given in the Tables 1 and 2. All studies except Skogsdal et al.[25] (66 preterm neonates between 30 and 37 weeks' gestation) included healthy term neonates.

### *Comparison 1: Breastfeeding versus control*

*Physiological parameters*. The heart rate tended to increase in both groups during the proce-

Table 1. Characteristics and Quality Assessment of Studies of Breastfeeding

| *Characteristics* | | *Carbajal* | *Gradin* | *Gray* | *Phillips* | *Shendurnikar* |
|---|---|---|---|---|---|---|
| Type of study | | RCT | RCT | RCT | RCT | RCT |
| Infants | Birth weight (g) | 3300 + 400 | 2185–4950 | 2390–4300 | N/A | 2865 (mean) |
| | Gestational age (weeks) | Term | 37–42 | 37–42 | Term | 38 (mean) |
| | Male:female | N/A | N/A | N/A | 38:58 | 53:47 |
| Study groups | Group 1 | Breastfeeding | Breastfeeding and 1 mL of sterile water | Breastfed and cuddled with full body contact | Breastfeeding | Breastfeeding |
| | Group 2 | Held in Mother's arms without breastfeeding | Breastfeeding and 1 mL of 30% glucose | Swaddled and placed on their side in the crib | Held by mother holding pacifier in infant's mouth | Swaddled and placed on a cradle |
| | Group 3 | Sterile water without pacifier | Fasting and 1 mL of sterile water | N/A | Held by research assistant holding pacifier in infant's mouth | N/A |
| | Group 4 | 30% glucose followed by a pacifier | Fasting and 1 mL of 30% glucose | N/A | N/A | N/A |
| Masking of randomization | | Yes | Yes | Yes | Yes | Yes |
| Allocation concealment | | Yes | Yes | Yes | Yes | Yes |
| Masking of intervention | | No | Yes | No | No | No |
| Masking of outcome assessment | | Yes<br>Yes | Yes<br>Yes | No<br>Yes | Yes/no<br>Yes | No<br>Yes |
| Completeness of follow-up | | | | | | |
| Outcomes assessment | | Douleur Aigue Nouveau-ne (DAN), PIPP, breastfeeding adequacy | PIPP, Visual Analogue Scale, crying time | Changes in facial grimacing, crying time rate | % of infants cried, cry time, HR, BP and $SaO_2$ change | Behavioral, HR, breathing pattern, Composite score |

RCT, randomized controlled trial; N/A, not applicable; PIPP, Premature Infant Pain Profile; HR, heart rate; BP, blood pressure.

Table 2. Characteristics and Quality Assessment of Studies of Supplemental Breastmilk

| *Characteristics* | | *Blass* | *Bucher* | *Ors* | *Skogsdal* | *Upadhyay* | *Uyan* |
|---|---|---|---|---|---|---|---|
| Type of study | | Quasi RCT | RCT | RCT | RCT | RCT | Quasi RCT |
| Infants | Birth weight (g) | 2400–4200 | 2640–5000 | 2390–4300 | N/A | 2000–3500 | 2750–4500 |
| | Gestational age (weeks) | Term | Term | 37–42 | 66 term and 54 preterm | 36–40 | 38–41 |
| | Male:female | 27:33 | 37:43 | N/A | N/A | N/A | N/A |
| Study groups | Group 1 | 2 mL water via syringe | 2 mL of artificial sweetener via syringe | 2 mL of 25% sucrose | No intervention | Received 5 mL of expressed breastmilk | Received 2 mL of foremilk |
| | Group 2 | 2 mL colostrum via syringe | 2 mL of glycine via syringe | 2 mL of human milk | 1 mL of 30% glucose via syringe | Received 5 mL of distilled water | Received 2 mL of hindmilk |
| | Group 3 | 2 mL sucrose via syringe | 2 mL of breastmilk via syringe | N/A | 1 mL of 10% glucose via syringe | N/A | Received 2 mL of sterile water |
| | Group 4 | 2 mL water on a pacifier | 2 mL of sterile water via syringe | N/A | 1 mL of breast milk via syringe | N/A | N/A |
| | Group 5 | 2 mL colostrum on a pacifier | N/A | N/A | N/A | N/A | N/A |
| | Group 6 | 2 mL sucrose on a pacifier | N/A | N/A | N/A | N/A | N/A |
| Masking of randomization | | Can't tell | Yes | Can't tell | Yes | Yes | No |
| Allocation concealment | | Inadequate | Yes | Can't tell | Yes | Yes | Can't tell |
| Masking of intervention | | No | Yes | Can't tell | Yes | Yes | Yes |
| Masking of outcome assessment | | No | Yes | Yes | Yes | Yes | Yes |
| Completeness of follow-up | | Yes | Yes | Yes | Yes | Can't tell | Yes |
| Outcomes assessment | | % crying time, crying time, HR | HR change, % crying time, combined pain score | HR change and median crying time | Crying time HR change | Crying time, NFCS, HR, and $SaO_2$ change | Crying time, change in HR, NFCS |

RCT, randomized controlled trial; N/A, not applicable; PIPP, Premature Infant Pain Profile; NFCS, Neonatal Facial Coding System; HR, heart rate.

dure, but the increase was significantly lower in the breastfeeding group compared to the swaddled group[19] (MD −23; 95% CI −35 to −11) and the breastfeeding group and group of infants held by the mother holding a pacifier in the infant's mouth[20] (MD −11; 95% CI −21 to −1). There was a trend toward reduced change in heart rate (MD −7; 95% CI −15, 1) between the breastfeeding group and the group of infants held by the research assistant along with the use of a pacifier.[20] There was no difference in oxygen saturation change (MD 0.3; 95% CI −2.8, 3.4) or blood pressure change (MD −3.6; 95% CI −9.1, 1.9) between the breastfeeding group and the group of infants held by the mother holding a pacifier in the infant's mouth.[20] There was no difference in oxygen saturation change (MD 0.6; 95% CI −1.5, 2.7) or blood pressure change (MD 1.6; 95% CI −4.9, 8.1) between the breastfeeding group and the group of infants held by the research assistant holding a pacifier in the infant's mouth.[20]

*Cry variables*. There was statistically significant reduction in the percentage of time crying in the breastfeeding group compared to the swaddled group (MD −39; 95% CI −55 to

−23)[19] and compared to the group of infants held by the research assistant with a pacifier (MD −33; 95% CI −50, −13).[20] There was no statistically significant reduction in the percentage time crying between the breastfeeding group and the group of infants held by mothers with a pacifier (MD −12; 95% CI −28, 4).[20] Infants in the breastfeeding group compared to the fasting group had a significant reduction in the duration of crying (MD −50; 95% CI −79 to −22 seconds).[18] There was no statistically significant difference in the duration of crying (MD −5; 95% CI −37 to 26 seconds) for infants in the breastfeeding group compared to the glucose group.[18] Infants in the breastfeeding group compared to the swaddled group had a reduced duration of crying (MD −63; 95% CI −75 to −52 seconds).[19] Phillips et al.[20] reported crying during the procedure in 69% of infants in the breastfeeding group, 81% in the group held by the mothers with pacifier, and 100% in infants held by a research assistant with a pacifier ($p < 0.01$).

*Pain scales*. The PIPP scores in the breastfeeding group were significantly lower compared to the placebo group (MD −6; 95% CI −7 to −4) or the positioning in mother's arms group (MD −7; 95% CI −9 to −6).[17] The PIPP score between the breastfeeding and no-treatment group was not statistically significantly different (MD 0; 95% CI −2 to 1).[18] The PIPP score was statistically significantly higher in the breastfeeding group compared to the glucose group (MD 1.30; 95% CI 0.05 to 2.56).[17,18] The Douleur Aigue Nouveau-né (DAN) scores in the breastfeeding group compared to the placebo (MD −6; 95% CI −7 to −5) and breastfeeding groups compared to positioning in the mother's arms group (MD −7; 95% CI −8 to −6) were statistically significantly lower.[17] The DAN score between the breastfeeding group and the glucose group was not statistically significantly different (MD −0.8; 95% CI −2.0 to 0.5).[17] Shendurnikar et al.[21] reported a statistically significant decrease in the composite score (calculated based on heart rate, breathing pattern, facial expression, body movements, state of arousal, and crying) in the breastfeeding group compared to the swaddled group (MD −3; 95% CI −4, −2).

*Comparison 2: Supplemental breastmilk versus control*

*Physiological parameters*. There was no statistically significant difference in the heart rate change between the supplemental breastmilk group and the placebo (weighted MD −4; 95% CI −9 to 1 bpm; $p = 0.08$, $I^2 = 78\%$);[23,24,26,27] no treatment (MD −5; 95% CI −12 to 2 bpm; $p = 0.17$);[25] the 10% glucose (MD 3; 95% CI −5 to 11 bpm; $p = 0.50$);[25] the artificial sweetener (MD 8; 95% CI 0 to 16 bpm; $p = 0.05$),[23] and glycine (MD 4; 95% CI −3 to 11 bpm; $p = 0.25$).[23] Significant statistical heterogeneity[16] was identified when pooling data from breastmilk versus placebo studies ($I^2 = 78\%$; $p = 0.0004$), which is concordant with clinical heterogeneity observed between studies (different population and variable dose of breastmilk). Blass et al.[22] reported mean heart rate changes in the group given colostrum via a pacifier, and the groups given sucrose either via syringe or a pacifier were significantly less than the group given water, either by syringe or pacifier, and the group given colostrum via a syringe.[22] Ors et al.[24] reported a significantly higher increase in the heart rate change in the supplemental breastmilk group compared to 25% sucrose (MD 14; 95% CI 4 to 23). Skogsdal et al.[25] reported a significantly higher increase in heart rate change in supplemental breastmilk group compared to 30% glucose (MD 7; 95% CI 1, 13). There was no statistically significant difference in the change in oxygen saturation at 3 minutes (MD 0; 95% CI −2 to 2) in infants in the supplemental breastmilk group compared to the placebo.[26]

*Cry variables*. Blass et al.[22] reported a statistically significant reduction in the proportion of time crying in the group given sucrose (via syringe or pacifier) compared to the control and colostrum (via syringe or pacifier) ($p < 0.0015$), but not between the colostrum and the control. Bucher et al.[23] reported a statistically significant reduction in the percentage of time crying in the artificial sweetener group compared to the supplemental breastmilk (MD 15; 95% CI 2 to 28), but no statistically significant reduction between the supplemental breastmilk group and the placebo (MD 9; 95% CI 2 to 20) and the

glycine (MD 1; 95% CI −5 to 7). Blass et al.[22] reported a reduction in crying time; however, the data was not in a format that could be abstracted. Upadhyay et al.[26] reported a statistically significant reduction in the duration of crying among infants fed breastmilk compared to the placebo (71 seconds; 95% CI 37 to 105 seconds).[26] Combining the data from four studies[23–25,27] revealed no statistically significant difference in the duration of crying between the supplemental milk and the placebo (weighted MD −6; 95% CI −16 to 3 seconds). There was a statistically significant increase in the duration of crying in the supplemental breastmilk group compared to the 25% glucose (MD 33; 95% CI 12 to 54 seconds).[24] There was no statistically significant reduction in the duration of crying between the supplemental breastmilk and the 30% glucose (MD 13; 95% CI −3 to 29 seconds),[25] 10% glucose (MD 4; 95% CI −15 to 23 seconds),[25] and artificial sweetener (MD 41; 95% CI −7 to 89 seconds).[23] There was a statistically significant reduction in the duration of crying in the glycine compared to the supplemental breastmilk (MD 52; 95% CI 6 to 97 seconds).[23]

*Pain scales*. Bucher et al.[23] used five components of NFCS, and Upadhyay et al.[26] modified the score and collected data on only part of the components. Bucher et al.[23] reported no statistically significant difference between the supplemental breastmilk and the placebo (MD −0.09; 95% CI −0.58, 0.40). Upadhyay et al.[26] reported statistically significant reduction in the NFCS in the supplemental breastmilk compared to placebo (MD −2.0; 95% CI −2.8 to −1.2). Uyan et al.[27] reported no statistically significant difference between the supplemental breastmilk and placebo (MD −0.46; 95% CI −2.05, 1.13). There was marked heterogeneity in the data collection for NFCS. The data were not combined statistically due to this marked clinical heterogeneity. Bucher et al.[23] reported no statistically significant reduction in NFCS between supplemental breastmilk and artificial sweetener (MD −0.2; 95% CI −0.7 to 0.2) but a statistically significant reduction in NFCS in the supplemental breastmilk compared to glycine (MD −0.47; 95% CI −0.90 to −0.04). Bucher et al.[23] reported no statistically significant reduction in body pain score between the supplemental breastmilk and the placebo (MD 0.5; 95% CI −0.4 to 1.3), artificial sweetener (MD 0.2; 95% CI −0.7 to 1.0), and glycine (MD 0.4; 95% CI −0.5 to 1.4).

*Secondary outcome*

Carbajal et al.[17] reported that infants who underwent venepuncture while they were being breastfed did not suck less effectively after the procedure.

*Subgroup analyses*

Planned subgroup analyses according to gestational age groups were not performed in this version of the review because, with the exception of one study,[25] all other studies included only term infants. Other planned subgroup analyses according to type of intervention and type of procedure were not performed because there were not enough studies in each subgroup at this stage.

## DISCUSSION

All studies evaluated in this review assessed the effects of breastfeeding or supplemental breastmilk on a single painful procedure only. Breastfeeding was associated with reduction in changes in the heart rate change, duration of crying, percentage time crying, and improvement in validated and nonvalidated pain measures when compared to placebo/no intervention/positioning in neonates. Breastfeeding was not advantageous when compared to higher concentrations of glucose/sucrose (equally effective) for duration of crying, PIPP score, and DAN score. Supplemental breastmilk yielded variable results. Based on the available results of these studies we can conclude that neonates undergoing a single painful procedure should be provided either breastfeeding or supplemental breastmilk for analgesia compared to no intervention, positioning/pacifier/holding, and swaddling. If it is not available/feasible to give breastfeeding or supplemental breastmilk, alternatives such as glucose or sucrose should be considered. It appears that none of these agents completely

eliminate the pain. However, provision of breastfeeding or supplemental breastmilk for painful procedures may further encourage mothers to breastfeed their infants, facilitate bonding, and provide psychological advantage without any additional cost to the healthcare system.

There are several potential mechanisms of actions of breastmilk or breastfeeding. Components of breastfeeding that may be analgesic include presence of a comforting person (mother),[29] physical sensation (skin-to-skin contact with comforting person),[29] diversion of attention,[13] and sweetness (presence of lactose or other ingredients).[30] Compared to artificial formulas, breastmilk contains a higher concentration of tryptophan,[31] a precursor of melatonin which increases the concentration of beta endorphins.[32] Preterm neonates incapable of direct breastfeeding from the mother may benefit from placement of breastmilk on the tongue or administering breastmilk via the naso/orogastric route (supplemental breastmilk) through some of the mechanisms listed above. Among the analgesics studied for neonatal pain, breastfeeding/breastmilk is a natural, easily available, easy to use, and potentially risk free[33] intervention that could be easily adopted from the perspectives of healthcare providers and parents. No adverse effects of breastfeeding apart from rare transmission of microorganisms have been reported.

For preterm and sick full-term neonates who are subjected to repeated painful procedures during hospitalization, the ideal analgesic has not yet been identified. Johnston et al.[34] evaluated effects of repeated administration of sucrose prior to painful procedures in infants <31 weeks postconceptional age. Use of sucrose was associated with reduced scores on motor development, vigor, alertness, and orientation at 36 weeks; affected motor development and vigor at 40 weeks and higher Neurobiological Risk Score at 2 weeks postnatal age. Although unproven, breastmilk may be an effective and safe alternative to sucrose, even for repeated use. Placing small amount of solution in the oral cavity of small preterm infants was only associated with minor complication such as transient desaturation or transient choking, which did not require any intervention.[35] As breastmilk is the most natural/physiological substance available for oral stimulation, repeated exposure is not perceived to be associated with complications of oral aversion or repeated tongue thrusting. However, this needs to be studied.

Several methodological challenges were apparent during this review. First, assessment of pain varied between studies. This has been a problem encountered in previous review of sucrose for procedural pain in neonates.[15] Use of only validated pain scales should be the framework of further research. Second, studies should include preterm or term neonates who require repeated painful stimuli to assess side effects of repeated oral administration of breastmilk. Additionally, it should also measure the future success of breastfeeding as an outcome, as repeated conditioning may prime infant to refuse breastfeeding at a later stage. This is an important consideration, particularly for preterm neonates. Only one study[17] that evaluated maternal perception regarding sucking after single venepuncture while breastfeeding found no changes; however, effect of repeated exposure is not studied. Third, there was marked heterogeneity between studies in terms of control intervention, amount/time of prior exposure to breastfeeding or breastmilk, time interval between this exposure, and type of painful procedure.

In conclusion, if available, breastfeeding or breastmilk should be used to alleviate procedural pain in neonates undergoing a single painful procedure compared to placebo or positioning or no intervention. When repeated painful procedures are needed, the safety or effectiveness of breastfeeding or supplemental breastmilk is not established. Further randomized controlled studies are needed to assess the efficacy and effectiveness of breastfeeding and breastmilk for repeated painful procedures in neonates, especially preterm neonates.

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P.S. developed the search strategy, identified trials, assessed the methodological quality of studies, extracted data, carried out the statistical analyses, and drafted parts of the review. L.A. wrote the initial protocol, extracted data, validated the assessment of methodological quality of studies. V.S. checked the data, edited, and revised the protocol and review, and functioned as an adjudicator in cases of disagreement. P.S. is the guarantor.

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## APPENDIX. SEARCH STRATEGY

MEDLINE (1966—August 2006) was searched using following terms with all of the subheadings connected by "and":
Population: Infant-Newborn (MeSH) OR Infant-premature (MeSH) OR Infant, Low Birth Weight (MeSH) OR Infant, Very Low Birth Weight (MeSH) OR Infant, Small for Gestational Age (MeSH) OR Infant, Premature, Disease (MeSH) OR Infant, Newborn, Diseases (MeSH) OR newborn (text word) OR infant (text word) OR neonate (text word)
Intervention: Breast (MeSH) OR Breast Feeding (MeSH) OR Milk, Human (MeSH) OR Breastmilk (MeSH) OR Human, Milk (MeSH)
Comparison: Clinical trials (MeSH) OR Controlled Clinical Trials (MeSH) OR Randomized Controlled Trials (MeSH) OR Random Allocation (MeSH) OR Multicenter studies (MeSH) OR Control groups (MeSH) OR Evaluation studies (MeSH)
Outcome: Pain (MeSH) OR Pain Measures (MeSH) OR Pain measurement (MeSH)

Other databases that were searched include: EMBASE (1980–August 2006); CINAHL (1982–August 2006); the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2005) and the reference lists of identified trials, abstracts from the annual meetings of the Society for Pediatric Research, American Pediatric Society and Pediatric Academic Societies published in Pediatric Research (1994–2006), and major pediatric pain conference proceedings. Reference lists of the identified articles were searched. No language restrictions were applied.

The following types of articles were excluded: letters (which do not contain original data), editorials, reviews, lectures, and commentaries.