Breastfeeding or breast milk for procedural pain in neonates (Review)

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[Intervention Review]

Breastfeeding or breast milk for procedural pain in neonates

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ABSTRACT

Background

Physiological changes brought about by pain may contribute to the development of morbidity in neonates. Clinical studies have shown reduction in the changes in physiological parameters and pain score measurements following pre-emptive analgesic administration in situations where the neonate is experiencing pain or stress. Nonpharmacological measures (such as holding, swaddling, breastfeeding) and pharmacological measures (such as acetaminophen, sucrose and opioids) have been used for this purpose.

Objectives

The primary objective of this review was to evaluate the effectiveness of breastfeeding or supplemental breast milk in reducing procedural pain in neonates. The secondary objective was to conduct subgroup analyses based on the type of control intervention, type of painful procedure, gestational age and the amount of supplemental breast milk given.

Search methods

A literature search was performed using MEDLINE (1966 - Feb 2006), EMBASE (1980 - Feb 2006), CINAHL (1982 - Feb 2006), Cochrane Central Register of Controlled Trials (Issue 4, 2005 of Cochrane Library), abstracts from the annual meetings of the Society for Pediatric Research (1994 - 2006) and major pediatric pain conference proceedings. No language restrictions were applied.

Selection criteria

Randomized or quasi-randomized controlled trials of breastfeeding or supplemental breast milk versus no treatment/other measures in neonates were eligible for inclusion in this review. The study must have reported on either physiologic markers of pain or validated pain scores.

Data collection and analysis

The methodological quality of the trials was assessed using the information provided in the studies and by personal communication with the authors. Data on relevant outcomes were extracted and the effect size was estimated and reported as relative risk (RR), risk difference (RD) and weighted mean difference (MD) as appropriate.

Main results

Eleven eligible studies were identified. Marked heterogeneity in terms of control intervention and pain assessment measures were noted among the studies. Neonates in the breastfeeding group had statistically significantly less increase in the heart rate, reduced proportion of crying time and reduced duration of crying compared to swaddled group or pacifier group. Neonates in the breastfeeding group had a significant reduction in duration of crying compared to fasting (no intervention) group, but there was no significant difference when compared to glucose group. Premature Infant Pain Profile scores were significantly different between the breastfeeding group when compared to placebo group and the group positioned in mother's arms. However, these scores were not statistically significantly different in the breastfeeding group when compared to the no treatment group and the glucose group. Douleur Aigue Nouveau-ne scores were significantly different in the breastfeeding group when compared to the placebo group and the group positioned in mother's arms, but not when compared to the glucose group. Neonates in the supplemental breast milk group had significantly less increase in the heart rate and Neonatal Facial Coding Score compared to the placebo group. The differences in the duration of crying time and oxygen saturation change between supplemental breast milk group and the placebo group were not statistically significant. Neonates in the supplemental breast milk group had significantly higher increase in the heart rate changes and duration of crying time compared to glucose/sucrose group. No study was identified that has evaluated safety/effectiveness of repeated administration of breastfeeding or supplemental breast milk for pain relief.

Authors' conclusions

If available, breastfeeding or breast milk should be used to alleviate procedural pain in neonates undergoing a single painful procedure compared to placebo, positioning or no intervention. Administration of glucose/sucrose had similar effectiveness as breastfeeding for reducing pain. The effectiveness of breast milk for repeated painful procedures is not established and further research is needed. These studies should include various control interventions including glucose/ sucrose and should target preterm neonates.

PLAIN LANGUAGE SUMMARY

Breastfeeding or breast milk for procedural pain in neonates

Plain language summary will be included with future update.

BACKGROUND

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (AAP 2000). Evaluation 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 (Marshall 1980; Craig 1993), facial expressions (Grunau 1987; Stevens 1993), cry (Johnston 1993; Grunau 1987) and changes in physiologic parameters like heart rate, blood pressure, oxygen saturation and respiratory rate. Various changes have been compiled to create various scores (Abu-Saad 1998). Validated scores for the assessment of pain include Neonatal Facial Coding System (Craig 1994), Neonatal Infant Pain Scale (Lawrence 1993) or Premature Infant Pain Profile (Stevens 1996). These reactions to pain may contribute to the development of hypoxia, hypercarbia, acidosis, ventilator asynchrony, pneumothoraces, reperfusion injury and venous congestion and subsequent late intraventricular hemorrhage (IVH) or late extension of early intraventricular hemorrhage and periventricular leukomalacia (Abdel-Rahman 1994; Anand 1998). These behavioral changes may also disrupt postnatal adaptation, parent-infant bonding and feeding schedules.

Clinical studies have shown beneficial effects of pre-emptive analgesic administration in decreasing neonatal pain and stress (Anand 1989). Pharmacological interventions include acetaminophen, sucrose and opioid analgesics. Nonpharmacological interventions include reduction of noxious stimuli (Schechter 1997), implementation of neurobehaviorally supportive relationship-based care (Corff 1995; Gunnar 1984), limitation of the number of painful procedures (Anand 2001) and breastfeeding during the actual procedure.

There are several potential mechanisms by which breast milk or breast feeding might provide an analgesic effect. Components of breast feeding that may be analgesic include presence of a com-

forting person (mother) (Blass 1995), physical sensation (skin to skin contact with comforting person) (Blass 1995), diversion of attention (Gunnar 1984) and sweetness of breast milk (presence of lactose or other ingredients present in the breast milk) (Blass 1997). Compared to artificial formulas, breast milk contains a higher concentration of tryptophan (Heine 1999), a precursor of melatonin. Melatonin is shown to increase the concentration of beta endorphins (Barrett 2000) and could possibly be one of the mechanisms for the nociceptive effects of breast milk. Preterm neonates incapable of direct breastfeeding from the mother may benefit from placement of breast milk on the tongue or administering breast milk via the naso/orogastric route (supplemental breast milk) through some of the mechanisms listed above. Among the analgesics studied for neonatal pain, breastfeeding/breast milk is a natural, easily available, easy to use and potentially risk free (Schollin 2004) intervention. It is an intervention that could be easily adopted from the perspectives of health care providers and parents. No adverse effects of breastfeeding apart from rare transmission of micro-organisms have been reported.

In a systematic review, 24% sucrose was found to be effective in alleviating procedural pain in neonates (Stevens 2004). Both opioid and non-opioid mechanisms were suggested for its effectiveness. Breast milk contains only 7% lactose and may not be as effective as sucrose. On the other hand, interventions like pacifiers or positioning may result in an effect similar to breastfeeding or supplemental breast milk without interruption of the regular breastfeeding schedule.

To our knowledge, the topic of breastfeeding or breast milk for procedural pain in neonates has not been systematically evaluated.

OBJECTIVES

The overall objective was to evaluate the effect of breastfeeding or supplemental breast milk on procedural pain in neonates as assessed by physiologic (heart rate, respiratory rate, oxygen saturation and blood pressure) and/or behavioural (cry duration, proportion time crying, facial actions) pain indicators and/or validated composite pain scores.

Specific objectives were:

Primary

1. Compare breastfeeding with control (placebo, no treatment, sucrose, glucose, pacifiers or positioning)

2. Compare breast milk with control (placebo, no treatment, sucrose, glucose, pacifiers or positioning)

Secondary

Within each comparison, to conduct subgroup analyses according to:

1. Types of control intervention: placebo, no treatment, sucrose, glucose, pacifiers and positioning

2. Type of painful procedure: heel lance and venepuncture

3. Gestational age: preterm (< 37 weeks) and full term (≥ 37 weeks)

Within the group of supplemental breast milk, subgroup analysis based on the amount of breast milk was planned to be carried out if data were available.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials of breastfeeding/supplemental breast milk (given via naso/orogastric tube or orally) to alleviate procedural pain in neonates.

Types of participants

Both term (≥ 37 completed weeks postmenstrual age) and preterm infants (< 37 completed weeks postmenstrual age) up to maximum of 44 weeks postmenstrual age undergoing heel lance or venepuncture for diagnostic and/or therapeutic procedures. Studies which have included both completely breastfed and partially breastfed infants were planned to be included for review.

Types of interventions

Breastfeeding or supplemental breast milk (breast milk placed on the tongue or given through naso/oro gastric tube) prior to or during the painful procedure versus placebo or no treatment or sucrose or glucose or pacifiers or positioning.

Types of outcome measures

Primary outcome

Pain as assessed by (at least one of the following):
1. Physiological parameters:
a. Changes in the heart rate
b. Changes in the respiratory rate
c. Changes in the oxygen saturation
d. Changes in the blood pressure
2. Cry variables:
a. Percentage time crying
b. Duration of crying (in seconds)
3. Validated pain measures:

a. Neonatal Infant Pain Score (Lawrence 1993)
b. Premature Infant Pain Profile (PIPP score) (Stevens 1996)
c. Neonatal Facial Coding System (NFCS) (Craig 1994)
d. Other pain scores as reported: We identified during this review that other non-validated scores such as Douleur Aigue Nouveauné score (DAN) (Carbajal 2003); composite score (Shendurnikar 2005), body pain score (Bucher 2000) and visual analogue scale (VAS) (Gradin 2004) were reported by authors and have been reported in this review.

Secondary outcomes

1. Any clinically important outcome reported by authors (not prespecified)
2. Any harmful effects reported by any author

Search methods for identification of studies

MEDLINE (1966 - Feb 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 Breast Milk (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 - Feb 2006); CINAHL (1982 - Feb 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.

Data collection and analysis

All published articles identified as potentially relevant by the literature search were assessed for inclusion in the review by LA and PS. Data from the authors were obtained where published data provided inadequate information for the review or where relevant data could not be abstracted. Retrieved articles were assessed and data were abstracted independently by LA and PS (VS rechecked when there was discrepancy). Discrepancy regarding inclusion/exclusion of the studies were resolved by consensus.
Quality of included trials was evaluated independently by all review authors using the following criteria:
1. Masking of randomization
2. Masking of intervention
3. Completeness of followup
4. Masking of outcome assessment

There were three potential answers to these questions - yes, no and can't tell.
The data were compared for the outcomes outlined in the previous section as follows (planned primary and subgroup analyses):
Comparison 1: ***Breastfeeding vs. control*** *(The infant must be actually feeding from the breast at the time of intervention)*
Category 1: Type of control intervention
Subgroups: A. Breastfeeding vs. placebo, B. Breastfeeding vs. no treatment, C. Breastfeeding vs. sucrose or glucose, D. Breastfeeding vs. pacifiers E. Breastfeeding vs. positioning
Category 2: Type of procedure
Subgroups: 1. Heel lance 2. Venepuncture
Category 3: Gestational age
Subgroups 1: Preterm (< 37 weeks gestational age) 2. Term (≥ 37 weeks gestation age)
Comparison 2: ***Supplemental breast milk vs. control*** *(The infant may be receiving breast milk via oral or nasogastric tube in the intervention group)*
Category 1: Type of control intervention
Subgroups: A. Supplemental breast milk vs. placebo, B. Supplemental breast milk vs. no treatment, C. Supplemental breast milk vs. sucrose or glucose, D. Supplemental breast milk vs. pacifiers E. Supplemental breast milk vs. positioning
Category 2: Type of procedure
Subgroups: 1. Heel lance 2. Venepuncture
Category 3: Gestational age
Subgroups 1. Preterm (< 37 weeks gestational age) 2. Term (≥ 37 weeks gestation age)
RevMan 4.2 was used for statistical analysis. Statistical parameters included relative risk (RR), risk difference (RD), number needed to treat (NNT), number needed to harm (NNH) and weighted mean difference (WMD) when appropriate. Ninety-five percent confidence intervals (CI) were reported for estimates of treatment effects. A fixed effect model was used for meta-analyses. Tests for between study heterogeneity including the I^2 test was applied to assess the appropriateness of combining studies.
Post-hoc subgroups for comparison were added when it was identified that comparison of breastfeeding or supplemental breast milk have been reported with artificial sweetener and glycine.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

A total of eleven studies eligible for inclusion were identified. Five studies evaluated breastfeeding and six studies evaluated supplemental breast milk. Clinical details regarding the participants, interventions and outcomes are given in the table "Characteristics of Included Studies". One report Bilgen 2001 was excluded from the review because it is a duplicate publication of the same data reported by Ors 1999.

Blass 2001 compared the effects of supplemental breast milk (colostrum) to water and sucrose. This was a quasi-randomized controlled trial of 60 full-term infants. The infants were randomly assigned to one of the following groups (10 neonates in each group):

Group 1: water via syringe;
Group 2: colostrum via syringe;
Group 3: sucrose via syringe;
Group 4: water on a pacifier;
Group 5: colostrum on a pacifier and Group 6: sucrose on a pacifier.

The infants were between 30 - 55 hrs of age at the time of blood collection for routine neonatal screening using the heel lance procedure. Two ml of the allocated solution was given either by slow administration via syringe over a span of two minutes or by allowing infant to suck a pacifier dipped in the solution every 30 seconds for two minutes. Prior to the procedure, baseline data were obtained for 60 seconds and continuous monitoring was done throughout and after the procedure during the recovery time. The blood collection was done by an experienced phlebotomist for 49 of the 60 infants. The outcomes measured were reduction in the percentage crying and grimacing times during the procedure; the mean crying time following the procedure and the mean heart rate change during and following the procedure. Despite repeated requests, data regarding individual groups were not obtained from the authors.

Bucher 2000 compared the effects of commercially available artificial sweetener (containing 10 parts cyclamate and one part saccharin) to glycine (sweet amino acid), expressed breast milk and sterile water. This was a randomized controlled trial of 80 full-term infants. The infants were randomly assigned to one of the following groups (20 neonates in each group):

Group 1: 2 ml of artificial sweetener via syringe;
Group 2: 2 ml of glycine via syringe;
Group 3: 2 ml of breast milk via syringe;
Group 4: 2 ml of sterile water via syringe.

The infants were studied on postnatal day four at the time of blood collection for routine neonatal screening using the heel lance procedure. Two ml of the allocated solution was given via syringe on the anterior part of tongue by a nurse not involved in the study. Prior to the procedure, baseline data were obtained and continuous monitoring was done throughout and after the procedure during the recovery time. The blood collection was performed two minutes after administration of solution by a research nurse. The procedure was video taped and evaluated by two independent observers unaware of allocation. The outcomes measured were heart rate change, percentage time crying, body pain score, facial pain score (five components of NFCS) and body pain score (torso movements 1 = one side, 2 = both sides; head movements = 1; arm movements 1 = one arm, 2 = both arms; hand movements 1 = one hand, 2 = both hands; bringing hands to face (mouth) = 1 point; maximum score was 8 points, minimum score was 0 points) during and after blood collection. The data were presented in graphical format. Numerical data were obtained by contacting the author.

Carbajal 2003 compared the effects of breastfeeding to positioning, sterile water and 30% glucose. This was a randomized controlled trial of 180 term neonates. The infants were randomized to one of the four groups:

Group 1: breastfeeding (n = 44);
Group 2: held in mother's arms without breastfeeding (n = 45);
Group 3: sterile water without pacifier (n = 45);
Group 4: 30% glucose followed by a pacifier (n = 45).

In Group 1 and 2, the interventions were started two minutes before the procedure and continued throughout the procedure. In groups 3 and 4 the intervention was commenced two minutes prior to the procedure respectively. Venepuncture was performed when infants were at least 24 hours of age and had not been fed for the previous 30 minutes. The primary outcome measure was the DAN scale (Carbajal 1997), a behavioral scale developed to rate acute pain in term and preterm neonates. The score comprised of three items namely facial expressions, limb movements, and vocal expression with values in each ranging from zero (no pain) to 10 (maximum pain). The secondary outcome measure was the PIPP score. Mothers were interviewed 48 - 72 hours after the study by standardized questionnaires to assess any change in the sucking behavior. One infant was excluded from the analysis as the outcome measure could not be assessed properly due to the mother's head partially covering her infant's face. Data from all four groups were used in their respective appropriate comparisons.

Gradin 2004 compared the effects of breastfeeding to sterile water and 30% glucose. This was a randomized controlled trial of 120 full term neonates. The infants were randomized to four groups:

Group 1: breastfeeding and 1 ml of sterile water (n = 27);
Group 2: breastfeeding and 1 ml of 30% glucose (n = 29);
Group 3: fasting and 1 ml of sterile water (n = 26);
Group 4: fasting and 1 ml of 30% glucose (n = 29).

Infants underwent routine neonatal screening procedure using venepuncture at 3 - 5 days of age. The data from the Group 3 were not used for this review. For the breast fed group, the infants were allowed breastfeeding *ad libitum* 45 minutes prior to blood

sampling while infants in the fasting group had blood sampling performed at least two hours after the last feeding. One ml of either sterile water or 30% glucose was administered through a syringe into the infants mouth, and one minute later the blood sampling was performed. After sampling the infants were left undisturbed for three minutes during recovery phase. The outcomes measured were the PIPP score and mean crying time. Parents were asked to assess pain using a Visual Analogue Scale (VAS). The agreement between the parental assessment of pain and the PIPP score and crying time was determined. The primary author provided missing data. Nine infants were excluded from the study by the authors mostly due to technical problems with the video recordings (n = 6) and maternal choice to withdraw their infants from the study (n = 3). Data from group 1, 3 and 4 were used for this review as the combination of breastfeeding and glucose was not planned to be compared a priori.

Gray 2002 compared the effects of breastfeeding to positioning. This was a randomized controlled trial of 30 full term neonates. The infants were randomized to two groups (15 neonates in each group):

Group 1: breast fed and cuddled with full body skin to skin contact;

Group 2: swaddled and placed on their side in the crib.

All infants underwent heel lance for routine neonatal screening procedure. Mean postnatal age at procedure was 46 hours in Group 1 and 40 hours in Group 2. The outcomes measured were differences in crying, grimacing and heart rate between the two groups before, during and after blood collection. The primary author provided additional information.

Ors 1999 compared the effects of supplemental breast milk to water and 25% sucrose. This was a randomized controlled trial of 102 healthy term neonates. The infants were randomized to three groups:

Group 1: received 2 ml of 25% sucrose (n = 35);

Group 2: received 2 ml of human milk (n = 33);

Group 3: received 2 ml of sterile water (n = 34).

All infants underwent heel lance blood sampling by a single performer. The allocated solution was given by syringe into the baby's mouth over one minute. The heel prick was performed two minutes after administration of the solution. Crying duration and heart rate at three minutes were recorded from the time of the heel prick. The outcomes measured were crying time, percentage change in heart rate and recovery time for the heart rate. The primary author provided additional information. Data from all three groups were used for this review in their respective appropriate comparisons.

Phillips 2005 compared the effects of breastfeeding in three groups in a randomized controlled trial of 96 healthy term neonates:

Group 1: Breastfeeding (n = 32);

Group 2: neonates held by mother holding pacifier in infant's mouth (n = 39);

Group 3: neonates held by research assistant holding pacifier in infant's mouth (n = 25).

All infants underwent heel lance blood sampling by a single performer. Mothers held babies in their bed while giving pacifier (group 2) while research assistant held infants in bedside chairs (group 3). The outcomes measured were crying duration, percentage of infants crying, changes in the heart rate, blood pressure and oxygen saturation. The primary author provided additional information. The purpose of studying three groups was to assess the differences in outcome measures caused by one of the component of the act of breastfeeding (maternal contact).

Shendurnikar 2005 compared the effects of breastfeeding to positioning (swaddling). The authors provided details about the study as it was published as a letter to the editor. This was a randomized controlled trial of 100 full term neonates. The infants were randomized to two groups (50 neonates in each group):

Group 1: breastfeeding group;

Group 2: swaddled and placed on a cradle.

Infants in group 1 were breastfed for 15 minutes prior to heel prick. All infants underwent heel lance procedure for clinical indication such as measurement of packed cell volume or bilirubin. The outcomes measured were behavioral (state of arousal, cry, facial expression, body movements); physiological (breathing pattern, heart rate) and composite score (non validated) between the two groups before, during and after blood collection. The primary author provided additional information. The composite score was calculated using the following criteria:

(a) heart rate (0 = < 120/minute; 1 = 120 - 160/minute and 2 = > 160/minute)

(b) breathing (0 = relaxed; 1 = changed)

(c) facial expression (0 = relaxed; 1 = grimaced)

(d) body movements (0 = relaxed; 1 = no gross movement; 2 = gross body movement)

(e) state of arousal (0 = sleepy; 1 = awake; 2 = fussy)

(f) cry (0 = no; 1 = whimper; 2 = vigorous) and combining the score.

The minimum score was 0 and maximum score was 10. This study was published as a letter to editor and authors provided additional data.

Skogsdal 1997 compared the effects of no intervention to 30% oral glucose, 10% oral glucose and breast milk. This was a randomized controlled trial of 120 neonates (66 preterm neonates between 30-37 weeks and 54 term neonates). The infants were randomly assigned to one of the following groups (30 neonates in each group):

Group 1: no intervention;

Group 2: 1 ml of 30% glucose via syringe;

Group 3: 1 ml of 10% glucose via syringe;

Group 4: 1 ml of breast milk via syringe.

The infants were studied on mean (SD) postnatal day of five at the time of blood collection for their routine care using the heel lance procedure. One ml of the allocated solution was given via

syringe by a nurse not aware of allocation. Prior to the procedure, baseline data were obtained and continuous monitoring was done throughout and after the procedure during the recovery time. The blood collection was performed two minutes after administration of solution. The outcomes measured were heart rate change and duration of crying. The data were presented in graphical format, however, contact author provided the data necessary for the review. As this study had two comparative groups with different concentrations of glucose, for the purpose of analyses the group who received 30% glucose was combined with data from Ors 1999 study where they used 25% sucrose in one group (presuming very minimal difference in pain responses between 25 and 30% sugar solution). The group who received 10% glucose was compared with breast milk group separately.

Upadhyay 2004 compared the effects of supplemental breast milk to sterile water. This was a randomized controlled trial of 87 full term neonates. The infants were randomized to two groups:

Group 1: received 5 ml of expressed breast milk (n = 40);

Group 2: received 5 ml of distilled water (n = 41) prior to venepuncture.

Venepuncture was performed based on clinical indications. Three babies from each group were excluded from the study by the authors due to venepuncture failure and failure to attain state 3 or 4 of wakefulness. Data from 81 infants were analyzed. The primary outcome was the duration of the cry after the venepuncture. The secondary outcomes included changes in physiological parameters namely heart rate and oxygen saturation from baseline to one and three minutes after venepuncture and the modified NFCS. Only five easily recordable parameters of the NFCS (out of ten) were assessed by investigators. Data on heart rate, oxygen saturation were provided as mean and standard deviation at baseline and three minutes. Authors were contacted to provide data on mean changes in these parameters, but no response was obtained. The mean difference and standard deviation of the difference were calculated assuming 50% correlation between baseline and subsequent findings by the review authors.

Uyan 2005 compared the effects of supplemental breast milk (two groups foremilk and hindmilk) to water. This was a quasi-randomized controlled trial of 62 healthy term neonates. The infants were randomized to three groups:

Group 1: received 2 ml of foremilk (n = 20);

Group 2: received 2 ml of hindmilk (n = 21);

Group 3: received 2 ml of sterile water (n = 21).

All infants underwent heel lance blood sampling by single performer. The allocated solution was given by syringe into the baby's mouth. The heel prick was performed two minutes after administration of the solution. Crying duration and heart rate changes at one, two, and three minutes were recorded from the time of the heel prick. The outcomes measured were crying time, percentage change in heart rate and NFCS at one, two and three minutes. The data from the group 1 and 2 were combined for the analyses. Authors provided data on combined groups.

Risk of bias in included studies

The methodological quality of the reviewed studies are given in the table "Characteristics of Included Studies." The information was extracted from the published paper and by contacting the primary authors.

Blass 2001: The infants were initially assessed to determine whether they were successfully breastfed or not and then randomized into the colostrum groups and non-colostrum groups. Investigators initially planned the assignment of the infants based on a table of random numbers. Group assignment needed to be adjusted because some mothers were unable to obtain sufficient colostrum. After passing the exclusion criteria, investigators assessed mother's success regarding breastfeeding. If the mother was unsuccessful, she was assigned to groups that didn't involve breast milk (group 1, 3, 4 and 6). If breastfeeding was established the infant was assigned to group 2 or 5. The phlebotomist who performed the heel-lance was unaware of allocation, study's purpose or hypotheses. The authors did not define what constituted successful breastfeeding. The data collection for sucrose, water and pacifier groups completed in June 1998, while colostrum data collection ended in March 1999. Although the phlebotomist and the person who rated video data were unaware of treatment allocation, this could have introduced a degree of bias. Masking of intervention was not possible in this study since it involved the use of a pacifier and a liquid (colostrum) that differed in color from two other solutions. Masking of outcome assessment was possible with crying time and heart rate changes, but not so when assessing the grimacing since the intervention involved the use of a pacifier. A number of infants in the water and colostrum groups were excused (data collection not continued and infant allowed to be comforted in other ways) after 90 seconds of recovery period due to excessive crying, though all infants were included in the final analysis with the assumption that these behaviors would have continued at the same level for the rest of the recovery period.

Bucher 2000: The randomization was done through sealed envelopes. One nurse administered solution in the absence of investigators and was not involved in heel prick or data collection. Masking of outcome assessment was done by blinding observer as to the assignments to the study group.

Carbajal 2003: The randomization was done by research assistant using numbered envelopes. Allocation was concealed from the investigators. Masking of the intervention was not possible in this study since it involved breastfeeding, the use of a pacifier and cuddling before and throughout the procedure. The outcome assessment was masked as the observers who assessed the outcome measures were not aware as to the purpose and hypothesis of the study. However, personal bias on the part of outcome observer could not be excluded.

Gradin 2004: The randomization was done through sealed envelopes. The intervention involved the use of placebo to mask the solution in question. Masking of outcome assessment was done by blinding observer as to the assignments to the study group.

Gray 2002: The randomization was done through sealed envelopes. The masking of intervention was not possible since it involved breastfeeding before and throughout the procedure. Masking of outcome assessment was also not possible. All participants were accounted for in the analysis of outcomes.

Ors 1999: The manner of randomization was not discussed by the authors. Masking of the intervention was made possible by using a placebo and by performing the heel prick one minute after giving the solutions. The two investigators who analyzed the data were unaware of the treatment intervention, hence, the outcome measure analysis was blinded. All infants were accounted for in the analysis.

Phillips 2005: The randomization was done through envelopes containing allocation cards. Masking of intervention was not possible since it involved breastfeeding before and throughout the procedure. Masking of outcome assessment (from video recordings) was not done; however, data from monitors (heart rate, saturation and blood pressure) were analyzed in a masked manner. All participants were accounted for in the analysis of outcomes; however, for some analyses complete data were not available from all patients.

Shendurnikar 2005: Primary author provided this information. The randomization was done by the primary author asking mother to choose from a collection of randomization cards. The masking of intervention was not possible since it involved breastfeeding before and throughout the procedure. Masking of outcome assessment was not done and primary author collecting data was aware of the allocation and hypothesis of the study. All participants were accounted for in the analysis of outcomes.

Skogsdal 1997: The randomization was done through random digit table. The heel prick and administration of allocated solution was done by the same nurse. Outcome data collection was done by a different nurse who was unaware of allocation. All participants were accounted for in the analysis of outcomes.

Upadhyay 2004: The randomization was performed using computer generated numbers. Allocation was adequately concealed. The observers were blinded as to the intervention given to the infants. The data of the 81 subjects were available for analysis because in six infants, either there was technical problem or the infants were not fully awake.

Uyan 2005: The authors provided further information on method of randomization indicating that it was quasi-randomized (based on number or day of the procedure). According to authors the intervention was masked. The two investigators who analyzed the data and the person who recorded video for the NFCS coding were unaware of the treatment allocation; hence, the outcome measure analysis was blinded. All infants were accounted for in the analysis.

Effects of interventions

Primary outcome

Comparison 1: Breastfeeding vs. control

Five studies reported on this comparison (Carbajal 2003; Gray 2002; Gradin 2004; Phillips 2005; Shendurnikar 2005).

1. Physiological parameters

a. Outcome 01.01: Heart rate change (bests per minute)

Two studies (Gray 2002; Phillips 2005) reported on the heart rate change during heel lance. The heart rate tended to increase in both groups during the procedure, but the increase was significantly lower in the breastfeeding group compared to the swaddled group (Gray 2002) (mean difference [MD] -23; 95% confidence interval [CI] -35 to -11) and the breastfeeding group and group of infants held by mother holding a pacifier in the infant's mouth (Phillips 2005) (mean difference -11; 95% CI -21 to -1). There was no statistically significant difference in heart rate change between breastfeeding group and group of infants held by research assistant along with the use of pacifier (Phillips 2005) (MD -7; 95% CI -15, 1).

b. Changes in the respiratory rate

None of the studies included in this review reported on this outcome.

c. Outcome 01.02: Oxygen saturation change

One study (Phillips 2005) reported on the oxygen saturation change during heel lance. There was no difference in oxygen saturation change between the breastfeeding group and the group of infants held by mother holding a pacifier in the infant's mouth (MD 0.3; 95% CI -2.8, 3.4) and between the breastfeeding group and group of infants held by research assistant holding a pacifier in the infant's mouth (MD 0.6 95% CI -1.5, 2.7).

d. Outcome 01.03: Blood pressure changes

One study (Phillips 2005) reported on the blood pressure change during heel lance. There was no difference in blood pressure change between the breastfeeding group and the group of infants held by mother holding a pacifier in the infant's mouth (MD -3.6; 95% CI -9.1, 1.9) and the breastfeeding group and the group of infants held by research assistant holding a pacifier in the infant's mouth (MD 1.6 95% CI -4.9, 8.1).

2. Cry variables

a. Outcome 01.04: Percentage of time crying

Two studies (Gray 2002; Phillips 2005) reported percentage of time crying during heel lance. There was statistically significant reduction in the percentage time crying among infants in the breastfeeding group compared to the swaddled group (Gray 2002) (MD -39; 95% CI -55 to -23) and infants in the breastfeeding group compared to the group of infants held by research assistant holding a pacifier in the infant's mouth (Phillips 2005) (MD -33; 95% CI -50, -13). There was no statistically significant reduction in the percentage time crying between the breastfeeding group and the group of infants held by mothers holding a pacifier in the infant's mouth (Phillips 2005) (MD -12; 95% CI -28, 4).

b. Outcome 01.05: Duration of crying in seconds

Two studies (Gradin 2004; Gray 2002) reported on the duration of crying. Infants in the breastfeeding group compared to the fasting

group had a significant reduction in the duration of crying (Gradin 2004) (MD -50; 95% CI -79 to -22 sec). However, for infants in the breastfeeding group compared to the group given glucose, there was no statistically significant difference in the duration of crying (Gradin 2004) (MD -5; 95% CI -37 to 26 sec). Infants in the breastfeeding group compared to the swaddled group had a statistically significantly reduced duration of crying during heel lance (Gray 2002) (MD -63; 95% CI -75 to -52 sec).

Phillips 2005 reported that 69% of infants in the breastfeeding group cried during the procedure compared to 81% of the infants in the group held by mothers with pacifier use and 100% of infants in the group held by a research assistant and use of pacifier ($p < 0.01$).

3. Validated pain measures

a. Neonatal Infant Pain Score

None of the studies included in this review reported on this outcome.

b. Outcome 01.06: Premature Infant Pain Profile (PIPP) Score

Two studies reported on the PIPP scores (Carbajal 2003; Gradin 2004). The PIPP scores in the breastfeeding group were significantly lower compared to placebo group (MD -6; 95% CI -7 to -4) or the positioning in mother's arms group (MD -7; 95% CI -9 to -6). The PIPP score between breastfeeding and no treatment group was not statistically significantly different (MD 0; 95% CI -2 to 1). PIPP score was statistically significantly higher in the breastfeeding group compared to glucose group (MD 1.30; 95% CI 0.05 to 2.56).

c. Neonatal Facial Coding Score (NFCS)

None of the studies included in this review reported on this outcome.

d. Other pain scores as reported (non validated):

i. Outcome 01.07: Douleur Aigue Nouveau-né score (DAN) Scale

Only one study reported on DAN score (Carbajal 2003). The DAN scores in the breastfeeding group compared to placebo (MD -6; 95% CI -7 to -5) and breastfeeding group compared to positioning in mother's arms group (MD -7; 95% CI -8 to -6) were statistically significantly lower. The DAN score between breastfeeding group and glucose group was not statistically significantly different (MD -0.8; 95% CI -2.0 to 0.5).

ii. Outcome 01.08: Composite score

Shendurnikar 2005 calculated composite score. The composite score was calculated using the following criteria:

(a) heart rate (0 = < 120/minute; 1 = 120 - 160/minute and 2 = > 160/minute)

(b) breathing (0 = relaxed; 1 = changed)

(c) facial expression (0 = relaxed; 1 = grimaced)

(d) body movements (0 = relaxed; 1 = no gross movement; 2 = gross body movement)

(e) state of arousal (0 = sleepy; 1 = awake; 2 = fussy)

(f) cry (0 = no; 1 = whimper; 2 = vigorous) and combining the score

There was statistically significant decrease in the composite score in the breastfeeding group compared to swaddled group (MD -3; 95% CI -4, -2).

Comparison 2: Supplemental breast milk vs. control

Six studies reported on this outcome (Blass 2001; Bucher 2000; Ors 1999; Skogsdal 1997; Upadhyay 2004 and Uyan 2005)

1. Physiological parameters

a. Outcome 02.01: Heart rate change (beats per minute)

Six studies reported on changes in the heart rate (Blass 2001; Bucher 2000; Ors 1999; Skogsdal 1997; Upadhyay 2004 and Uyan 2005). The heart rate tended to increase in both groups during the procedure. There was no statistically significant difference in the heart rate change between the supplemental breast milk group and the placebo group (WMD -4; 95% CI -9 to 1 bpm; $p = 0.08$, $I^2 = 78\%$); supplemental breast milk and no treatment group (MD -5; 95% CI -12 to 2 bpm; $p = 0.17$); supplemental breast milk and 10% glucose group (MD 3; 95% CI -5 to 11 bpm; $p = 0.50$); supplemental breast milk and artificial sweetener group (MD 8; 95% CI 0 to 16 bpm; $p = 0.05$) and supplemental breast milk and glycine group (MD 4; 95% CI -3 to 11 bpm; $p = 0.25$). Statistical heterogeneity (Higgins 2003) was identified when pooling data from breast milk vs. placebo studies ($I^2 = 78\%$; $p = 0.0004$) which is concordant with clinical heterogeneity observed between studies (population and dose of breast milk). Blass 2001 reported on mean heart rate change during and following the heel lance in the form of a bar graph. The mean heart rate changes in the group given colostrum via a pacifier and the groups given sucrose either via syringe or pacifier were significantly less than the group given water, either by syringe or pacifier, and the group given colostrum via syringe. Ors 1999 reported significantly higher increase in the heart rate change in the supplemental breast milk group compared to 25% sucrose group (MD 14; 95% CI 4 to 23). Skogsdal 1997 reported significantly higher increase in heart rate change in supplemental breast milk group compared to 30% glucose group (MD 7, 95% CI 1, 13).

b. Changes in respiratory rate

None of the studies included in this review reported on this outcome.

c. Outcome 02.02: Oxygen saturation change

One study reported on the change in oxygen saturation (Upadhyay 2004). The infants in the supplemental breast milk group compared to placebo group had no statistically significant difference in the change in oxygen saturation at three minutes (MD 0; 95% CI -2 to 2).

d. Changes in blood pressure

None of the studies included in this review reported on this outcome.

2. Cry variables

a. Outcome 02.03: Percentage of time crying

Blass 2001 reported the mean time spent crying during the recovery period in the form of a linear graph. This study identified a statistically significant reduction in the proportion time crying in the group given sucrose (via syringe or pacifier) compared to the control group and the group given colostrum (via syringe or pacifier) ($p < 0.0015$). There was no statistically significant difference between the colostrum group and the control group. It was not possible to abstract data from the graphs. Bucher 2000 reported statistically significant reduction in the percentage time crying in the artificial sweetener group compared to the supplemental breast milk group (MD 15; 95% CI 2 to 28), but no statistically significant reduction between the supplemental breast milk group and the placebo group (MD 9; 95% CI 2 to 20) and the supplemental breast milk group and the glycine group (MD 1; 95% CI -5 to 7).

b. Outcome 02.04: Duration of crying (in seconds)

Six studies (Blass 2001; Bucher 2000; Ors 1999; Skogsdal 1997; Upadhyay 2004 and Uyan 2005) reported on the duration of crying. Blass 2001 reported the reduction in crying time, however, the data was not in a format that could be abstracted. Upadhyay 2004 reported statistically significant reduction in the duration of crying among infants fed breast milk compared to placebo (71 secs; 95% CI 37 to 105 secs); comparative data could not be abstracted. Combining the data from four studies Bucher 2000; Ors 1999; Skogsdal 1997 and Uyan 2005 revealed no statistically significant difference in the duration of crying between the supplemental milk and the placebo group (WMD -6; 95% CI -16 to 3 secs). Ors 1999 observed statistically significant increase in the duration of crying in the supplemental breast milk group compared to the 25% glucose group (MD 33; 95% CI 12 to 54 secs). There was no statistically significant reduction in the duration of crying between the supplemental breast milk and the 30% glucose group (MD 13; 95% CI -3 to 29 secs); the supplemental breast milk group and the 10% glucose group (MD 4; 95% CI -15 to 23 secs) and the supplemental breast milk group and the artificial sweetener group (MD 41; 95% CI -7 to 89 secs). There was statistically significant reduction in the duration of crying in the glycine group compared to the supplemental breast milk group (MD 52; 95% CI 6 to 97 secs).

3. Validated pain measures

a. Neonatal infant pain score

None of the studies included in this review reported on this outcome.

b. Premature Infant Pain Profile

None of the studies included in this review reported on this outcome.

c. Outcome 02.05: Neonatal Facial Coding Score at 3 minutes

Three studies (Bucher 2000; Upadhyay 2004; Uyan 2005) reported on NFCS. Bucher 2000 used five components of NFCS and Upadhyay 2004 modified the score and collected data on only part of the components. Bucher 2000 reported no statistically significant difference between the supplemental breast milk and the placebo group (MD -0.09; 95% CI -0.58, 0.40). Upadhyay 2004 reported statistically significant reduction in the NFCS in the supplemental breast milk group compared to the placebo group (MD -2.0; 95% CI -2.8 to -1.2). Uyan 2005 reported no statistically significant difference between the supplemental breast milk and the placebo group (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 2000 reported no statistically significant reduction in NFCS between supplemental breast milk group and artificial sweetener group (MD -0.2; 95% CI -0.7 to 0.2). However, a statistically significant reduction in NFCS was noted in the supplemental breast milk group compared to the glycine group (MD -0.47; 95% CI -0.90 to -0.04).

d. Other pain scores as reported (non validated)

i. Outcome 02.06: Body pain score

One study (Bucher 2000) reported on the body pain score outcome (maximum score was eight and minimum score was 0). There was no statistically significant reduction in body pain score between the supplemental breast milk and the placebo group (MD 0.5; 95% CI -0.4 to 1.3), the supplemental breast milk group and the artificial sweetener group (MD 0.2; 95% CI -0.7 to 1.0) and the supplemental breast milk group and the glycine group (MD 0.4; 95% CI -0.5 to 1.4).

Secondary outcome

Carbajal 2003 gathered information on infant's sucking behavior 48 to 72 hours after venepuncture by interviewing mothers. There was no difference in the number of infants in whom the suck was same or more effective among four groups ($p = 0.14$). The authors reported that infants who underwent venepuncture while they were being breast fed did not suck less effectively after the procedure.

Planned subgroup analyses according to gestational age groups was not performed in this version of the review because with the exception of one study (Skogsdal 1997), all other studies included only term infants. Other planned subgroup analyses according to type of intervention and type of procedure were not performed because subdividing the current data in these subgroup will have one and at the most two studies for comparison between groups at this point. However, in future updates of this review we plan to evaluate this subgroup analysis.

DISCUSSION

All studies evaluated in this review assessed the effects of breastfeeding or supplemental breast milk on 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 breast milk yielded variable results. In two studies higher concentrations of glucose were associated with a non-significant trend towards reduction in PIPP scores compared to the breastfeeding group. In another study, higher concentration of sucrose was associated with reduction in heart rate changes and duration of cry compared to supplemental breast milk. Based on the available results of these studies we can conclude that neonates undergoing single painful procedure should be provided either breastfeeding or supplemental breast milk for analgesia when available compared to positioning/pacifier/holding and swaddling. If it is not available/feasible to give breastfeeding or supplemental breast milk 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 breast milk for painful procedures may further encourage mothers to breast feed their infants, facilitate bonding, and provide psychological advantage for the mother in terms of her involvement in the care of her infant without any additional cost to the health care system.

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 2002 evaluated effects of repeated administration of sucrose prior to painful procedures in infants < 31 weeks post-conceptional age. Use of sucrose was associated with reduced scores on motor development, vigour, alertness and orientation at 36 weeks; affected motor development and vigour at 40 weeks and higher Neuro-Biological Risk Score at two weeks postnatal age. Although unproven, breast milk 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. As breast milk 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 (Stevens 2004). Behavioural and physiological parameters of pain and/or validated pain measures were used to assess pain at random in various studies. Standardization of utilizing only validated pain scales should be the framework of further research. Future studies of adequate sample size should only include validated measures of pain as outcomes. Second, all studies explored effects of breastfeeding or breast milk following a single painful procedure. Future studies should include preterm or term neonates who require repeated painful stimuli to assess side effects of repeated oral administration of breast milk. 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 that evaluated maternal perception regarding sucking after single venepuncture while breastfeeding and found no changes; however, effect of repeated exposure is not studied. Thirdly, there was marked heterogeneity between studies in terms of control intervention, amount/time of prior exposure to breastfeeding or breast milk, time interval between this exposure and type of painful procedure.

Though the reasons for the effectiveness of breastfeeding over simple measures such as positioning/no intervention are unclear, it is perceived to be due to psychological and/or chemical properties of breast milk. On the other hand, the effectiveness of sucrose over breastfeeding is probably due to higher concentration of sugar in the former, however, the mechanism of action of sucrose is also unclear.

AUTHORS' CONCLUSIONS

Implications for practice

If available, breastfeeding or breast milk should be used to alleviate procedural pain in neonates undergoing a single painful procedures compared to placebo or positioning or no intervention. When repeated painful procedures are needed, the safety or effectiveness of breastfeeding or supplemental breast milk is not established.

Implications for research

Further randomized controlled studies are needed to assess the efficacy and effectiveness of breastfeeding and breast milk for repeated painful procedures in neonates, especially preterm neonates.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blass 2001

Methods	Quasi-randomized controlled trial I. Masking of randomization - can't tell II. Masking of intervention - no III. Masking of outcome assessment - no IV. Completeness of follow up - yes
Participants	60 stable full term newborn infants undergoing routine newborn screening (heel lance) between 30 and 55 hours of age were randomly assigned to one of the 6 treatment groups (10 neonates in each group) Mean (range) BW - 3200 (2400-4200) grams Male: Female - 27:33
Interventions	Group 1: 2 ml water given over 2 minutes via syringe Group 2: 2 ml colostrum given over 2 minutes via syringe Group 3: 2 ml of 12% sucrose given over 2 minutes via syringe Group 4: 2 ml water given on a pacifier dipped in water every 30 seconds for 2 minutes Group 5: 2 ml of colostrum given on a pacifier dipped in colostrum every 30 seconds for 2 minutes Group 6: 2 ml of sucrose given on a pacifier dipped in sucrose every 30 seconds for 2 minutes
Outcomes	Percentage of time crying during the procedure in relation to control Percentage of time grimacing during the procedure Mean crying time during the recovery phase Mean changes in heart rate during and following the procedure
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Bucher 2000

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - yes III. Masking of outcome assessment - yes IV. Completeness of follow up - yes
Participants	80 stable full term newborn infants undergoing routine newborn screening (heel lance) on postnatal day 3 were randomly assigned to one of the 4 treatment groups Group 1: 20 neonates Mean (range) BW - 3420 (2650-5000) grams

Bucher 2000 (*Continued*)

	Male: Female - 10: 10 Group 2: 20 neonates Mean (range) BW - 3430 (2640-3960) grams Male: Female- 10:10 Group 3: 20 neonates Mean (range) BW - 3350 (2720-4200) grams Male: Female-8:12 Group 4: 20 neonates Mean (range) BW - 3410 (2740-4170) grams Male: Female-9:11
Interventions	Group 1: 2 ml of artificial sweetener Group 2: 2 ml of glycine Group 3: 2 ml of breast milk Group 4: 2 ml of sterile water
Outcomes	Heart rate change Percentage time crying Body pain score Facial pain score Combined pain score
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Carbajal 2003

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - no III. Masking of outcome assessment - yes IV. Completeness of follow up - yes
Participants	179 healthy term neonates Inclusion criteria: healthy term (>/= 37 weeks GA) undergoing venepuncture for diagnostic evaluation. Exclusion criteria: medical instability, received naloxone in the last 24 hours, received sedative or major analgesic in the last 48 hours. Group 1: 44 neonates Mean GA - 39.7 (1.15) weeks Mean BW - 3306 (382.8) grams Group 2: 45 neonates Mean GA - 39.8 (1.23) weeks Mean BW - 3304 (483.0) grams

Carbajal 2003 (*Continued*)

	Group 3: 45 neonates Mean GA - 40.0 (1.14) weeks Mean BW - 3420 (418.8) grams Group 4: 45 neonates Mean GA - 39.6 (1.20) weeks Mean BW - 3313 (401.2) grams
Interventions	Group 1: Breastfeeding 2 minutes before and throughout the procedure Group 2: Cuddled in mother's arms without breastfeeding starting 2 minutes prior to procedure Group 3: One ml of placebo (sterile water) without pacifier 2 minutes before the procedure while lying supine on the table Group 4: One ml of 30% glucose followed by pacifier 2 minutes prior to venepuncture while lying supine on the table
Outcomes	Douleur Aigue Nouveau-ne (DAN) rating scale for pain in neonates Premature Infant Pain Profile (PIPP) Standardized questionnaires to mothers to determine the effect of venepuncture on breastfeeding at 48-72 hours after the venepuncture
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gradin 2004

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - yes III. Masking of outcome assessment - yes IV. Completeness of follow up - no
Participants	120 full term infants at 3-5 days of age undergoing venepuncture for metabolic screening Exclusion criteria: feeding problems or suspicion of illness Group 1: 27 neonates Mean (range) GA - 39.4 (37-42) weeks Mean (range) BW - 3638 (2325-4425) grams Group 2: 29 neonates Mean (range) GA - 39.5 (37-42) weeks Mean (range) BW - 3637 (2700-4830) grams Group 3: 26 neonates Mean (range) GA - 39.4 (37-42) weeks Mean (range) BW - 3442 (2185-4560) grams Group 4: 29 neonates Mean (range) GA - 39.4 (37-42) weeks

Gradin 2004 (*Continued*)

	Mean (range) BW - 3660 (3025-4950) grams
Interventions	Group 1: Breastfeeding and 1 ml sterile water Group 2: Breastfeeding and 1 ml 30% glucose Group 3: Fasting and 1 ml sterile water Group 4: Fasting and 1 ml 30% glucose For breastfed group, breastfeeding was allowed for as long as the infant wanted within 45 mins prior to blood sampling For the fasting group, blood sampling performed at least 2 hrs after the last feed Venepuncture was done 1 minute after giving 30% glucose or sterile water
Outcomes	Premature Infant Pain Profile Visual Analogue Scale Median crying time
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Gray 2002

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - no III. Masking of outcome assessment - no IV. Completeness of the follow up - yes
Participants	30 term neonates Inclusion criteria: Healthy full term neonates delivered by normal spontaneous vaginal delivery undergoing heel lance for newborn screening Exclusion criteria: Patients with evidence of congenital abnormalities, medical complications, drug exposure, history of oxygen administration or ventilatory support Group 1: 15 neonates Mean GA - 39.8 weeks Mean BW - 3480 grams Group 2: 15 neonates Mean GA - 39.9 weeks Mean BW - 3524 grams
Interventions	Group 1: Breastfeeding during procedure Group 2: Swaddled in the bassinet during procedure
Outcomes	Changes in facial grimacing, crying time and heart rate before, during and after blood collection

Gray 2002 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ors 1999

Methods	Randomized controlled trial I. Masking of randomization - can't tell II. Masking of intervention - can't tell III. Masking of outcome assessment - yes IV. Completeness of the follow up - yes
Participants	102 healthy term infants at median age of 1.6 days undergoing routine heel lance blood sampling Exclusion criteria: Infants < 24 hours of age, Apgar score < 7 at 1 minute and on any medication were excluded Group 1: 35 neonates Median (range) GA - 40.0 (37-42) weeks Median (range) BW - 3220 (2445-4210) grams Group 2: 33 neonates Median (range) GA - 39.5 (37-42) weeks Median (range) BW - 3200 (2390-4200) grams Group 3: 34 neonates Median (range) GA - 39.0 (37-42) weeks Median (range) BW - 3380 (2450-4300) grams
Interventions	All infants were fed 1 hour before the procedure Group 1: 2 ml of 25 % sucrose Group 2: 2 ml of human milk Group 3: 2 ml of sterile water The solutions were administered by syringe over 1 minute Heel lance was performed 2 minutes after administration of the solution
Outcomes	Recovery time Percentage change in heart rate at 1, 2 and 3 minutes Median crying time
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Phillips 2005

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - no III. Masking of outcome assessment - not done for outcome recorded on video camera (cry duration, percentage time crying), outcomes on monitors (heart rate, saturation, blood pressure) were masked IV. Completeness of follow up - yes
Participants	96 stable full term newborn infants undergoing routine newborn screening (heel lance) were randomly assigned to one of the 3 treatment groups Group 1: 32 neonates Mean (range) age at procedure - 37 (9) hours Male: Female - 13: 19 Group 2: 39 neonates Mean (range) age at procedure 36 (8) hours Male: Female- 13:26 Group 3: 25 neonates Mean (range) age at procedure 38 (14) hours Male: Female- 12:13
Interventions	Group 1: Breastfeeding Group 2: Held by mother with use of pacifier Group 3: Held by research assistant with the use of pacifier
Outcomes	Percentage of infants cried Proportion of cry time Heart rate, blood pressure and oxygen saturation change before and after the procedure
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Shendurnikar 2005

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - no III. Masking of outcome assessment - no IV. Completeness of follow up - yes
Participants	100 full term newborn infants who underwent heel lance were randomly assigned to one of the 2 treatment groups Group 1: 50 neonates GA: 38.2 weeks Male: Female= 22:28

Shendurnikar 2005 (*Continued*)

	Group 2: 50 neonates GA: 38.6 weeks BW: 2865 grams Male: Female =31:19 Postnatal age 3.4 days BW: 2910 grams Postnatal age 3.1 days Inclusion criteria: Full term neonates >2500g BW Exclusion criteria: Septicemia, birth asphyxia, major congenital malformation
Interventions	Group 1: Breastfeeding group Group 2: Swaddled group
Outcomes	Behavioral (state of arousal, cry, facial expression, body movements) Physiological (heart rate, breathing pattern) Composite score
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Skogsdal 1997

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - yes III. Masking of outcome assessment - yes IV. Completeness of follow up - yes
Participants	120 stable newborn infants (66 preterm and 54 full term) undergoing heel lance for blood collection for their care between 1 to 30 days of age were randomly assigned to one of the 4 treatment groups (30 neonates in each group) Exclusion criteria: age <24 hours, analgesic or sedative drug given within last 5 days, gestational age <30 weeks, ventilator or CPAP treatment, oxygen requirement > 40%, neurological symptoms, antibiotic therapy and age > 1 month Mean (SD) GA - 35.5 (2.3) weeks Mean (SD) age at testing - 5.4 (4.9) days
Interventions	Group 1: no treatment group Group 2: 1 ml of 30% glucose Group 3: 1 ml of 10% glucose Group 4: 1 ml of breast milk

Skogsdal 1997 (*Continued*)

Outcomes	Crying time Heart rate change
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Upadhyay 2004

Methods	Randomized controlled trial I. Masking of randomization - yes II. Masking of intervention - yes III. Masking of outcome assessment - yes IV. Completeness of follow up - can't tell
Participants	81 neonates requiring venepuncture for clinical indication Inclusion criteria: GA of 37-41weeks who were </= 4 weeks of postnatal age and required venepuncture for clinical indication Exclusion criteria: Perinatal asphyxia (Apgar score < 7 at 1 min), major congenital malformations, admission to neonatal intensive care unit, maternal anesthesia, opiates administration before delivery or within 48 hours of sampling, babies given naloxone or phenobarbitone Group 1: 40 neonates Mean (SD) GA - 38 (0.9) weeks Mean (SD) BW - 2600 (300) grams Group 2: 41 neonates Mean (SD) GA - 38 (0.8) weeks Mean (SD) BW - 2900 (300) grams
Interventions	Group 1: 5 ml of expressed breast milk Group 2: 5 ml of distilled water The solutions were administered over 2 minutes prior to venepuncture
Outcomes	Duration of crying after venepuncture Neonatal Facial Coding Score at 1 and 3 minutes after the venepuncture Changes in heart rate and oxygen saturation
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Uyan 2005

Methods	Quasi-randomized controlled trial I. Masking of randomization - no II. Masking of intervention - yes III. Masking of outcome assessment - yes IV. Completeness of the follow up - yes
Participants	62 term infants undergoing heel lance blood sampling for screening tests Exclusion criteria: preterm neonates, neonates with Apgar score < 7 at 5 minutes, neonates with low birth weight, sick neonates and neonates on any medication Group 1: 20 neonates Median (range) GA - 39 (38-41) weeks Median (range) BW - 3300 (2800-4260) grams Group 2: 21 neonates Median (range) GA - 39 (38-41) weeks Median (range) BW - 3510 (2750-4030) grams Group 3: 21 neonates Median (range) GA - 40 (38-41) weeks Median (range) BW - 3300 (2800-4500) grams
Interventions	All infants were fed 1 hour before the procedure Group 1: 2 ml of foremilk Group 2: 2 ml of hindmilk Group 3: 2 ml of sterile water The solutions were administered by syringe Heel lance was performed 2 minutes after administration of the solution
Outcomes	Crying time Duration of first cry Percentage change in heart rate at 1, 2 and 3 minutes Neonatal Facial Coding Score
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

GA = gestational age
BW = birth weight
g = grams
w = weeks

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bilgen 2001	Article is retracted by the journal. We have not used any of the data from this report because the data were previously reported by Ors 1999.

DATA AND ANALYSES

Comparison 1. Breastfeeding vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate change (beats per minute)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Breastfeeding vs positioning	1	30	Mean Difference (IV, Fixed, 95% CI)	-23.0 [-34.55, -11.45]
1.2 Breastfeeding vs pacifier use (neonate held by mother)	1	65	Mean Difference (IV, Fixed, 95% CI)	-10.9 [-20.95, -0.85]
1.3 Breastfeeding vs pacifier use (neonate held by research assistant)	1	54	Mean Difference (IV, Fixed, 95% CI)	-7.10 [-15.50, 1.30]
2 Oxygen saturation change	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Breastfeeding vs pacifier use (neonate held by mother)	1	64	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.79, 3.39]
2.2 Breastfeeding vs pacifier use (neonate held by research assistant)	1	53	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.48, 2.68]
3 Blood pressure changes (mm of Hg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Breastfeeding vs pacifier use (neonate held by mother)	1	62	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-9.08, 1.88]
3.2 Breastfeeding vs pacifier use (neonate held by research assistant)	1	48	Mean Difference (IV, Fixed, 95% CI)	1.60 [-4.86, 8.06]
4 Percentage of time crying	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Breastfeeding vs positioning	1	30	Mean Difference (IV, Fixed, 95% CI)	-39.0 [-55.03, -22.97]
4.2 Breastfeeding vs pacifier use (neonate held by mother)	1	71	Mean Difference (IV, Fixed, 95% CI)	-11.80 [-27.95, 4.35]
4.3 Breastfeeding vs pacifier use (neonate held by research assistant)	1	57	Mean Difference (IV, Fixed, 95% CI)	-32.60 [-49.83, -15.37]
5 Duration of crying (secs)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Breastfeeding vs no treatment	1	51	Mean Difference (IV, Fixed, 95% CI)	-50.43 [-78.97, -21.89]
5.2 Breastfeeding vs sucrose/glucose	1	53	Mean Difference (IV, Fixed, 95% CI)	-5.49 [-37.26, 26.28]
5.3 Breastfeeding vs positioning	1	30	Mean Difference (IV, Fixed, 95% CI)	-63.3 [-74.54, -52.06]
6 Premature Infant Pain Profile Score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Breastfeeding vs placebo	1	89	Mean Difference (IV, Fixed, 95% CI)	-5.95 [-7.42, -4.48]
6.2 Breastfeeding vs no treatment	1	29	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-2.39, 1.41]

6.3 Breastfeeding vs sucrose/glucose	2	127	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.05, 2.56]
6.4 Breastfeeding vs positioning	1	89	Mean Difference (IV, Fixed, 95% CI)	-7.49 [-8.95, -6.03]
7 Douleur Aigue Nouveau-né (DAN) Scale	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Breastfeeding vs placebo	1	89	Mean Difference (IV, Fixed, 95% CI)	-6.24 [-7.38, -5.10]
7.2 Breastfeeding vs sucrose/glucose	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.97, 0.47]
7.3 Breastfeeding vs positioning	1	89	Mean Difference (IV, Fixed, 95% CI)	-6.77 [-7.78, -5.76]
8 Composite score	1	100	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-3.51, -2.29]

Comparison 2. Supplemental breast milk vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate change (beats per minute)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Supplemental breast milk vs placebo	4	250	Mean Difference (IV, Fixed, 95% CI)	-4.22 [-8.94, 0.50]
1.2 Supplemental breat milk vs no treatment	1	60	Mean Difference (IV, Fixed, 95% CI)	-5.10 [-12.37, 2.17]
1.3 Supplemental breast milk vs 25% sucrose	1	68	Mean Difference (IV, Fixed, 95% CI)	13.80 [4.23, 23.37]
1.4 Supplemental breas milk vs 30% glucose	1	60	Mean Difference (IV, Fixed, 95% CI)	6.80 [0.70, 12.90]
1.5 Supplemental breast milk vs 10% glucose	1	60	Mean Difference (IV, Fixed, 95% CI)	2.70 [-5.11, 10.51]
1.6 Supplemental breast milk vs artificial sweetener	1	40	Mean Difference (IV, Fixed, 95% CI)	8.0 [-0.15, 16.15]
1.7 Supplemental breast milk vs Glycine	1	40	Mean Difference (IV, Fixed, 95% CI)	4.0 [-2.82, 10.82]
2 Oxygen saturation change	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Supplemental breast milk vs placebo	1	81	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Percentage of time crying	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Supplemental breast milk vs placebo	1	40	Mean Difference (IV, Fixed, 95% CI)	9.0 [-1.99, 19.99]
3.2 Supplemental breast milk vs artificial sweetener	1	40	Mean Difference (IV, Fixed, 95% CI)	15.0 [2.38, 27.62]
3.3 Supplemental breast milk vs glycine	1	40	Mean Difference (IV, Fixed, 95% CI)	1.0 [-4.61, 6.61]
4 Duration of crying (secs)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Supplemental breast milk vs placebo	4	229	Mean Difference (IV, Fixed, 95% CI)	-6.12 [-15.67, 3.44]
4.2 Supplemental breast milk vs 25% sucrose	1	68	Mean Difference (IV, Fixed, 95% CI)	33.17 [12.08, 54.26]

4.3 Supplemental breast milk vs 30% glucose	1	60	Mean Difference (IV, Fixed, 95% CI)	12.91 [-3.26, 29.08]
4.4 Supplemental breast milk vs 10% glucose	1	60	Mean Difference (IV, Fixed, 95% CI)	3.84 [-15.20, 22.88]
4.5 Supplemental breast milk vs artificial sweetener	1	40	Mean Difference (IV, Fixed, 95% CI)	41.0 [-6.61, 88.61]
4.6 Supplemental breast milk vs glycine	1	40	Mean Difference (IV, Fixed, 95% CI)	51.8 [6.33, 97.27]
5 Neonatal Facial Coding Score at 3 minutes	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Supplemental breast milk vs placebo	3		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 Supplemental breast milk vs artificial sweetener	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.3 Supplemental breast milk vs glycine	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Body pain score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Supplemental breast milk vs placebo	1	40	Mean Difference (IV, Fixed, 95% CI)	0.48 [-0.38, 1.34]
6.2 Supplemental breast milk vs artificial sweetener	1	40	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.72, 1.04]
6.3 Supplemental breast milk vs glycine	1	40	Mean Difference (IV, Fixed, 95% CI)	0.43 [-0.51, 1.37]

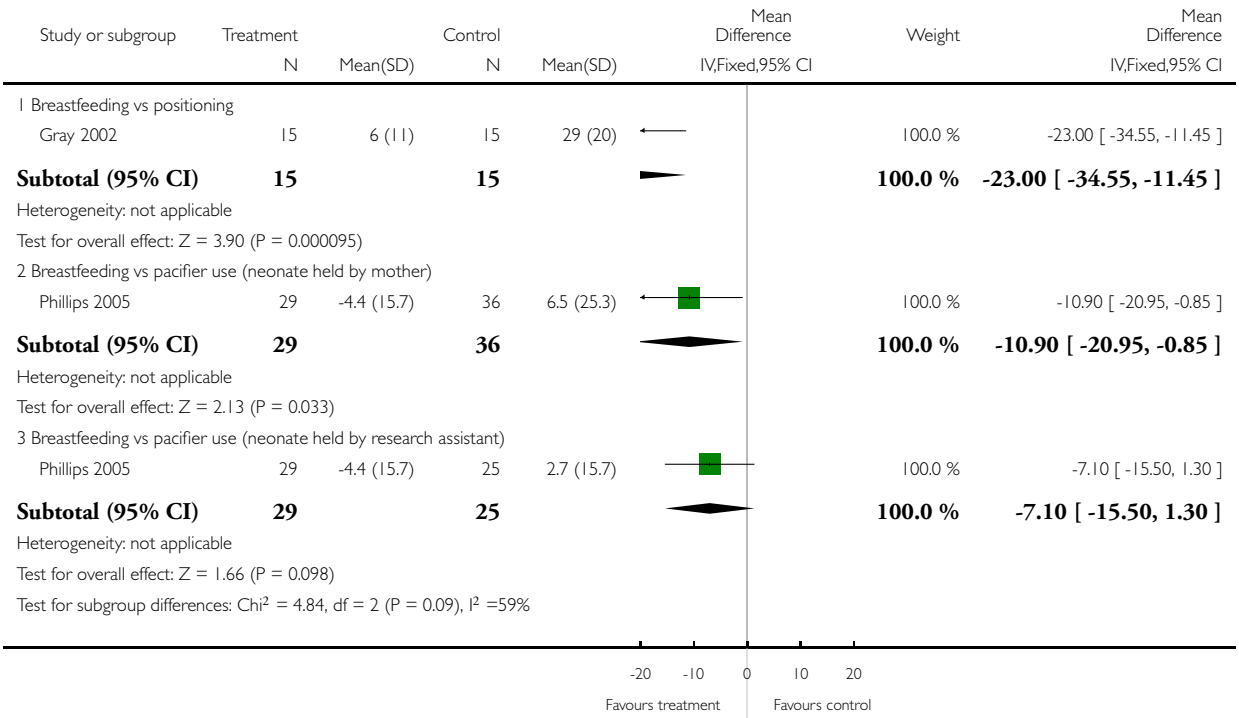
Analysis 1.1. Comparison 1 Breastfeeding vs control, Outcome 1 Heart rate change (beats per minute).

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 1 Heart rate change (beats per minute)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Breastfeeding vs positioning							
Gray 2002	15	6 (11)	15	29 (20)		100.0 %	-23.00 [-34.55, -11.45]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-23.00 [-34.55, -11.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.90 (P = 0.000095)							
2 Breastfeeding vs pacifier use (neonate held by mother)							
Phillips 2005	29	-4.4 (15.7)	36	6.5 (25.3)		100.0 %	-10.90 [-20.95, -0.85]
Subtotal (95% CI)	**29**		**36**			**100.0 %**	**-10.90 [-20.95, -0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.13 (P = 0.033)							
3 Breastfeeding vs pacifier use (neonate held by research assistant)							
Phillips 2005	29	-4.4 (15.7)	25	2.7 (15.7)		100.0 %	-7.10 [-15.50, 1.30]
Subtotal (95% CI)	**29**		**25**			**100.0 %**	**-7.10 [-15.50, 1.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.66 (P = 0.098)							
Test for subgroup differences: Chi^2 = 4.84, df = 2 (P = 0.09), I^2 =59%							

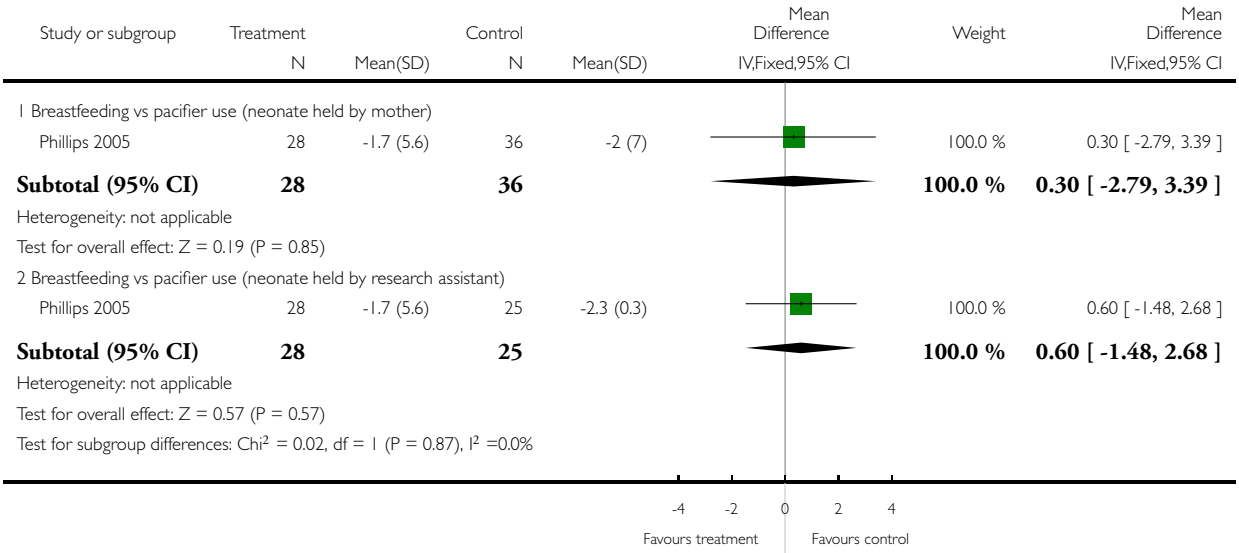


Analysis 1.2. Comparison 1 Breastfeeding vs control, Outcome 2 Oxygen saturation change.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 2 Oxygen saturation change

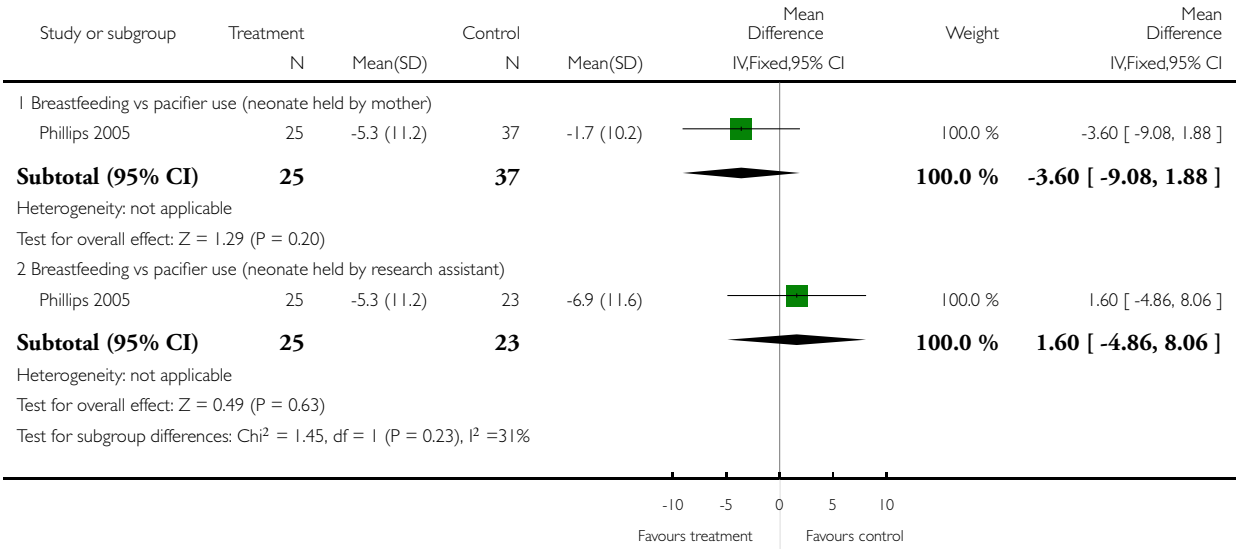


Analysis 1.3. Comparison 1 Breastfeeding vs control, Outcome 3 Blood pressure changes (mm of Hg).

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 3 Blood pressure changes (mm of Hg)

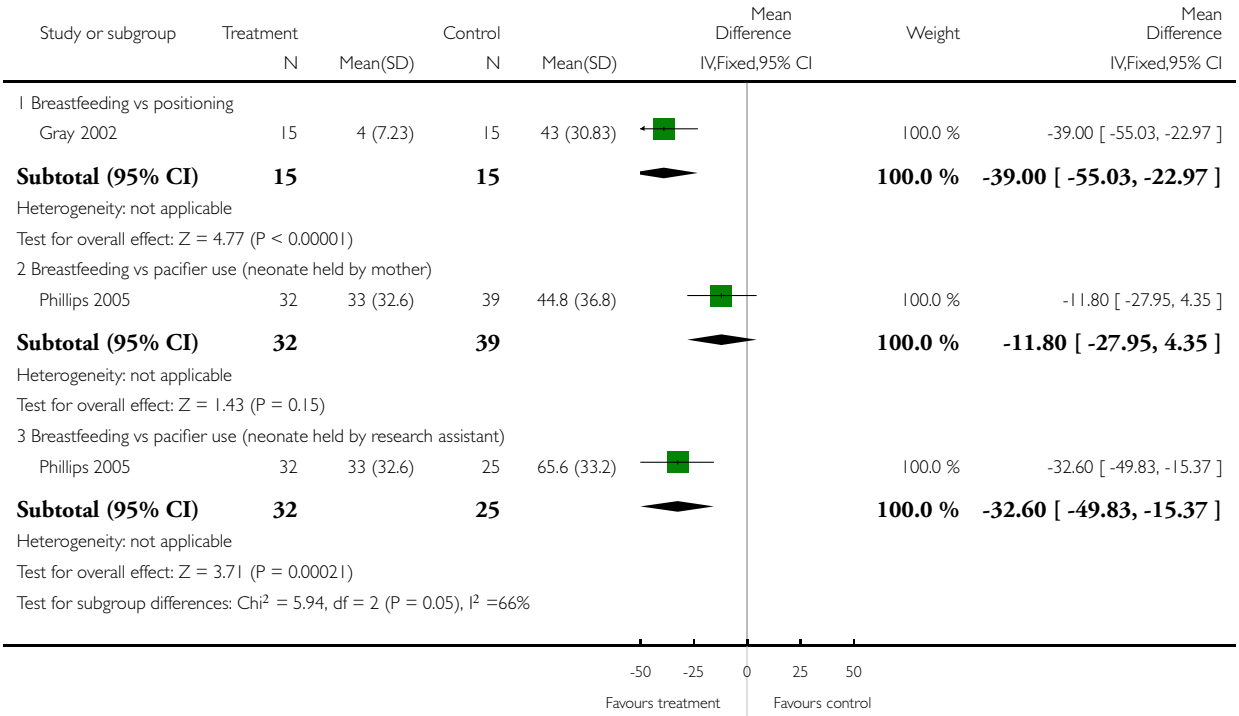


Analysis 1.4. Comparison 1 Breastfeeding vs control, Outcome 4 Percentage of time crying.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 4 Percentage of time crying

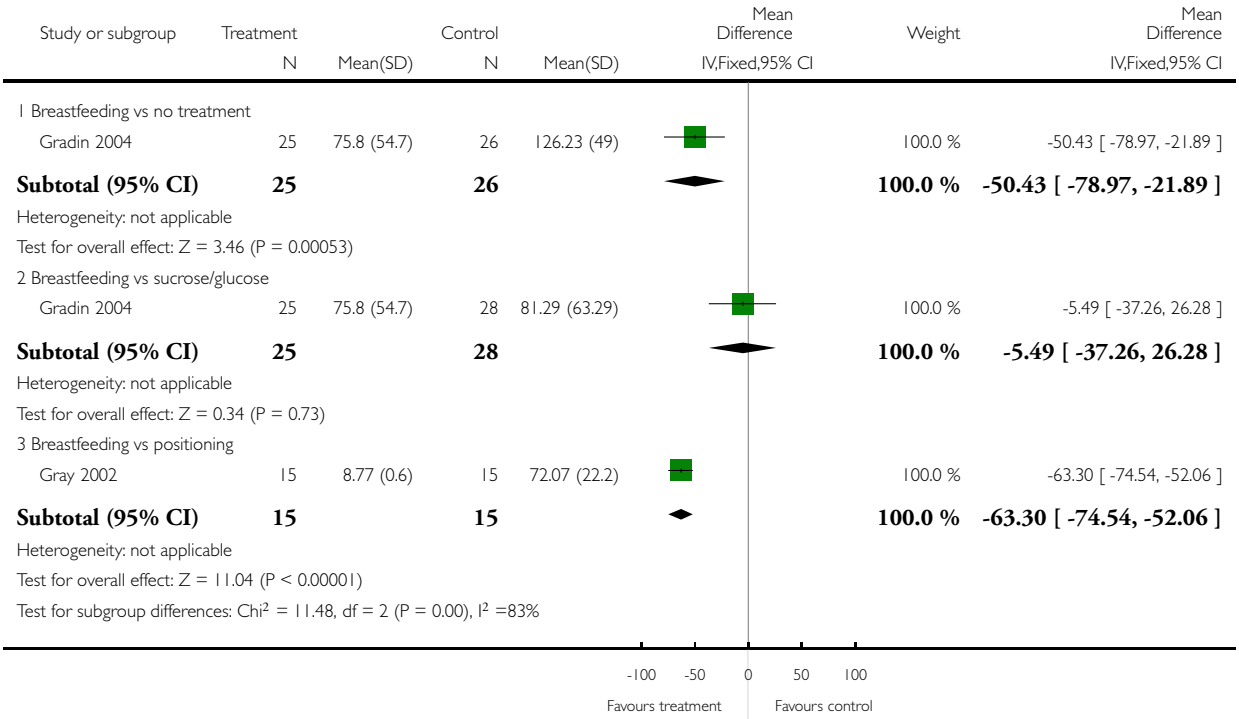


Analysis 1.5. Comparison 1 Breastfeeding vs control, Outcome 5 Duration of crying (secs).

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 5 Duration of crying (secs)

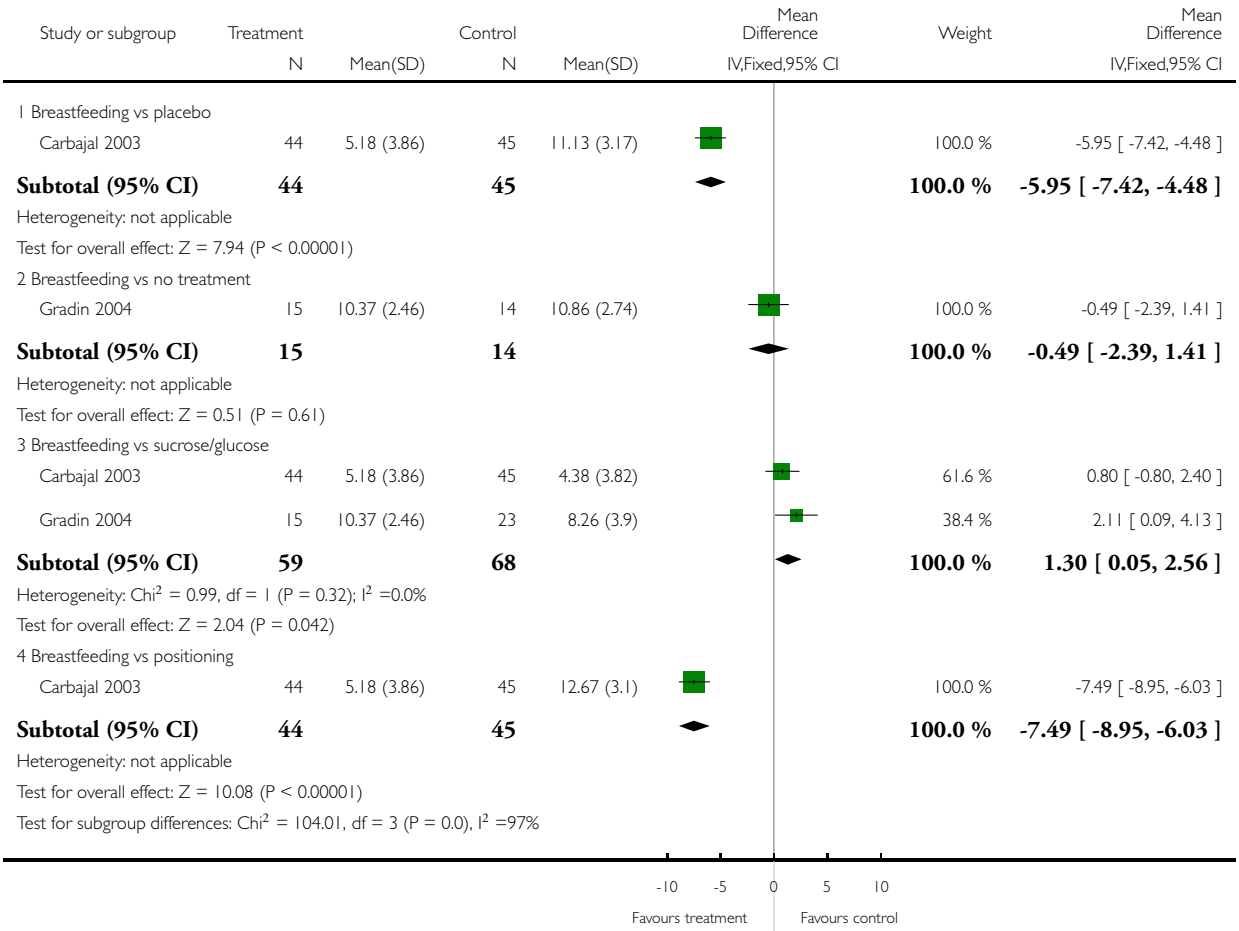


Analysis 1.6. Comparison 1 Breastfeeding vs control, Outcome 6 Premature Infant Pain Profile Score.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 6 Premature Infant Pain Profile Score

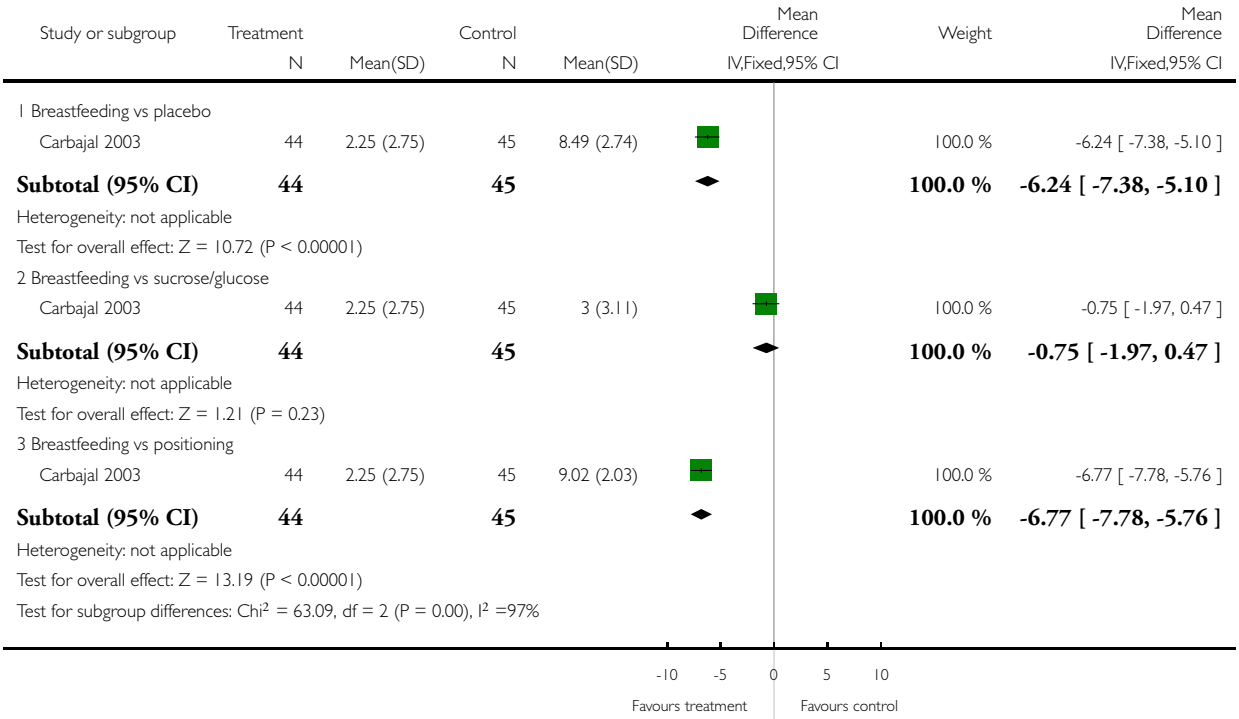


Analysis 1.7. Comparison 1 Breastfeeding vs control, Outcome 7 Douleur Aigue Nouveau-né (DAN) Scale.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 7 Douleur Aigue Nouveau-n (DAN) Scale



Analysis 1.8. Comparison 1 Breastfeeding vs control, Outcome 8 Composite score.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 1 Breastfeeding vs control

Outcome: 8 Composite score

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Shendurnikar 2005	50	5.38 (1.77)	50	8.28 (1.31)		100.0 %	-2.90 [-3.51, -2.29]
Total (95% CI)	**50**		**50**			**100.0 %**	**-2.90 [-3.51, -2.29]**

Heterogeneity: not applicable

Test for overall effect: Z = 9.31 (P < 0.00001)

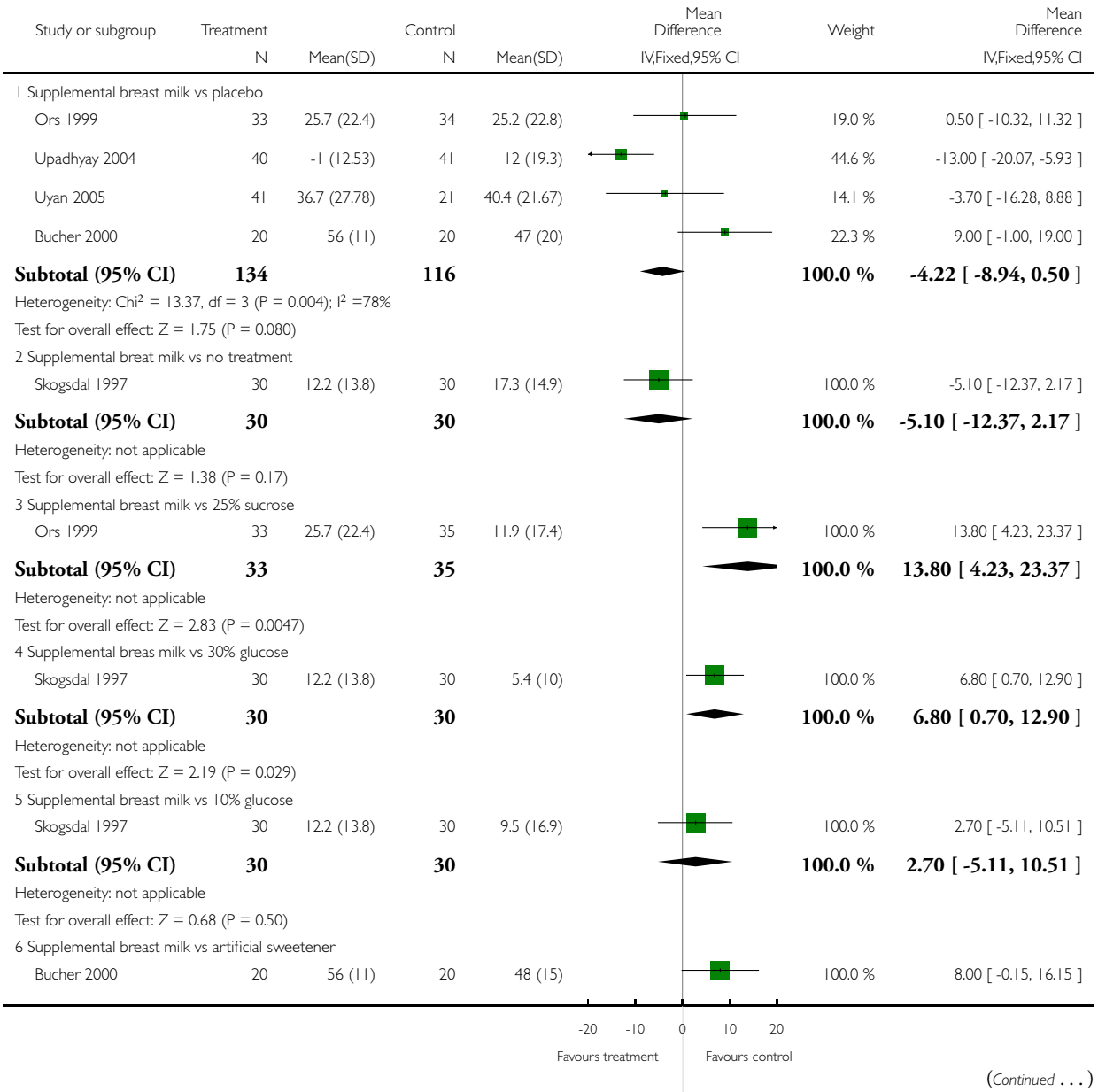
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Supplemental breast milk vs control, Outcome 1 Heart rate change (beats per minute).

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 2 Supplemental breast milk vs control

Outcome: 1 Heart rate change (beats per minute)



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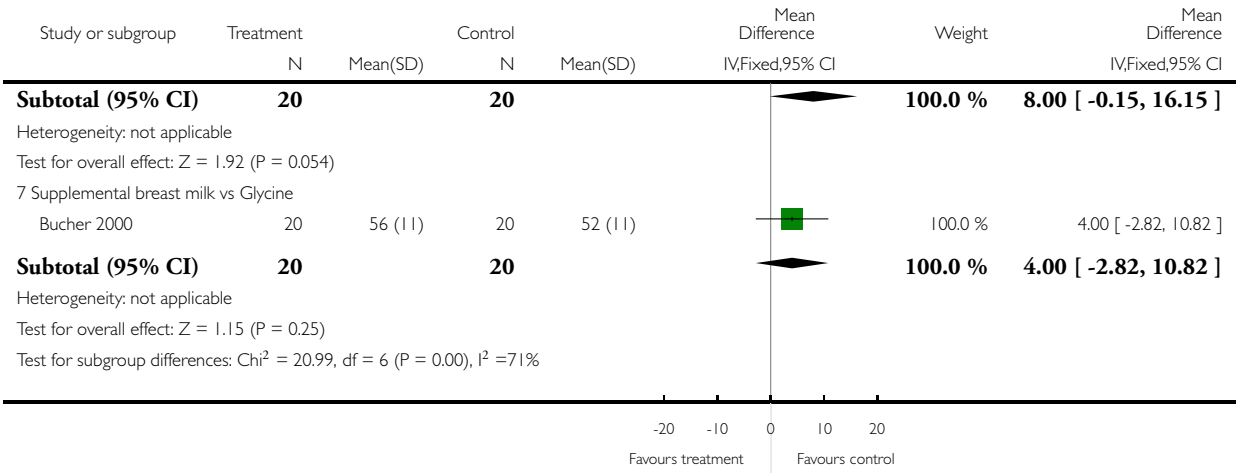
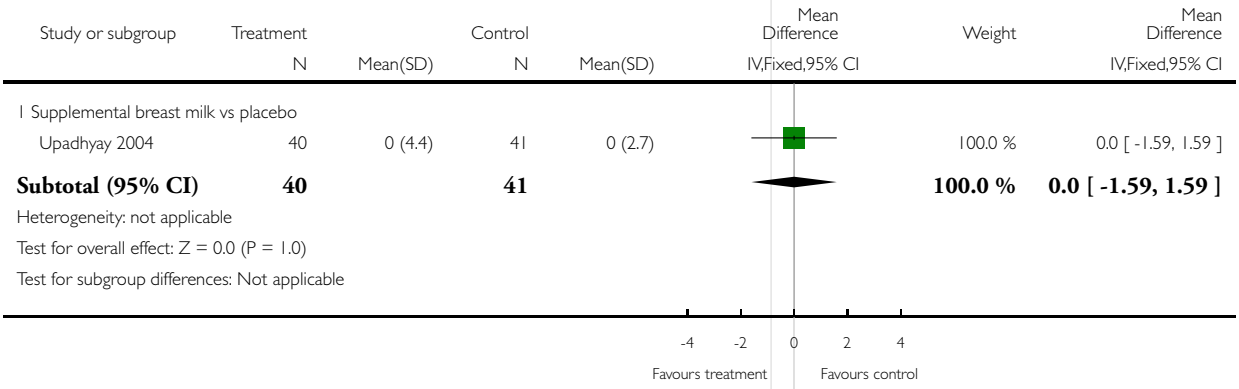


Analysis 2.2. Comparison 2 Supplemental breast milk vs control, Outcome 2 Oxygen saturation change.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 2 Supplemental breast milk vs control

Outcome: 2 Oxygen saturation change

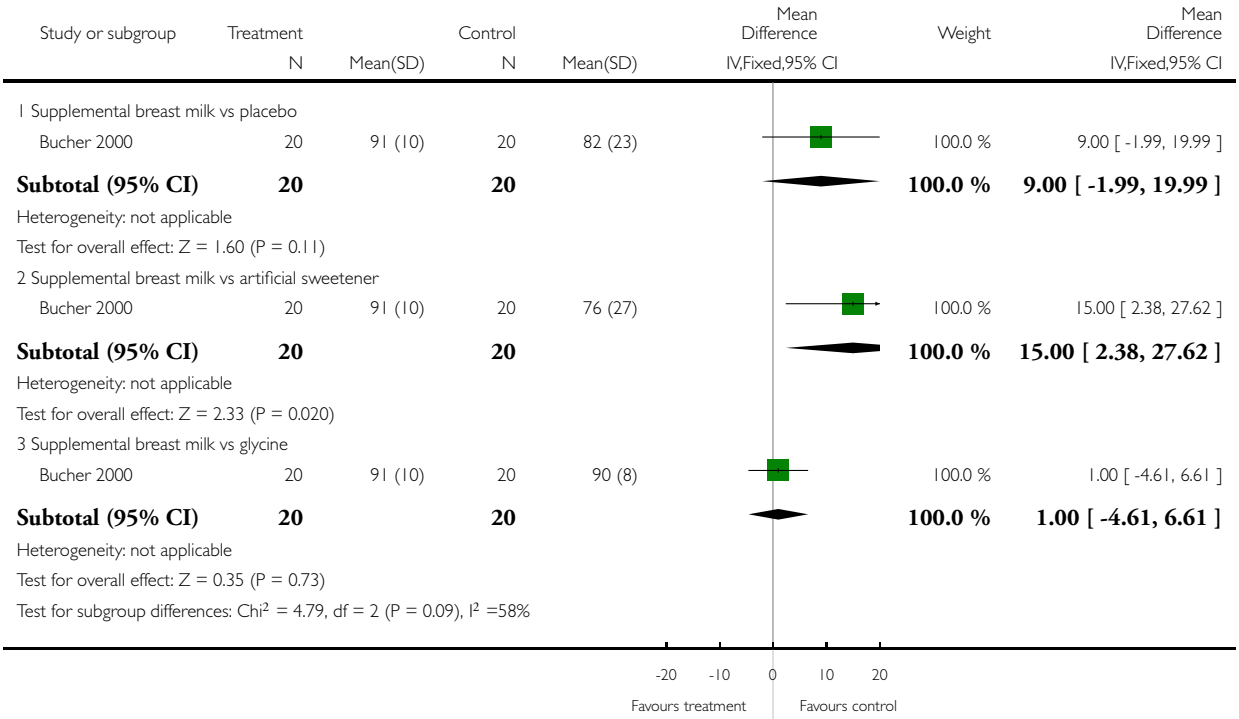


Analysis 2.3. Comparison 2 Supplemental breast milk vs control, Outcome 3 Percentage of time crying.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 2 Supplemental breast milk vs control

Outcome: 3 Percentage of time crying

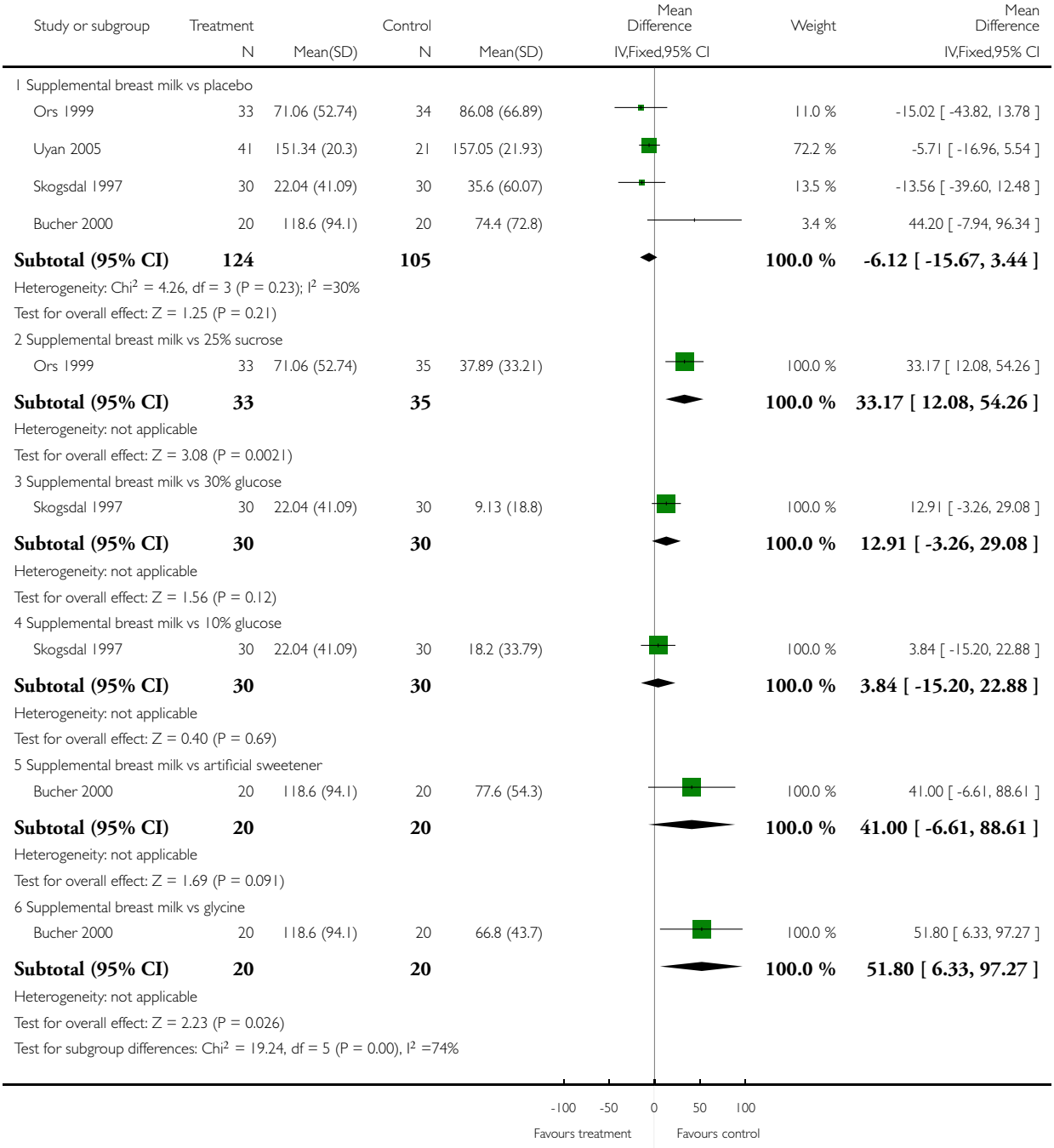


Analysis 2.4. Comparison 2 Supplemental breast milk vs control, Outcome 4 Duration of crying (secs).

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 2 Supplemental breast milk vs control

Outcome: 4 Duration of crying (secs)



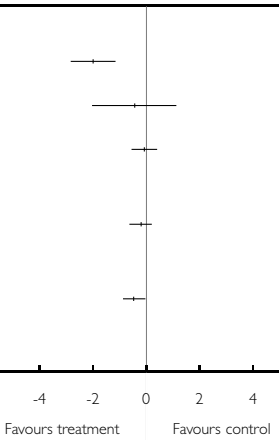
Analysis 2.5. Comparison 2 Supplemental breast milk vs control, Outcome 5 Neonatal Facial Coding Score at 3 minutes.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 2 Supplemental breast milk vs control

Outcome: 5 Neonatal Facial Coding Score at 3 minutes

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Supplemental breast milk vs placebo						
Upadhyay 2004	40	0.6 (1.3)	41	2.6 (2.4)		-2.00 [-2.84, -1.16]
Uyan 2005	41	3.08 (2.77)	21	3.54 (3.14)		-0.46 [-2.05, 1.13]
Bucher 2000	20	2.86 (0.84)	20	2.95 (0.73)		-0.09 [-0.58, 0.40]
2 Supplemental breast milk vs artificial sweetener						
Bucher 2000	20	2.86 (0.84)	20	3.08 (0.49)		-0.22 [-0.65, 0.21]
3 Supplemental breast milk vs glycine						
Bucher 2000	20	2.86 (0.84)	20	3.33 (0.52)		-0.47 [-0.90, -0.04]

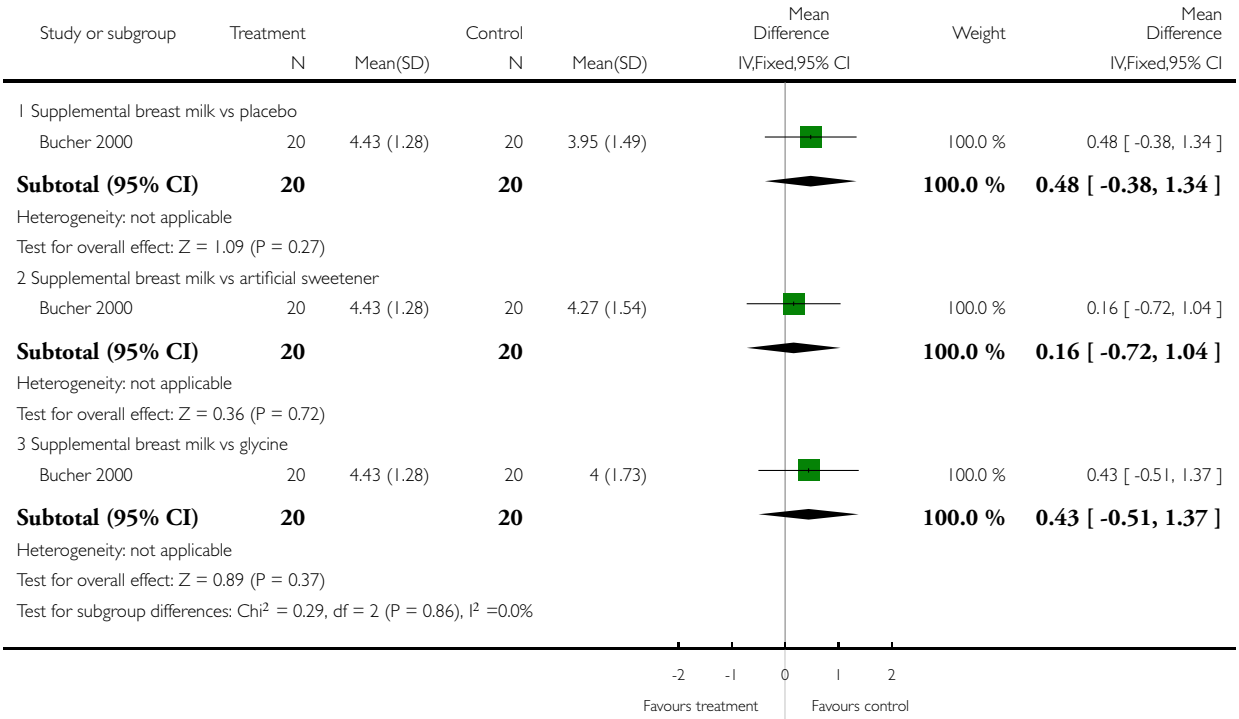


Analysis 2.6. Comparison 2 Supplemental breast milk vs control, Outcome 6 Body pain score.

Review: Breastfeeding or breast milk for procedural pain in neonates

Comparison: 2 Supplemental breast milk vs control

Outcome: 6 Body pain score



WHAT'S NEW

Last assessed as up-to-date: 20 April 2006.

Date	Event	Description
11 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 3, 2006

CONTRIBUTIONS OF AUTHORS

P Shah

Protocol development

Editing the protocol

Identification of trials

Writing the review

Editing the review

Collecting and entering data in Revman

Revision of review

L Aliwalas

Protocol writing

Review writing

Identification of studies

Entering data in Revman

Revision of review

V Shah

Protocol editing

Review editing

Checking the search for trials

Identification of studies

Checking the data in Revman

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Shared Fellowship Program in Neonatal Perinatal Medicine, University of Toronto, Canada.
- Mount Sinai Hospital, University of Toronto, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Breast Feeding; *Milk, Human; Crying [physiology]; Hemodynamics [physiology]; Infant Care; Infant, Newborn; Pacifiers; Pain [physiopathology; *prevention & control]; Phlebotomy [*adverse effects]; Punctures [*adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Humans